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TRENDS AND ANALYSIS FOR THE BIO/PHARMA INDUSTRY

13 YEARS

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Report and Survey of Biopharmaceutical Manufacturing Capacity and Production

A Study of Biotherapeutic Developers and Contract Manufacturing Organizations

APRIL 2016

13th Annual

Report and Survey of Biopharmaceutical Manufacturing Capacity and Production

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BioPlan Associates, Inc.
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Layout and Cover Design: ES Design

ISBN 978-1934-106-28-0

COVER1: Automated Allegro systems for single use downstream operations.
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ACKNOWLEDGMENT

We wish to recognize our sponsoring institutions, and our media sponsors. Their efforts in assuring the cooperation and participation in the survey of their respective memberships helped guarantee the large group of survey participants to ensure data accuracy.

Our ***Institution Partners,*** all of whom contributed their time and effort to ensure the broad, international coverage of this project, include:

- AusBiotech (Malvern, Victoria, Australia)
- ABO China (Beijing, China)
- Beijing Pharma and Biotech Center (Beijing, China)
- BIO (Biotechnology Industry Organization, Washington, D.C.)
- Bio-Process Systems Alliances/SOCMA (BPSA) (Washington, D.C.)
- BioMaryland (Rockville, MD)
- California Life Sciences Association (CLSA) (San Francisco, CA)
- Colorado BioScience Association (Denver, CO)
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- Massachusetts Life Sciences Center (Waltham, MA)
- MichBio (Ann Arbor, MI)
- North Carolina BioSciences Organization (Research Triangle Park, NC)
- North Carolina Biotechnology Center (Research Triangle Park, NC)
- Pharma & Biopharma Outsourcing Association (PBOA) (Ringwood, NJ)
- Washington Biotechnology & Biomedical Association (WBBA) (Seattle, WA)

To ensure global coverage for this project, we again invited major ***Media Sponsors*** to support our outreach to biopharmaceutical decision-makers. Our media sponsors, who helped ensure broad and representative coverage of industry participation, include:

- American Pharmaceutical Review (Fishers, IN)
- BioPharm International (Iselin, NJ)
- BioProcess International, (Westborough, MA)
- BioProcessing Journal (Winthrop, MA)
- Contract Pharma, (Ramsey, NJ)
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- Pharmaceutical Processing (Rockaway, NJ)
- Pharmaceutical Technology (Iselin, NJ)
- Pharmaceutical Technology Europe (Iselin, NJ)

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. As always, their continued support was 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 for almost 30 years. 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.

We prepare custom studies, and provide public information our clients require to make informed strategic decisions, define objectives, and identify customer needs. With market information, our clients are better able to make informed, market-based decisions because they understand the trends and needs in high technology industries.

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Mr. Langer is President and Managing Partner and President of BioPlan Associates, Inc., a biotechnology and life sciences consulting company that has been providing management and market strategy services, and technology analysis to biopharmaceutical and healthcare organizations since 1989. He has over 25 years' experience in biotechnology and life sciences management and market assessment. He is an experienced medical and biotechnology industry practitioner, strategist, researcher, and science writer. He has held senior management and marketing positions at biopharmaceutical supply companies. He teaches Biotechnology Marketing, Marketing Management, Services Marketing, Advertising Strategy, and Bioscience Communication at Johns Hopkins University, American University, and lectures extensively on pricing and channel management topics. Mr. Langer has a degree in Chemistry and a Masters in International Business. He has written and consulted extensively for companies involved in: large scale biopharmaceutical manufacturing, global biotechnology in China, Asia, and the Middle East; he has expertise in cell culture markets, media, sera, tissue engineering, stem cells, diagnostic products, blood products, genetics, DNA/PCR purification, blood components, and many other areas.

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Mr. Ronald A. Rader has written and edited dozens of books and studies on biotechnology topics. He created the first biosimilars pipeline database, and is qualified with a B.S. (Microbiology), M.L.S. (Library Science). He has nearly 30 years' experience as a biotechnology, pharmaceutical and chemical information specialist and publisher. From 1988, he was Editor/Publisher of the Antiviral Agents Bulletin, the only periodical specializing in antiviral/HIV drug and vaccine development. In 1994, he published the Federal Bio-Technology Transfer Directory, abstracting and indexing all federal laboratory, e.g., NIH, inventions and technology transfers in biotech/biomedical areas, further marketed as an online database until 2000. Mr. Rader published Biopharmaceutical Products in the U.S. Market first in April 2001. Mr. Rader has been Manager of Information Services, Porton International plc, Prior to that he served as a biomedical/chemical information specialist/manager/analyst with companies including Gillette Medical Evaluation Labs., Gillette Co.; MITRE Corp.; Biospherics; Computer Sciences Corp. (CSC); Technical Resources Inc.; and Bio-Conversion Labs.

13th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production • April 2016

A Study of Biotherapeutic Developers and Contract Manufacturing Organizations

CONTENTS

FIGURES

TABLES

METHODOLOGY

This report is the thirteenth 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 222 qualified and responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations in 27 countries; plus 191 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.

We continue to provide additional in-depth analysis of specific issues affecting the industry in Chapter 2. 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. We also have included this year a chapter on Fill-and Finish operations. Over the past few years, advances in technologies, drug delivery, and single-use applications have increasingly made this segment an area of interest for innovation.

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 included a diverse group of biopharmaceutical senior managers and executives covering a spectrum of global biopharmaceutical and CMO firms. In addition, in Chapter 13, we include responses from global suppliers and vendors in this industry. As in previous years, we included firms of all sizes. 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 individuals at organizations around the world, including input from facilities in 27 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 their company's manufacturing plans and needs. This offers a means for understanding the industry and its future course. The breakdown of organizations into CMOs 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.

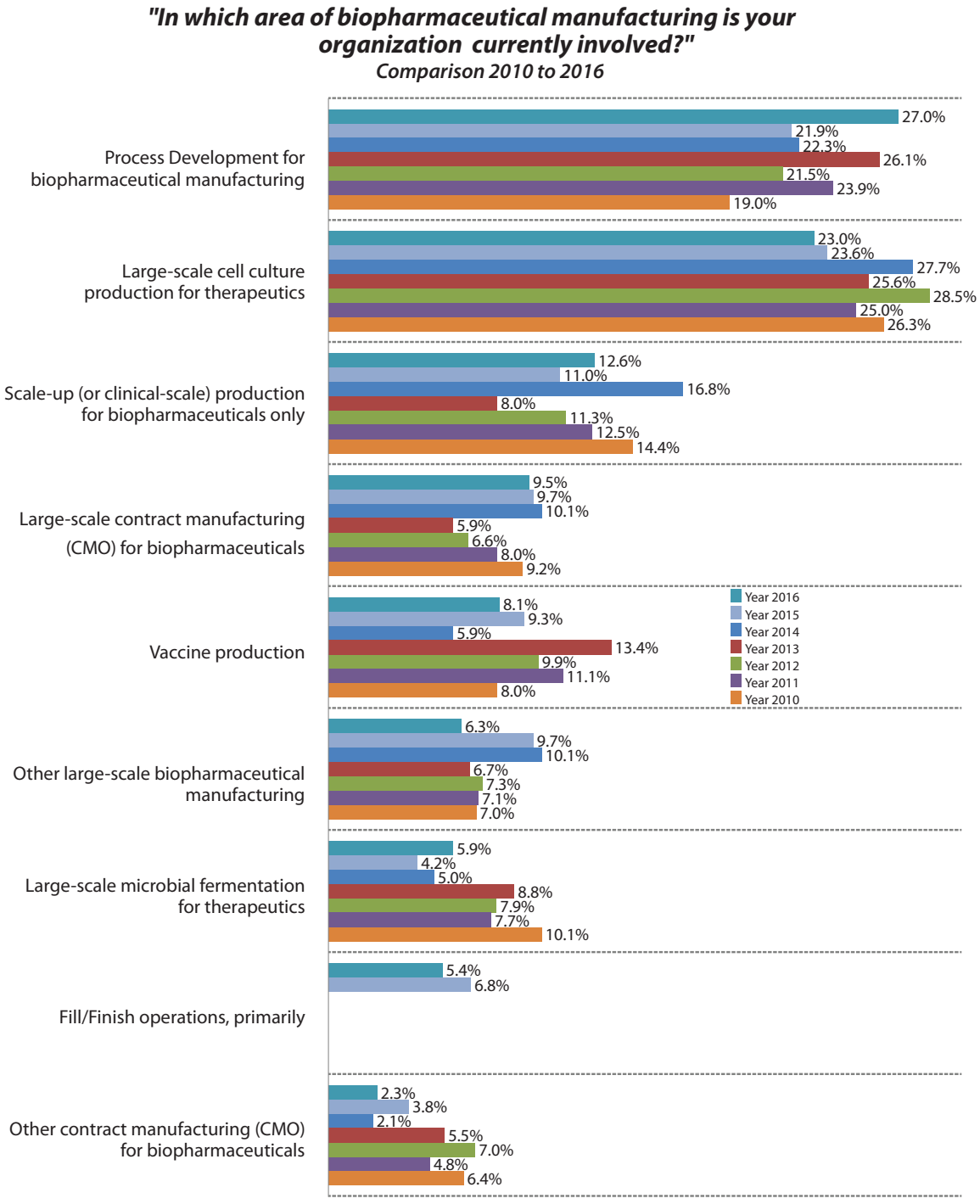
0-1 RESPONDENTS' AREA OF INVOLVEMENT

Of the 222 biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) staff responding to this year's survey, 23.0% were primarily involved in *Large-scale cell culture production for therapeutics,* slight decrease down from 23.6% last year, and continued decline from 27.7% in 2014. 27.0% were involved primarily in *Process Development for biopharmaceutical manufacturing,* an almost 6% percentage point increase from 21.9% last year, and back up to levels seen in 2013; 12.6% were involved in scale-up (or clinical-scale) production for biopharmaceuticals only, a small increase from 11.0% last year.

