The 9th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production is the most recent study of biotherapeutic developers and contract manufacturing organizations’ current and projected future capacity and production. The survey includes responses from 302 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations from 29 countries. The survey methodology includes input from an additional 185 direct suppliers of raw materials, services, and equipment to this industry. In addition to current capacity issues, this study covers downstream processing problems, new technologies, expression systems, quality initiatives, human resources and training needs of biopharmaceutical manufacturers, growth rates of suppliers to this industry, and many other areas.
9th Annual
Report and Survey of Biopharmaceutical Manufacturing Capacity and Production

A Study of Biotherapeutic Developers and Contract Manufacturing Organizations

April 2012
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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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Photo Gallery – Bioreactors

There is a growing interest in single use devices typically employed in biopharmaceutical manufacturing. To define these products, we include examples from various manufacturers in the industry throughout this book.

PBS Biotech’s innovative 15 L disposable bioreactor with patented pneumatic mixing technology. 3 L through 80 L, (up to 2500 L late 2011). PBS Biotech offers PVDF single-use bioreactors that are scalable from bench-top through commercial production with very low shear mixing. Photo courtesy of PBS Biotech, Camarillo, CA. wwwpbsbiotech.com

3 liter PBS Biotech bioreactor; desktop entry-level unit ideal for lab solutions across all cell culture applications and processes. Photo courtesy of PBS Biotech, Camarillo, CA. www.pbsbiotech.com
METHODOLOGY

This report is the ninth in our annual evaluations of the state of the biopharmaceutical manufacturing industry. The strength of the 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 302 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations in 29 countries worldwide; plus 186 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 brought in experts from the industry to provide in-depth analysis of the events shaping the past year, and the trends that will shape biopharmaceutical manufacturing in 2012-2017.

In addition, we partnered with global organizations that contributed their time and effort to ensure accurate coverage of the worldwide biopharmaceutical industry. Our industry partners are included in our acknowledgment section. In addition, to ensure our coverage, we include this year our media partners, without whose assistance we would not have been as able to reach the high quality of respondents:

Additional 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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SciLog Single-Use Gravimetric Fluid Handling Platform. SciLog WeighPro is mounted with several accessories. Multiple configurations available. Photo courtesy of SciLog, all rights reserved.
CHAPTER 1: INTRODUCTION AND DISCUSSION

INTRODUCTION

The pharmaceutical and biopharmaceutical industries remain active, profitable and growing segments, despite the slow ongoing recovery 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 41,000 ongoing clinical trials. Among these, an estimated 40% or likely over 4,000-5,000 candidate products in R&D are biopharmaceuticals. This is a considerable increase from as short a five years ago and reflects a basic shift in the pharmaceutical industry from small molecule drugs to biopharmaceuticals for new, innovative and profitable products.

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 pipeline may well be shrinking somewhat. But this may well currently be counter-balanced by established companies increasingly moving into biopharmaceuticals. But even if the pipeline is shrinking (which will only be evident in hindsight), this is not necessarily an indictor of problems. Any current 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 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. 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, but 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 is increasingly being performed using 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 increasingly implement cost-saving efforts, often including cutting back on the number of products in the development pipeline.

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 the development pipeline, and outsourcing many 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 who 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 the 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 OVERVIEW OF MARKET TRENDS

The biopharmaceutical industry has survived recent years’ worldwide economic downturn, has done rather well for itself during this period, with the industry not contracting or losing much at all in recent years and now showing clear signs of clearly being on a path for full recovery and growth. As much of the world economy slowly improves, the biopharmaceutical industry continues to remain dynamic and growing. This year’s survey results show that companies are spending and investing more in their R&D and bioprocessing capacity, staff and other infrastructure, although often more selectively. 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 are decreasing, but this may simply reflect reaching the limits of eliminating in-house expertise and facilities. Some specific trends are discussed below.

• **Industry Remains Healthy and Its Status is Improving**: The world market for biopharmaceuticals is now about >$145 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 has crossed the $100 billion/year landmark. The continued high growth rate in biopharmaceutical markets will continue to drive investment in the industry, including at the expense of traditional small molecule drug developers. Biopharmaceuticals have simply proven themselves to be profitable investments, e.g., with much higher profits per sale; and attaining success, including capturing market share, is 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.

• **Industry Spending/Investment is Up**: Survey results indicate that companies are investing more in biopharmaceutical R&D, including hiring staff and expanding manufacturing capacity. Increased spending is occurring in:
  - New technology
  - Capital equipment
  - Process development and optimization.
  - Personnel training and development

The prior overall trend of lay-offs of bioprocessing and other biopharmaceutical professionals has stopped, and budgets for hiring and staff are now up, particularly for those with high-level expertise, among the first to go in prior waves of lay-offs. Equipment and system developers and vendors’ are also investing more in product development and new and better technology, including automation, control, information and quality systems, in addition to bioprocessing systems and facilities.

• **Outsourcing Trend Remains But is Slowing**: Outsourcing, including contract manufacture, continues as a major trend. However, recent survey data indicate the rate of outsourcing is slowing. Industry is likely simply running out of tasks susceptible to outsourcing that haven’t already been outsourced, i.e., outsourcing is starting to approach its inherent limits. Looking toward the future, it appears that contract manufacturing will not be the primary manufacturing approach in the future, as it would be if prior high growth in outsourcing continued to grow. But particularly as biosimilars and biobetters enter the major U.S. market, many of these developers,
perhaps about half, can be expected to use CMOs for manufacture. Thus, the number of marketed products manufactured by CMOs will likely grow in coming years. With this the number of CMOs with commercial manufacturing experience, currently relatively few, will expand.