Respondents involved with Large-scale *Microbial Fermentation* for therapeutics accounted for 5.9%, an increase in 1.7% percentage points and a change from last year's decline of 4.2%, and 8.1% of respondents indicated they were primarily involved in Vaccine production, down from 9.3% reported last year. 'Other' large-scale biopharmaceutical manufacturing respondents accounted for 6.3% of the total this year, a decline from 9.7% in 2015, and 'Other' contract manufacturing (CMO) for biopharmaceuticals accounted for 2.3% of respondents, down from 3.8% last year. Lastly, 9.5% were employed in Large-scale contract manufacturing (CMO) for biopharmaceuticals, the slightest decrease from most prior years. This year, 5.4% of

respondents accounted for Fill/Finish operations, a slight decline from 6.8% last year. Overall, the makeup of respondents remains overall consistent with prior years' studies, with the most significant changes seen in Process Development for biopharmaceutical manufacturing and 'Other' large-scale biopharmaceutical manufacturing. Despite variations, including decreases, in reporting involvement in aspects of biopharmaceutical manufacturing, this year's data continues to fall within the range defined by prior years' data reporting, with the relative rankings remaining largely unaffected.

Fig 0.1: Area of Primary Involvement in Biopharmaceutical Manufacturing, 2010 to 2016

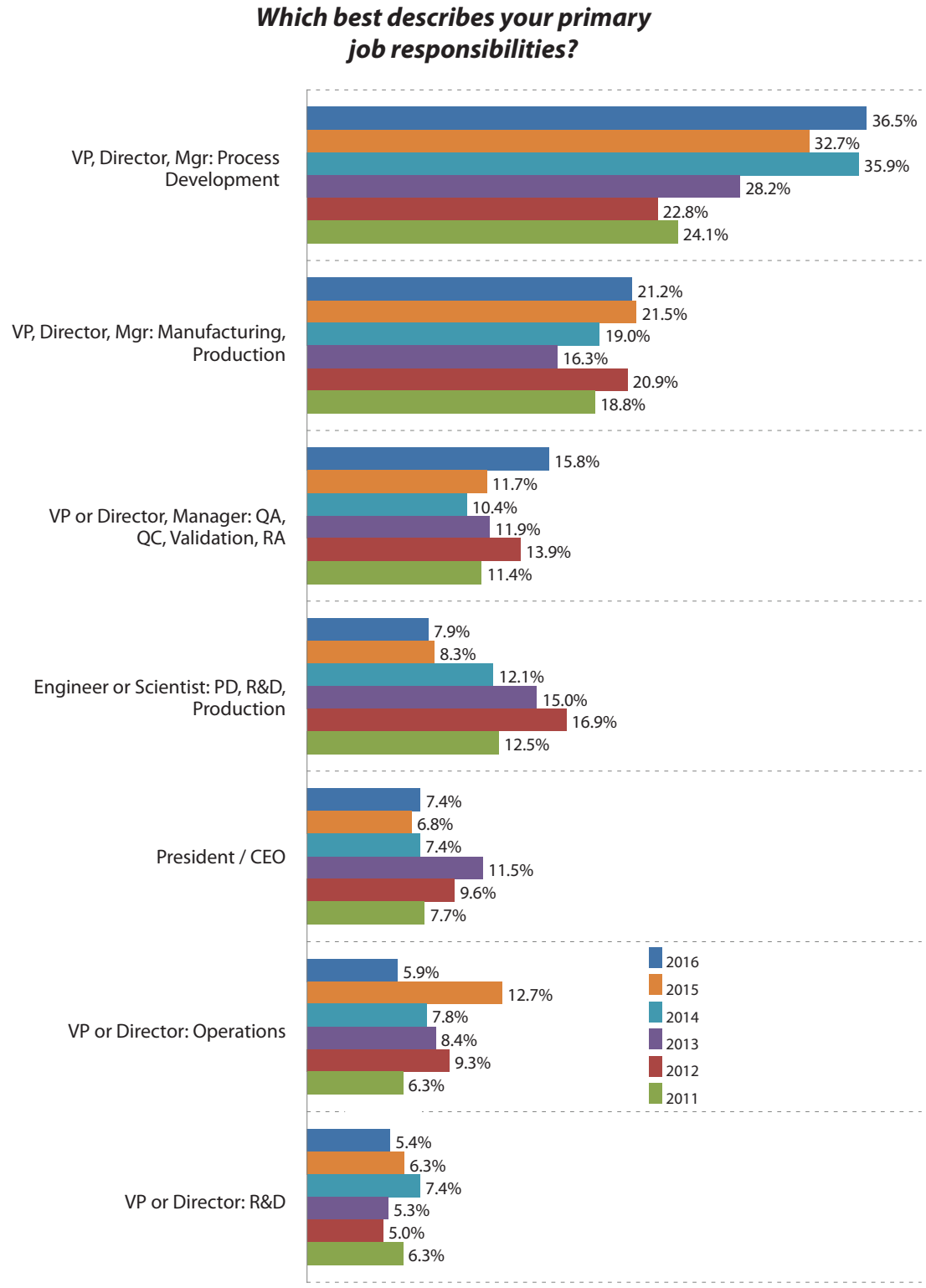


0-2 RESPONDENTS QUALIFICATIONS

Respondents were asked about their areas of responsibility, as indicated by job titles. Over 92% had titles of *VP, Director or President/CEO,* consistent with last year's 91.7% and nearly 88% in 2014. *VPs, Directors or Managers of Manufacturing, Production, and Operations* comprised 27.1% of respondents, a sharp decline from 34.2% last year. Combining *VPs* with *Process Development Directors and Managers,* the percentage comes to 63.6%, a 3.3%-point decrease from last year's 66.9%, and closer to 62.7% reported in 2014.

Biopharmaceutical *Scientist* or *Engineer* respondents lacking VP/Director/Manager responsibilities in Process Development, R&D or Production made up 7.9%, another persistent decline from prior year respondents (8.3% in 2015 and 12.1% in 2014.) This year, 15.8% of respondents indicated they were *VPs, Directors or Managers* of *QA, QC, Validation, or RA,* the largest number of respondents in this area since data collection started in 2011. *Presidents/ CEOs* represented 7.4% of respondents, a reversal from the decline seen in prior years; and *VPs or Directors of R&D* accounted for 5.4% of respondents, still averaging similar totals seen in past years. The largest percentage change this year continues for those reporting *VP or Director: Operations* responsibilities, with a 6.8%-point decrease from last year.

Fig 0.2: Respondents' Job Responsibilities, 2011 - 2016

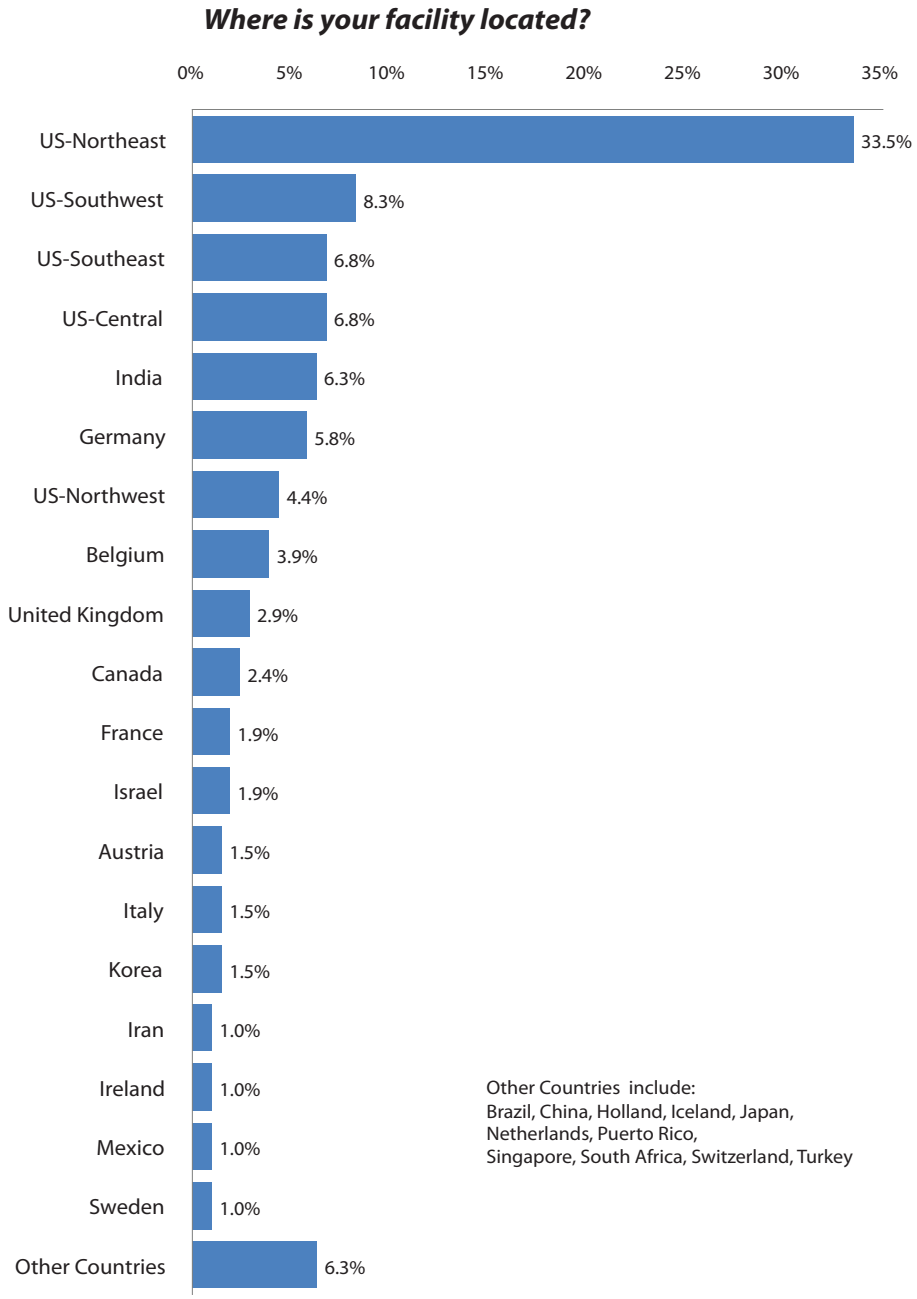


0-3 FACILITY LOCATIONS

This year we surveyed respondents based in 27 countries. Almost 62% of the respondents were from the United States, with the Northeastern U.S. continuing to make up the largest group of respondents in the U.S., at 33.3%, no change from last year's total. Respondents from Western Europe made up 21.4% of the total, a continued increase from last year's 19.7%. Other countries in the survey ("Rest of World") made up 17.5% of the respondents.

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).

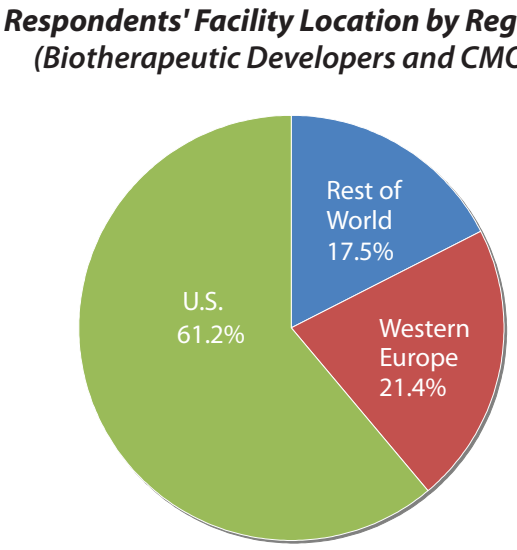
Fig 0.3: Facility Location



We note that U.S. respondents continued its steady rate at 61.2%, down 1.7%-points from 62.9% last year, 65.8% in 2014, and nearly consistent with the 61.7% U.S. respondents in 2011. Western European responses remain relatively constant near 20% since 2011, with the slightest increase to 21.4% this year.

This year ROW responses only rose 0.1 point from last year's 17.4%, although still off the peak of 22.0% in 2013. This year we see a slight uptick in Western European respondents and U.S. bioprocessing professionals remain to be more motivated to participate in this and other industry surveys.

Fig 0.4: Facility Location, by Region



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

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

0-4 AREAS OF BIOPHARMACEUTICAL MANUFACTURING OPERATIONS

Mammalian Cell Culture systems continue to dominate product development and manufacture. Further, a large percentage of products in the pipeline entering the market are mammalian-expressed, including various recombinant monoclonal antibody products. With the recent and on-going increases in mammalian system titers and yields, many facilities are standardizing using mammalian vs. microbial systems; in some cases, even products that could be manufactured in microbial systems are now being considered for manufacture in mammalian systems, if these will get the job done, such as to produce pre-clinical or early clinical supplies.

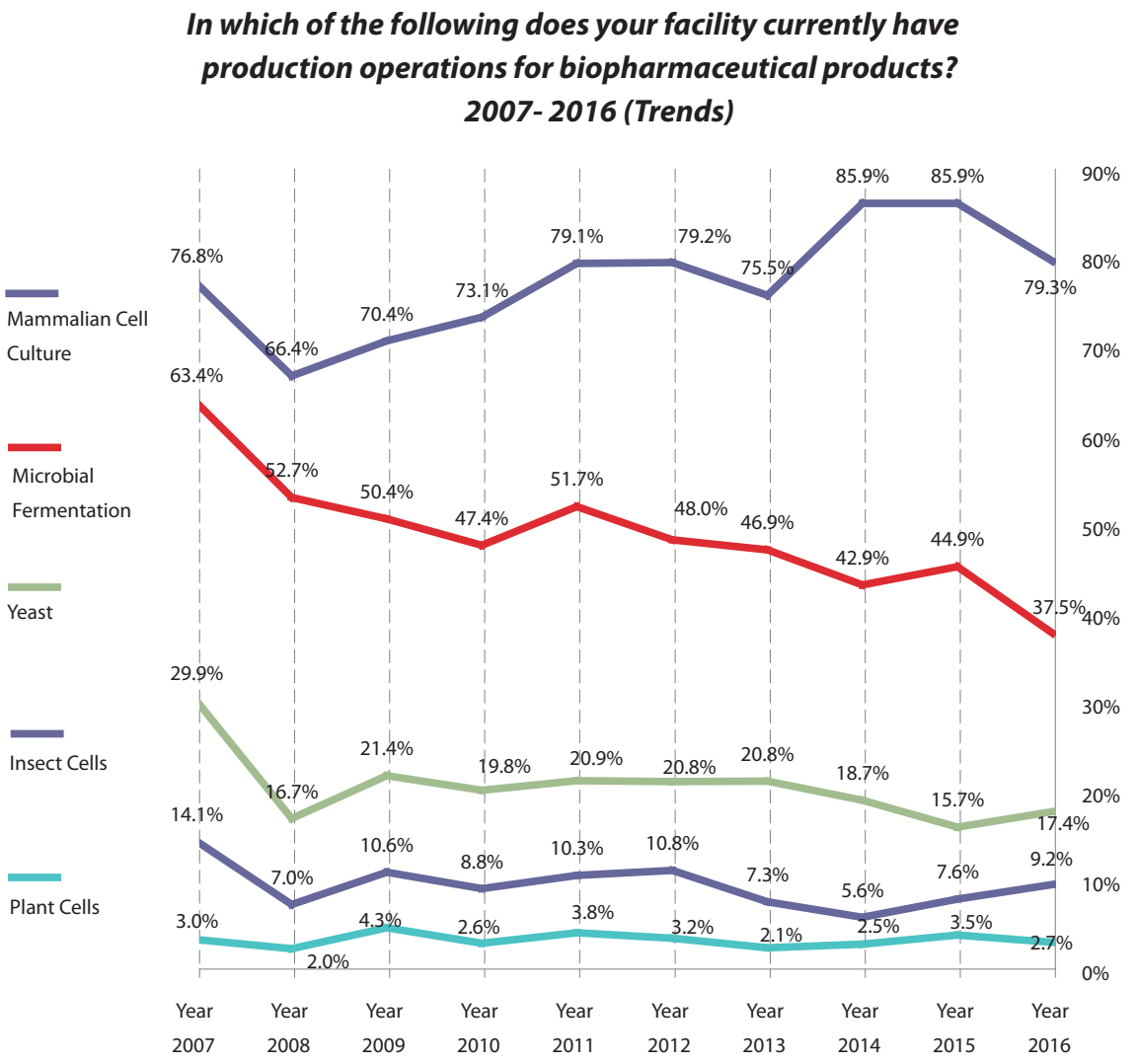
This year, we see a decrease in Mammalian Cell Culture and Microbial Fermentation; small upticks in the overall percentage of respondents for Yeast and *Insect cells*.

Respondents involved in *Mammalian Cell Culture* decreased from last year's study (79.3% vs. 85.9%). Although respondents were permitted to select multiple platform systems, the modest drop in mammalian systems is possibly due to more facilities standardizing on one or another platform.

We saw a similar decrease for *Microbial Fermentation* systems where 37.5% of respondents noted involvement in this area, a 7.4%-point decrease from the previous year (44.9%), and continuing the decrease seen in prior years.

On the other hand, less common systems including yeast, plant saw modest increases. For this year, 17.4% said that their facility had production operations in Yeast, a reversal from the decline seen in recent years. The percentage of those involved with microbial manufacture, including Plant Cells, saw a slow rise over the past couple of years, which still continues in this year's study (9.2%). *Insect cells* declined to 2.7% this year, going back to levels seen in 2014.

Fig 0.5: Biopharmaceutical Manufacturing Systems, (2007-2016) Trends



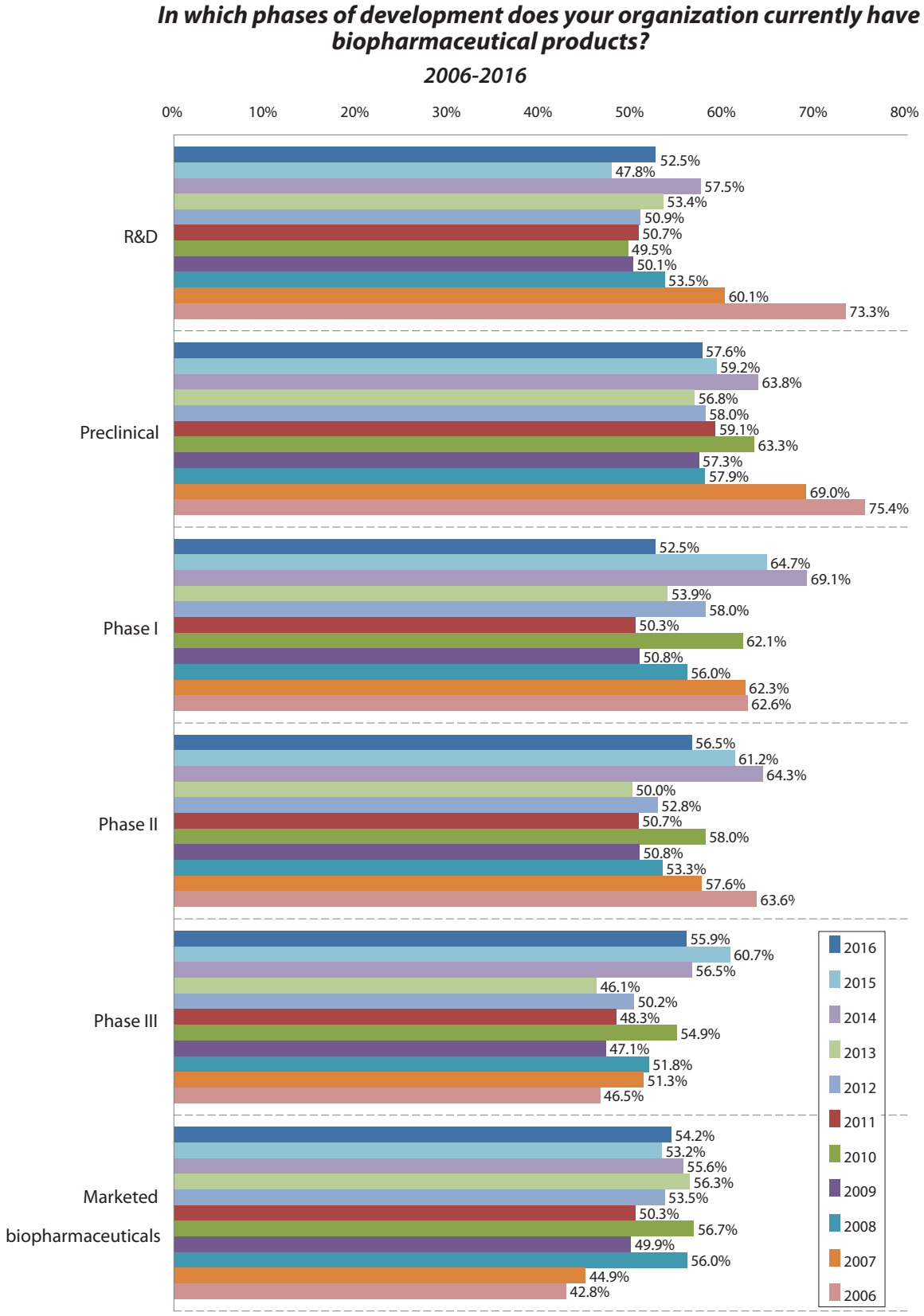
0-5 PRODUCTION OPERATIONS, PHASE OF DEVELOPMENT

We identified the phases of pipeline development in which respondents' organizations (companies) had products. This year, over half (52.5%) of respondent companies had *R&D* biopharmaceutical operations, a reversal from last year's decline of 47.8%, and readjusted with levels seen in prior years. 57.6% indicated their company having *Preclinical* operations, a continued small decline from last year's 59.2% and 63.8% in 2014. Respondent organizations involved with R&D have shifted back to their relative 50% level seen in almost all prior years, but still remain much lower than the 73.3% in 2006. Preclinical started at 75.4% in 2006, remained declining each year after, and has remained consistently near the 60% mark, as seen in this year's 57.6%.

The percentage of respondents whose companies have biopharmaceutical products on the market has slightly increased to 54.2%, up from 53.2% last year. The percentage involved with products in Phase III development decreased to 55.9% this year, down from its marked increase last year (60.7%), and relative to prior years.

This area continues to see small fluctuations as the industry continues its overall 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. Overall, the employers of the biopharmaceutical manufacturing professionals interviewed are rather evenly distributed over the pipelines from pre-clinical though commercial manufacturing, with each phase being worked on by 50+% of survey respondent organizations.

Fig 0.6: Phase of Development of Surveyed Respondents (2006-2016) Trends

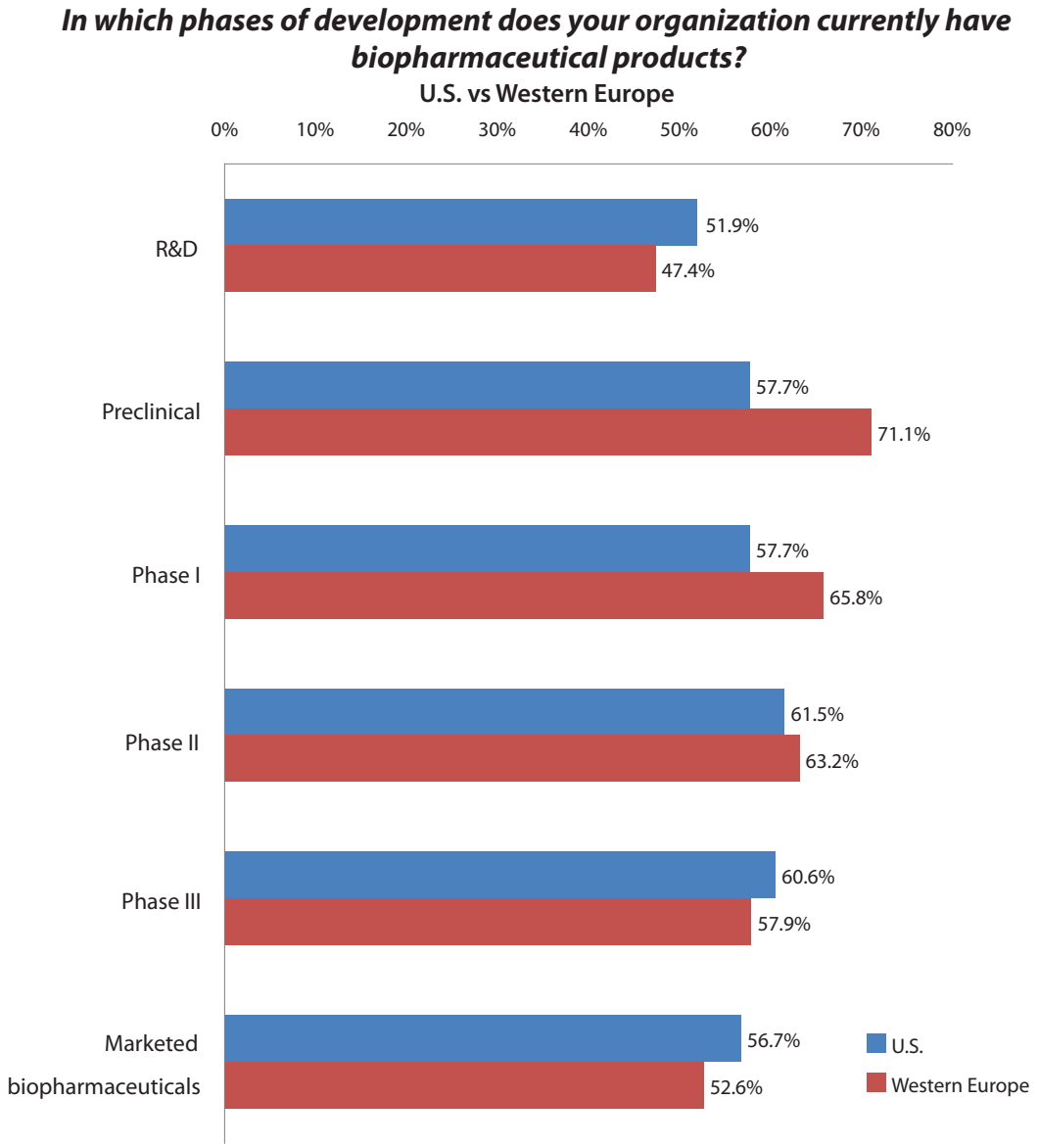


This year, we see Western Europe respondents indicating a higher response of involvement by their companies with *Preclinical* products at 71.1% vs. 57.7% for the U.S., a major shift from last year in which W.E. respondents indicated only 59.0% vs. 61.4%, respectively.

European respondents involved in commercial products declined significantly to 52.6%, (from 61.5% last year), while increasing for the U.S. to 56.7% (from 50.4% last year).

The U.S. continued to report lower percentages in Phase I clinical trials this year vs. Western Europe (57.7% vs. 65.8%), both global areas down from 67.7% and 69.2%, respectively, last year. Another major shift seen this year is significantly lower percentage in *Phase III* clinical trials for Western Europe vs. U.S., (57.9% and 60.6%), a big decrease from last year (71.8%) for Western Europe.

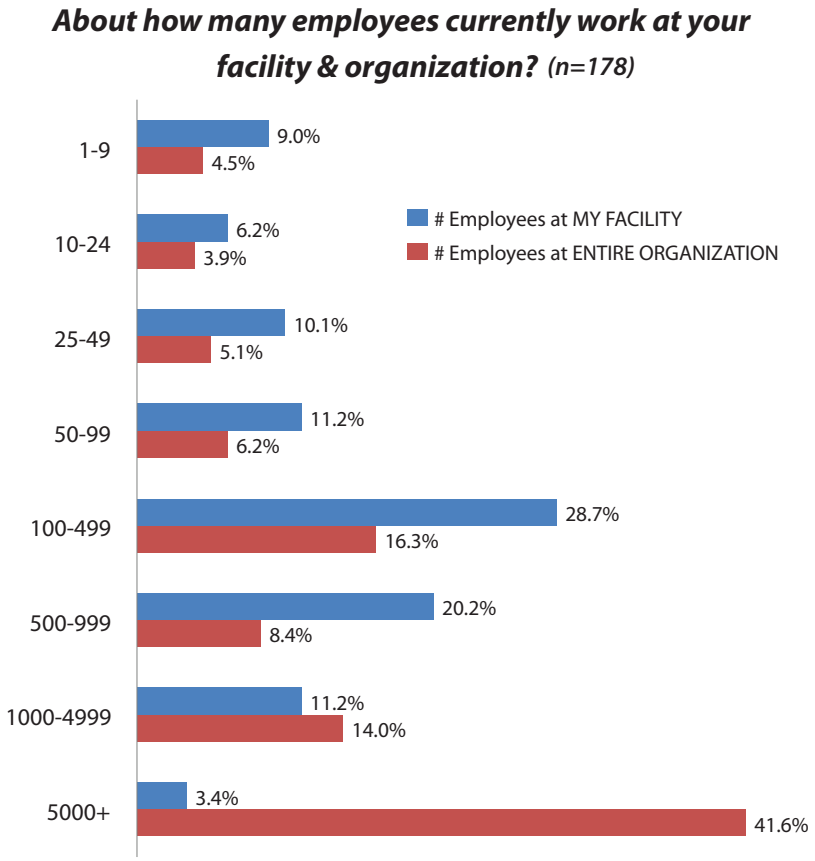
Fig 0.7: Phase of Development of Surveyed Respondents, (U.S. vs Western Europe)



Employees at Facility

To evaluate issues such as capacity, disposables usage and other factors, we asked respondents for the number of staff within their own facility, and within their total organization. The largest percentages of respondents remained to be at facilities with 100-499 employees. Continuing the trend, the largest share of respondents, 41.6%, tend to be from organizations with greater than 5,000 employees. This distribution reflects the distribution of bioprocessing and other professionals' employment in the (bio)pharmaceutical industry. This includes the increasing involvement and even dominance of larger companies in biopharmaceutical R&D and products marketing. And with most Big Pharma type companies continuing to move into biopharmaceuticals, the dominance of large companies as employers of biopharmaceutical manufacturing professionals will continue.

Fig 0.8: Distribution of Employees at Facility, and Organization



Batches Run at Facility per Year

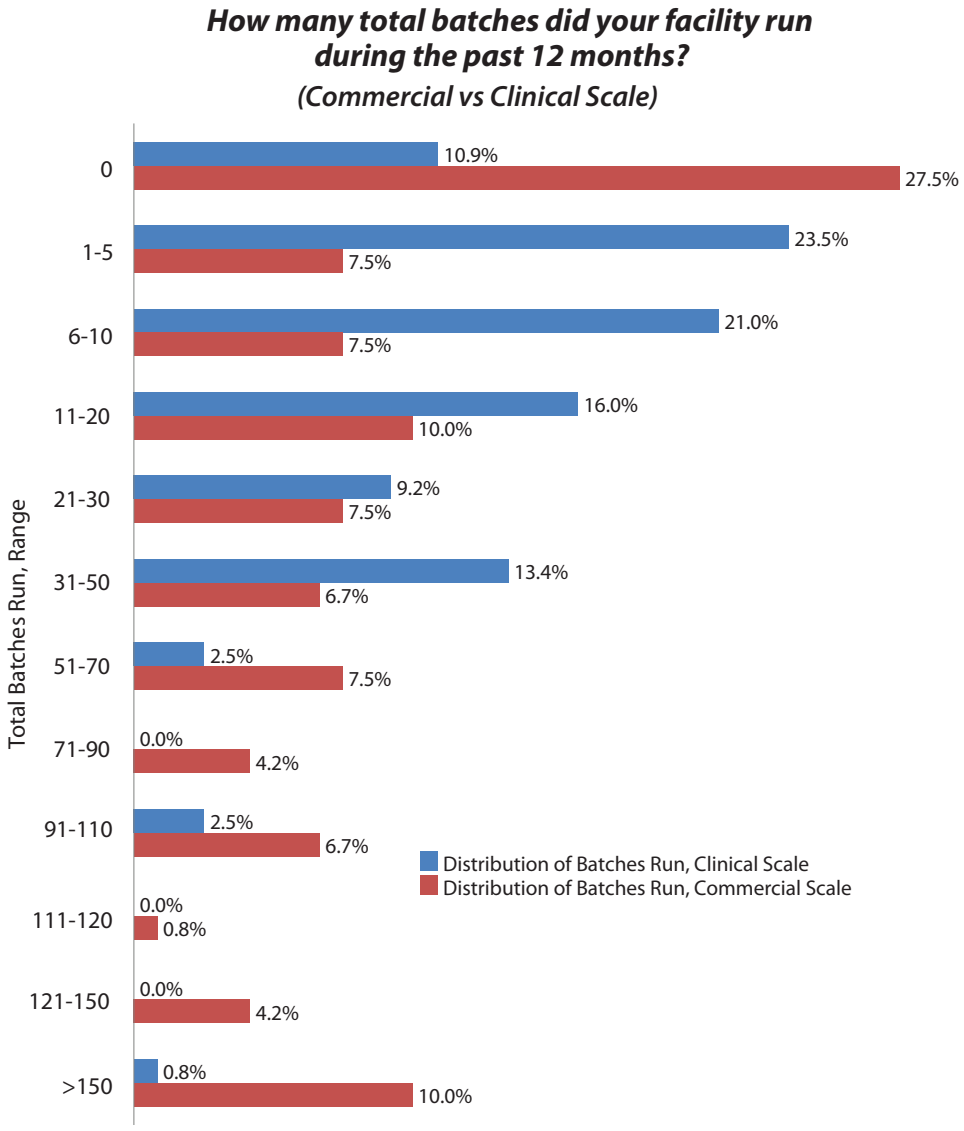
To continue our evaluation of issues such as batch failure rates, and to ensure we are capturing organizations involved in significant manufacturing processes at various scales of manufacture, we asked again this year for the number of batches or production runs the respondent's facility (not the organization) ran over the past 12 months.

We found that for *'Clinical Scale'* manufacturing, the largest number of facilities reported producing between 1 and 20 batches per year (71.4%), a continual increase from 63.5% last year and 60.9% in 2014. At the *'Commercial Scale',* only 10% reported producing over 150 batches per year, down from 14.9% last year; most (among those manufacturing) reported running between 0-70 batches per year (74.2%), up from 71.5% last year.

To compare consistency of respondents' operations, year-by-year, we evaluated the number of batches run/year. This year (asking about 2015), we found between "0-10" batches were run by 55.4% (Clinical Scale) and 42.5% (Commercial Scale) of respondents. So, fewer than half of respondents are operating at with no, or a low number of production runs for Clinical manufacturing, while 35% are at facilities doing ≥100 commercial runs/year.

Looking at prior years' studies, we have found that companies are running more batches this year. While Commercial Scale "0-10" batches remained consistent with 2009 levels (42.5%), Clinical Scale "0-10" batches have sharply increased to 55.4%, up from 40.5% last year. This increase in clinical manufacturing runs suggests an increase in preclinical studies and candidate products entering development.

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 economic activities, despite not all that long ago having recovered 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 1,400 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 or more years ago and also reflects a basic shift in the pharmaceutical industry from small molecule drugs to biopharmaceuticals for new, innovative and profitable products. The large number of biosimilars and biobetters in development indicate the maturation of the biopharmaceutical industry, as its current major products start to go off-patent.

However, as companies of all sizes, particularly Big Pharma-type companies that now do most biopharmaceutical R&D, continue to cut back on expenses as much as possible and consolidate R&D, some may be concentrating more on fewer products, so this may tend to shrink the pipeline somewhat. But in terms of biopharmaceuticals, any such decrease in overall large pharmaceutical company R&D is likely currently being 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 in early-stage clinical trials. Thus, a somewhat shrinking clinical pipeline could indicate better selection of products for development with a higher percentage ultimately being successful. 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 and increased productivity and profits, 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 active in developing biosimilars. These sources, along with

smaller biopharmaceutical developers, which have been the traditional original source for most innovative biopharmaceuticals, before licensing by larger companies, are continuing to expand the global biologics pipeline. Biosimilars are bringing in many new biopharmaceutical players. And new entrants based in China, India and other developing countries are also increasingly entering biopharmaceutical R&D. Thus, an increasing number and percentage of new pharmaceuticals entering the market will be biopharmaceuticals vs. small molecule drugs; and these will likely originate from more diverse sources. 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 and growth in international markets, the industry must also be capable of handling a large number of pipeline products. Most recent large capacity expansions generally have 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. However, recently there has been significant increase in new single-use commercial-scale manufacturing facilities under construction and coming online. This now includes modular facilities. The strategic importance of biopharmaceutical manufacturing and manufacturing capacity are increasing, and understanding the markets for biopharmaceuticals and bioprocessing technologies and services is becoming ever more important to those in the industry.

Planning and decision-making concerning the manufacture of biopharmaceuticals are becoming more complex as companies continue to implement cost-saving efforts, often 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 and stainless steel 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 more likely 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 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 commercial manufacture?

Effective planning within the biopharmaceutical and bioprocessing markets is required to avoid problems later on. This demands a high level of leadership, partnership, information sharing and communication between manufacturers, CMOs and bioprocessing technology and equipment suppliers as they develop new manufacturing technologies, devices and capacity to keep pace with industry needs. Strategic production decisions must be based on solid bioprocessing and sales projection data, combined with a broad understanding of trends 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 the external trends and issues affecting biopharmaceutical manufacture decision-making.

1-2 SOME BIOPHARMACEUTICAL MARKET TRENDS

The biopharmaceutical industry survived the relatively recent worldwide economic downturn. In fact, the industry has done rather well for itself during what for most other industries was a recovery period – not contracting or losing much at all in recent years – and has been showing consistent clear signs of full recovery and renewed growth. In fact, the biopharmaceutical industry continues to remain dynamic and growing. This year, as in 2015 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. 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 arbitrary 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 over $200 billion; growing at a healthy rate. New products and new markets, particularly internationally, continue to support market growth. The world market for recombinant protein therapeutics is now ≥$150 billion, with non-recombinant vaccines and blood/plasma products comprising the remainder. 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 commercial success, including capturing market share, with this often simpler or more straightforward with innovative biopharmaceuticals. Also, biopharmaceuticals vs. drugs tend to be developed for diseases and indications generally lacking current good options for treatment, assuring them of eager markets upon launch. A large portion of biopharmaceuticals coming to market still involve treatment of ignored or currently untreatable indications, making them particularly welcome and 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, 2016, like 2015, is fully expected to be a good year for the biotechnology and biopharmaceutical industries, with these remaining viable, relatively insulated from the worst of any major economic problems, growing and well-positioned for solid future growth.

Cost-containment and Controls: The past year was noisier than recent prior years in the U.S. in terms of protests over exceedingly high pharmaceutical prices. Most attention was directed not to biopharmaceutical products, rather to a few expensive hepatitis C drugs and marketed drug products where prices were drastically increased. The arrival of biosimilars in the U.S. and other major markets may take some pressure off of calls for increased government cost-containment and price controls in the U.S. and other major markets. In the U.S. and many other markets worldwide, drugs for chronic hepatitis C that are actually curative but set records for related costs are resulting in increased attention to pharmaceutical pricing practices. 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 increasingly effectively take control of prescriptions 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 other outright copies of innovator products that are simply marketed as substitutable for the innovator product (without much, if any, real testing, and without real GMP-quality manufacturing). Developed country-based companies seeking to expand in internationals 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. This can be seen in countries such as Brazil, and Cuba has long domestically manufactured diverse biopharmaceuticals for itself and international commerce.

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 geographically-spread 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% 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 for government programs, such as Medicare for older patients, the major U.S. health care overhaul legislation ("Obamacare') enacted in late 2010 is having minimal, apparently no, negative impact on biopharmaceutical usage. If anything, this health care overhaul actually provides continued long-term support for use of innovative (bio)pharmaceuticals, particularly if the alternatives are no treatment (none being available) are involve use of less effective therapeutics. 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. Along these lines, 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 each 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, which may result in lower consumer prices. 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 likely now over $200 billion/year. This continues to grow worldwide at ≤15%/year, making biopharmaceuticals a fairly recession-proof, growing and profitable industry. The market for recombinant proteins now is about $150 billion. Much of this growth in biopharmaceutical revenue is due to an increasing number and sales of recombinant monoclonal antibodies, now a >$50 billion 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 by now familiar 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, while new biosimilars may reduce overall prices slightly, but these lower price may well result in higher sales.

But despite the industry being healthy and growing, broader economic issues, the broader pharmaceutical industry's long-term problems with innovation and profits, investors now coming to expect constant cut-backs, layoffs, increased outsourcing, etc. 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 new smaller companies, although reported to have increased in 2015, will tend to remain restricted in 2016. 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 often 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 are the only viable options. These approaches reduce up-front capital and financing needs, because companies can avoid $50-$150 million or more 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.

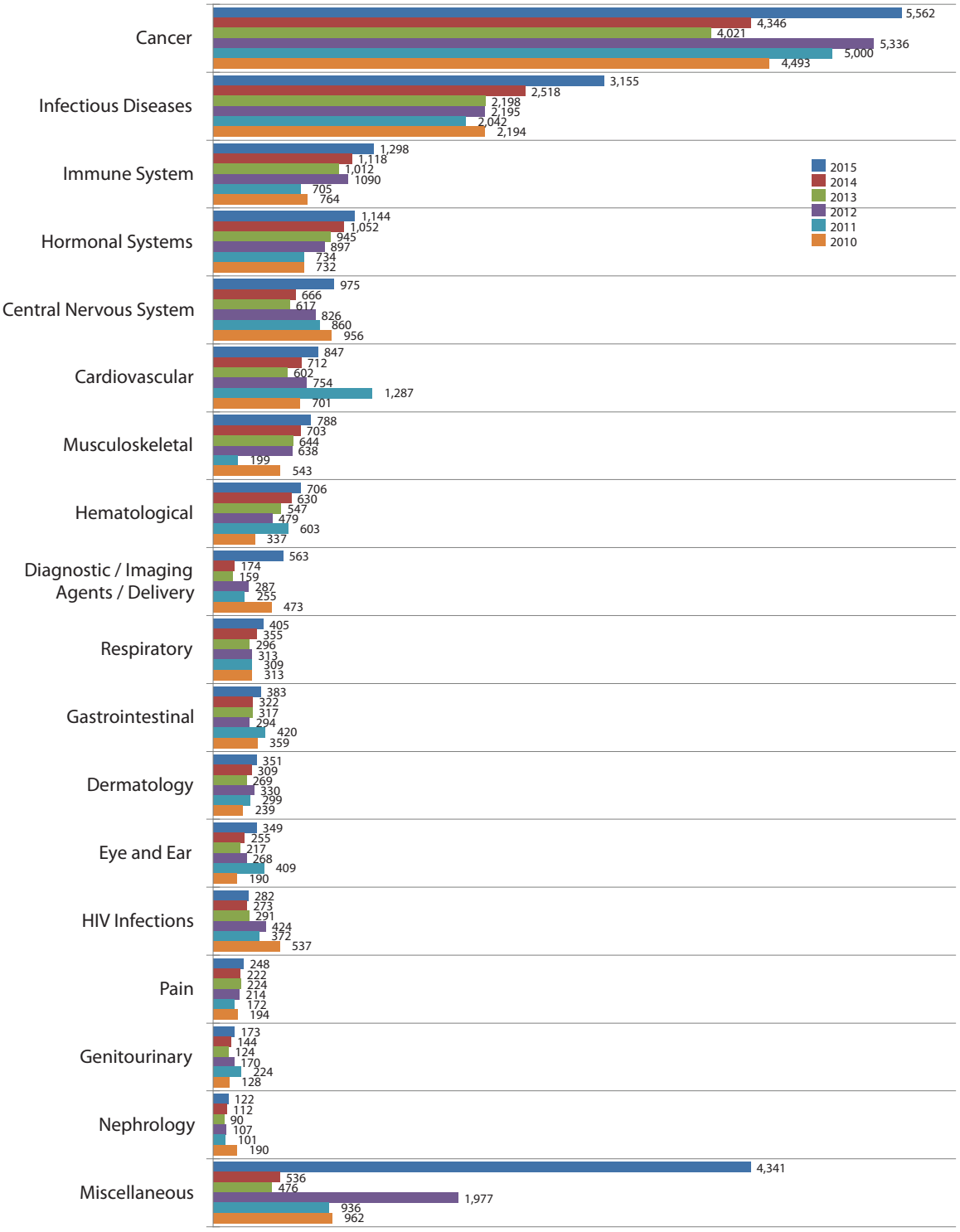
Despite the biopharma industry's bright future, successful companies in this complex worldwide industry will continue to require complete and accurate knowledge of the market and competing technologies, along with adequate lead-times, large capital expenditures, and careful planning. Biopharmaceutical development and manufacture are very costly, the industry is very competitive, investors increasingly demand higher stock prices and profits, and weak companies and products tend to die, so 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 2015 and early 2016. 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

Figure 1.1 shows survey respondent responses concerning the indications of the biopharmaceutical products their companies are working on. Cancer and infectious diseases continue to dominate the biopharmaceutical development pipeline. Trials have increased with most indications. Cancer treatment remains by far the most active area, with over 4,000 products now in development.

Fig 1.1: Investigational Drugs: Large Molecule (Protein Therapeutics), Worldwide, 2010 - 2015



Source: BioPharm Insight, www.infinata.com/biopharma-solution/by-product/biopharm-insight.html, February 2015

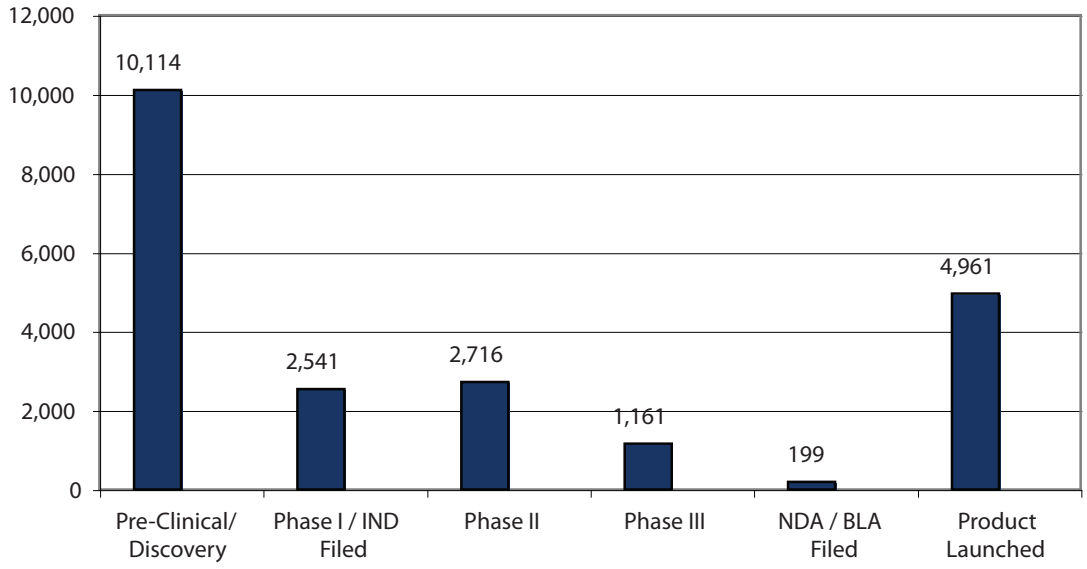
Note: Biopharm Insight includes multiple counts for the same therapeutic, when in multiple phases and locations of clinical trials. Therefore, the total counts will be higher than the actual number of drugs and relevant trials.

A trend in recent years has been a major increase in the number and percentage of monoclonal antibodies in clinical trials. This can be expected to further increase, as the key 'Cabilly' patents broadly covering most conventional recombinant monoclonal antibody manufacture, held by Genentech/Roche, expire in the U.S. in 2018; as blockbuster and other monoclonal antibody-related patents expire and; related to this, as a large number of biosimilar antibodies enter the market. An increasing portion of cancer therapeutics involve recombinant monoclonal antibodies or antibody fragments, further indicating that the number and percentage of marketed monoclonal antibodies will increase in coming years. And we may finally see antibody fragments and other microbially-manufactured antibody-like agents start to substantially supplement or even displace traditional mammalian antibody manufacture.

Figure 1.2 shows the breakout of the cumulative pipeline for large molecule biologics in various stages of development and launched (on the market). Typically, less than 10% of the total numbers of products that enter clinical development actually make it to the marketplace.

Fig 1.2: Worldwide Pipeline & Launched Products, Large Molecules, January 2015

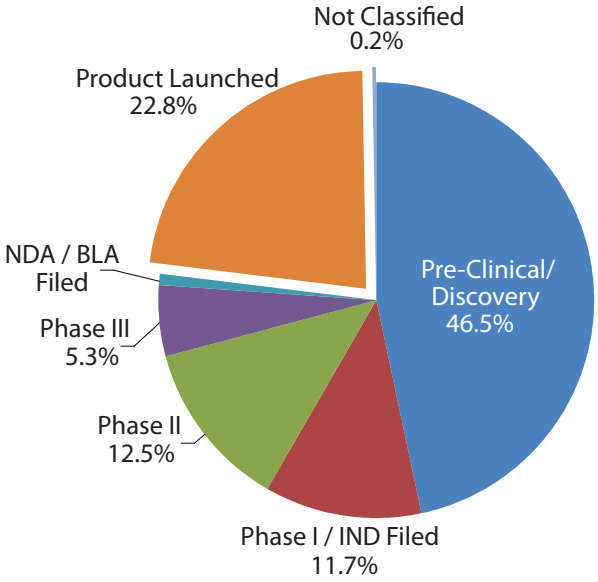
(Note: Cumulative Worldwide Pipeline, Large Molecules, Having Attained Various Stages of Development)



Source: BioPharm Insight, www.infinata.com/biopharma-solution/by-product/biopharm-insight.html January 2015

BioPharm Insight

Fig 1.3: Current Worldwide Pipeline & Launched Products, Large Molecules, January 2015



Source: BioPharm Insight, www.infinata.com/biopharma-solution/by-product/biopharm-insight.html, January 2015

BioPharm Insight

1-5 BIOSIMILARS IN THE PIPELINE

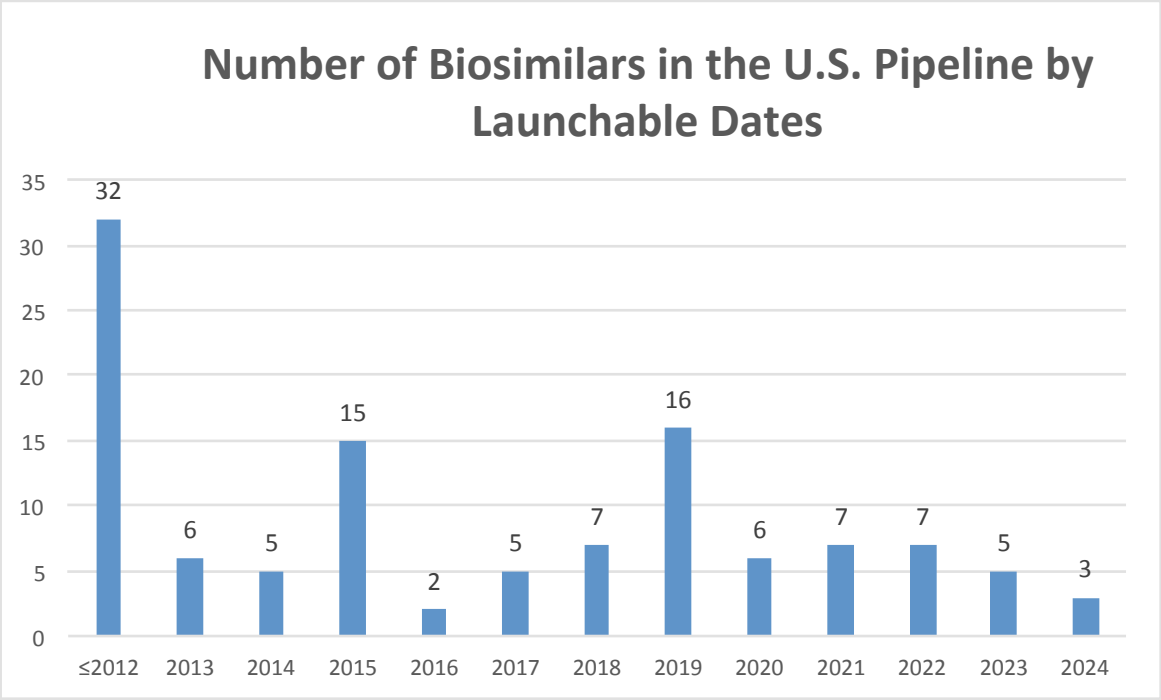
There is a very healthy pipeline of follow-on (biosimilar and biobetter) products in development targeted for the U.S., EU and other major markets (see www.biosimilarspipeline.com). Biosimilars are further discussed in more detail in another section below. This pipeline includes nearly 800 biosimilars, about ≥600 of these presumed targeted to major markets, and about 500 biobetters in development, a total of about 1,400 follow-on biopharmaceutical products in the development pipeline for over 100 currently-marketed biopharmaceuticals (see www.biosimilarspipeline.com). While biosimilars are finally starting to substantially penetrate the market in the European Union, in the U.S., despite approval of 2 biosimilars, including an antibody, in 2015, FDA is still moving at a glacial pace – only approving its first product about 5 full years after passage of BPCIA legislation enable FDA approval of biosimilars. FDA still has not yet issued many needed guidelines. Basic issues affecting biosimilars future markets, such as product names (nomenclature) and interchangeability, have yet to be resolved, with these among many issues making planning biosimilar development and marketing very difficult. At least the initial guidance and approvals from FDA are reassuring, in the sense that they contain few surprises and are unlikely to disrupt ongoing development activities.

Most biosimilars/biobetters are being manufactured using current vs. the generally decades-old legacy technology and equipment being used for most reference product manufacture. Biosimilars will include products pioneering new expression systems and other bioprocessing technologies. Ultimately, many of these products could well be significantly better in some or many respects, including safety and efficacy, such has having higher purity, than their usually several decades-old legacy reference products. If too different, including two better, this

would negate biosimilar approval (with full approval required). Many biosimilar developers are using CMOs for development and manufacturing services. Major CMOs report recent revenue increases of 15% attributable to biosimilar contracts.

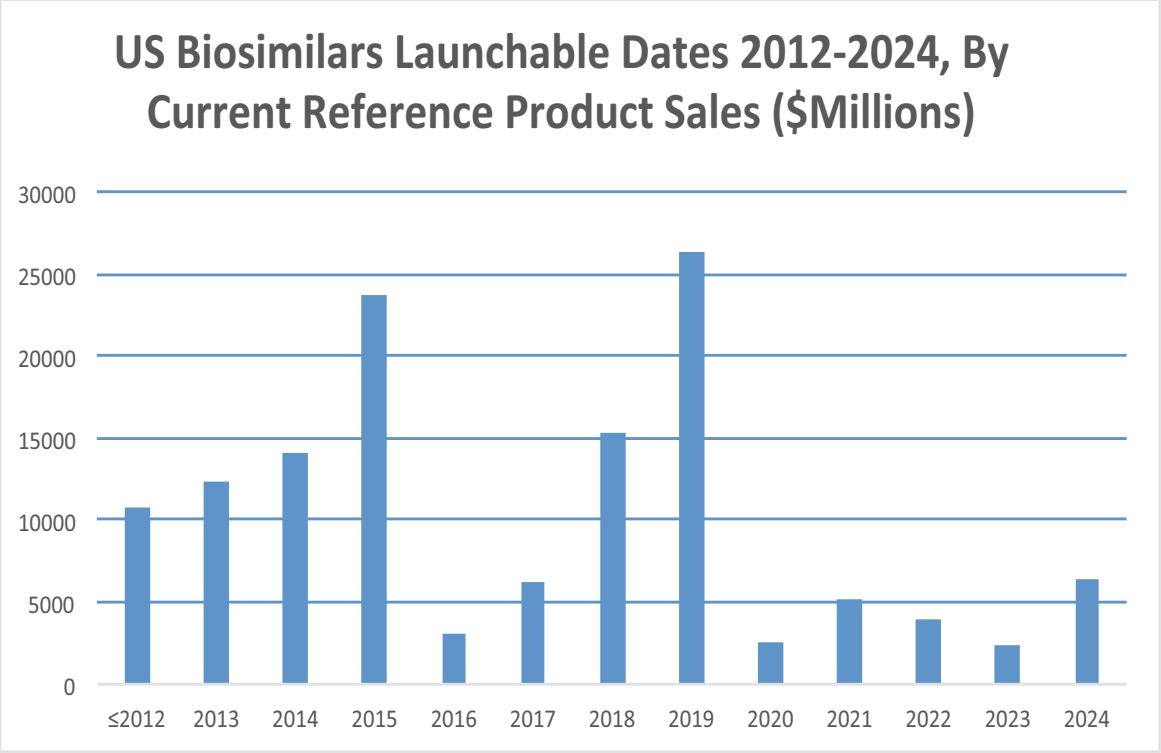
Fig 1.4 below shows the number of U.S.-marketed reference products by the years of their biosimilar versions' launchability in the U.S. Ability to launch requires both relevant patents and regulatory-granted market exclusivities, essentially orphan status and 12-year new exclusivity granted to all new full BLAs, be expired upon product launch. Note, in the U.S., there are large numbers of biosimilars likely to enter the market in the next few years, with another large group, including many blockbuster monoclonal antibodies, likely entering the market late in the decade.

Fig 1.4: Number of Reference Products by U.S. Biosimilars Launchable Dates



The projected economic impact of biosimilars/ biobetters, from a U.S.-centric perspective is portrayed in Fig 1.5. This shows the magnitude of cumulative current reference product sales by the year of likely biosimilars for these products first entering the U.S. market (i.e., expiration of all patent and market exclusivities.) With patents expiring on the majority of currently marketed biopharmaceuticals, including most recombinant proteins and mAbs, these products with current cumulative annual revenue of about $100 billion will encounter much new competition in the U.S. (and other major markets) from biosimilars (and biobetters) starting in just a few years.

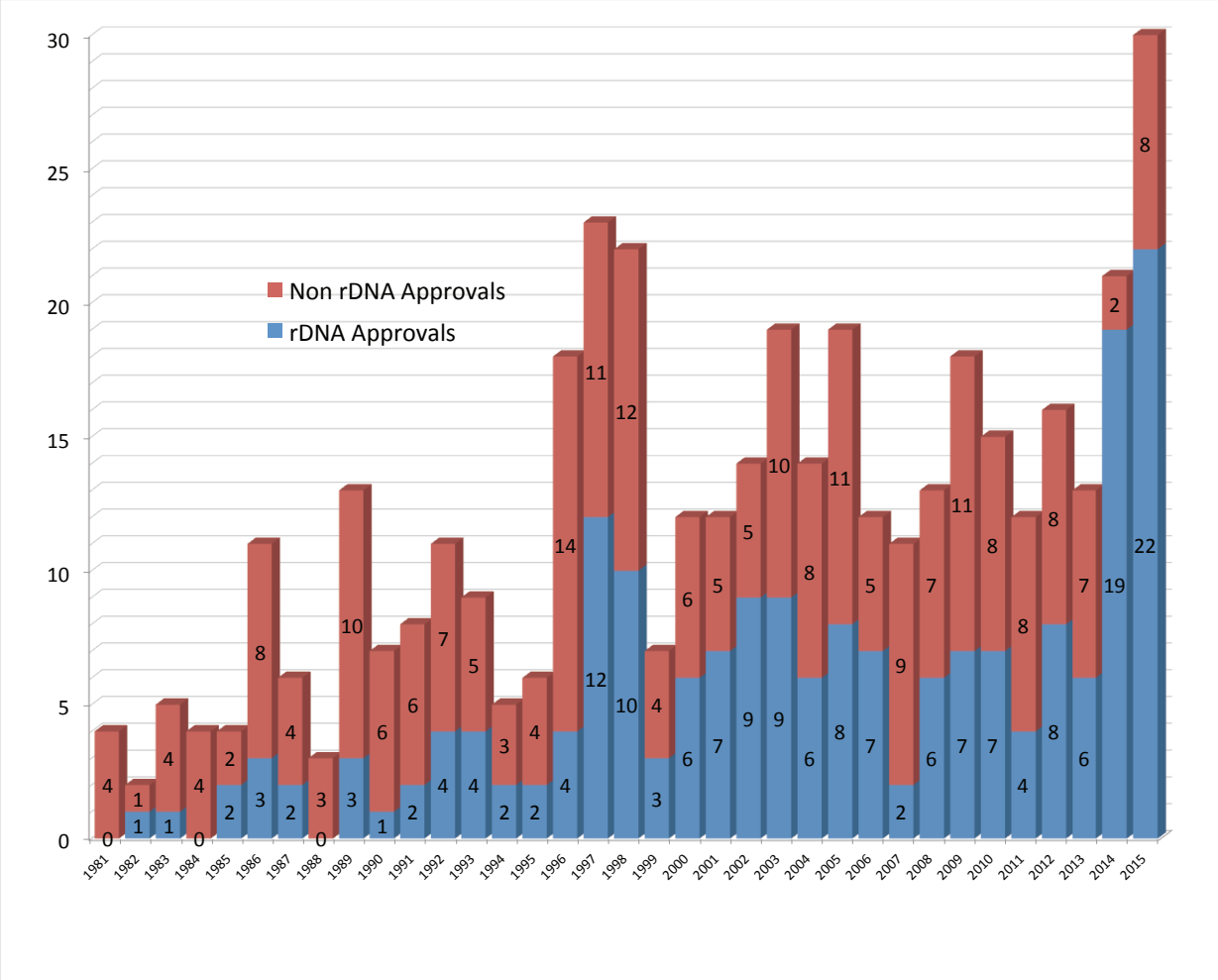
Fig 1.5: Biosimilars Launchable Dates by Sum of Current Reference Products Sales ($millions)



1-6 BIOPHARMACEUTICAL APPROVALS GENERIC

FDA approvals of biopharmaceutical products by year are shown in Figure 1.6.

Fig 1.6: FDA Approvals of New Biopharmaceutical Products 1982-2015



2015 was a record year for FDA biopharmaceutical approvals, including a record number of recombinant protein/mAb approvals. The spike of approvals is, likely, reflecting the increased number and percentage of biopharmaceuticals in the development pipeline. It remains to be seen in coming years whether this is part of trend for increasing FDA biopharmaceutical approvals.

Table 1.1 lists biopharmaceutical products approved (in rev. chron. order) by FDA in 2015.

Table 1.1: Biopharmaceutical Approvals Generic, 2015

insulin glargine rDNA [Basaglar; Abasria; LY2963016]	granted on 12/16/2015 to Boehringer Ingelheim for treatment of diabetes; Note, a 505(b)(2) drug approval, which many would now call a biosimilar
Faxtor X blood-derived [Coagadex; Coagulation Factor X (Human)]	granted on 12/16/2015 to Bio Products Laboratory Ltd. for treatment of for hereditary Factor X deficiency
von Willebrand factor rDNA [Vonvendi]	granted on 12/9/2015 to Baxalta U.S. (formerly Baxter) for treatment of von Willebrand's disease (VWD)
lyosomal acid lipase [Kanuma; sebelipase alfa]	chicken egg-expressed granted on 12/8/2015 to Alexion (from acquisition of Synageva) for treatment of lyosomal acid lipase (LAL) deficiency [2nd product from genetically engineered animals]
Influenza vaccine quadravelent [Fluad; influenza vaccine, inactivated, egg-cultured, quadravelent with MF59/squalene adjuvant]	granted on 12/3/2015 to Novartis (with product and its approval to be transferred to Seqirus, part of CSL Group) for prevention of influenza; first U.S. non-aluminum-based adjuvanted influenza vaccine
SLAMF7 mAb DNA [Empliciti; elotuzumab; Signaling Lymphocyte Activation Molecule Family member 7 monoclonal antibody, recombinant]	granted on 11/30/2015 to Bristol Myers Squibb (BMS; with Abbvie) for use in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received 1-3 prior therapies
EGFr mAb rDNA [Portrazza - necitumumab; epidermal growth factor receptor monoclonal antibody]	granted on 11/24/2015 to Janssen Biotech for treatment of metastatic squamous non-small cell lung cancer(VWD) in combination with gemcitabine and cisplatin
CD38 mAb rDNA [Darzalex - daratumumab]	granted on 11/16/2015 to Eli Lilly for treatment of multiple myeloma
Factor VIII rDNA, pegylated [Adynovate - BAX 111]	granted on 11/11/2015 to Baxalta (formerly Baxter) for treatment of hemophilia A
IL-5 mAb rDNA [Nucala; mepolizumab]	granted on 11/4/2015 to GlaxoSmithKline (GSK) for treatment of asthma
HSV-1/GM-CSF rDNA [Imlygic - alimogene laherparepvec; a live herpes simplex virus type 1 (HSV-1) oncolytic virus resulting in expression of GM-CSF]	granted on 10/27/2015 to Alexion Pharmaceuticals for treatment of unresectable recurrent cutaneous melanoma
alkaline phosphatase rDNA [Strensiq; asfotase alfa; an alkaline phosphatase catalytic domain fusion protein]	granted on 10/23/2015 to Alexion Pharmaceuticals for treatment of perinatal, infantile and juvenile-onset hypophosphatasia (HPP)
dabigatran mAb rDNA [Praxbind - idarucizumab]	granted on 10/16/2015 to Boehringer Ingelheim to reverse the blood-thinning effects of Pradaxa (dabigatran)
insulin degludec rDNA [Tresiba - insulin degludec]	granted on 10/16/2015 to Novo Nordisk for treatment of diabetes mellitus
insulin degludec/aspart rDNA [Ryzodeg 70/30 - a 70/30 mixture of insulin degludec (approved the same day) and insulin aspart]	granted on 10/16/2015 to Novo Nordisk for treatment of diabetes mellitus
Factor VIII [Nuwiq]	granted on 10/16/2015 to Octapharma USA for treatment of hemophilia A

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April 2016
ISBN 978-1934-106-28-0