- **Outsourcing is Becoming More Strategic:** Companies, including large companies that formerly eliminated in-house capabilities and outsourced everything feasible (and often more), are now taking a much more rational and sophisticated approach – carefully evaluating and weighing their options, including looking at options from a longer-term perspective. Thus, there appears to be a slowing of what often seemed to be arbitrary, often irrational, quarterly balance sheet-directed, downsizing, lay-offs and closing and divestment of in-house corporate capabilities. To the extent that companies have retained or are now rebuilding in-house manufacturing capacity, in some respects the biopharmaceutical industry may be moving towards becoming more production vs. research oriented. Otherwise, companies of all sizes worldwide continue to increase their outsourcing and use of CROs, particularly for screening/discovery and analytical and clinical studies. Recent survey data show 70% of biopharmaceutical companies outsourcing at least some activity. Among 24 areas of outsourcing surveyed, the primary outsourced activities included product characterization testing.

- **Big Mergers and Acquisitions Continue But are Slowing:** These continue at all levels throughout the industry. However, there appears to be a trend for fewer mega-mergers among the largest players, including Big Pharma-type companies. Besides there simply being fewer large international pharmaceutical companies due to decades of merging and purging, much of the industry is starting to realize that such mergers have had little, if any, positive outcome on the merged companies success. The combined development pipelines of merged large companies often appear to be thinner and less productive than either company, considered singly, had before merging. Large companies, many with ailing or failing development pipelines and many current products coming off-patent in coming years, continue, but now to a much lesser extent, to use mergers and acquisitions strategic ploys to distract investors with promises of cost-savings and bigger, better pipelines. Perhaps, the companies are getting smarter and/or investors are becoming tired of repeated cycles of merging and purging resulting in minimal, if any, improvements in companies’ financial health.

- **Mergers, Acquisitions and Partnering are Becoming More Strategic:** Whatever the cause, corporate mergers and acquisitions are becoming more rational, in terms of being directed to improving R&D pipelines rather than providing distractions for stockholders with promises of cost-savings from product line and facility consolidations and lay-offs. Associated with this, many large companies are now directing more attention to acquiring smaller companies and licensing-in candidate products. Partnering and acquisition activity has intensified as large biotech and pharma companies execute strategic initiatives in fill their pipelines with better R&D and products, with most every established biopharmaceutical company facing patent cliffs and increased competition for biosimilars, biobetters and other off-patent follow-on products.

- **New and Small Company Financing is Tight:** Financing available for new startup and smaller non-public companies continues to be tight, despite improving overall financial health and the pharmaceutical industry shifting its emphasis to biopharmaceuticals. Much or even most smaller company financing and expansion is being accomplished through partnerships and collaborations with larger (bio)pharmaceutical companies, many increasingly desperate to fill their failing product development pipelines, with recent prior years’ often excessive outsourcing, off-shoring, lay-offs and mothballing and divestment of facilities surely exacerbating this situation. The stock market is much less receptive to initial public offerings (IPOs) and many venture capital firms have largely abandoned biopharmaceutical investments, seeing much better and quicker returns in information, communications and other high tech fields. But luckily, the large
international pharmaceutical companies have stepped up and are providing increased funding for product-related R&D.

- **China, India and ROW as Biopharmaceutical Manufacturers:** Biopharmaceutical companies in many developing countries serving their domestic, regional or lesser-regulated international markets are experiencing rapid growth. Markets for biopharmaceuticals are growing in many developing countries with increased incomes, a new middle class and improved health care. However, BRIC and other developing countries have yet to pose any threat to U.S. and European dominance of the innovative biopharmaceutical industry, particularly related product development and manufacturing. Foreign-based CMOs and CROS will continue to capture market share, for as long as these companies provide perceived cost-effectiveness advantages. But in terms of commercial U.S./EU-level cGMP manufacturing expertise and infrastructure, companies such as India and China simply lack the needed critical mass of established institutional knowledge, business practices, business culture, trained and experienced staff, facilities, information and quality systems, etc. needed to attain and maintain true this level of quality. Despite the majority of drugs (mostly generics) now being manufactured in China and India, no Asian country yet manufactures biopharmaceutical products marketed in the U.S. or European Union. A few more advanced developing countries, such as South Korea, will be among major biopharmaceutical manufacturers, and will likely attain this goal in coming years. The Korean government is subsidizing domestic companies building of world class large-scale facilities, with biosimilars, particularly, U.S. markets, being targeted. In terms of off-shore (ex-U.S.) destinations for manufacture of biopharmaceuticals, Ireland seems to be the common choice these days for large companies to site biopharmaceutical manufacturing facilities. But with increasing competition among cities, regions and countries for siting of new biopharmaceutical facilities, companies are increasingly using this to bid-up and take advantage of government subsidies, loans and other inducements. With this, many facilities are increasingly being built wherever companies get the best deal.

- **Pipeline Shrinkage?:** Overall, the biopharmaceutical pipeline of products in development appears to no longer be significantly expanding and, if anything, appears to have somewhat contracted. Most companies are now concentrating and devoting their resources to fewer products in development. Whether this concentration on fewer products will result in getting more and more profitable products more rapidly to market remains to be seen. Pipeline shrinkage could also simply be due to streamlined or leaner staff and delayed investments in recent years, with the industry simply not able to support an expanded development pipeline.

- **Single-use/disposable Equipment:** The trend towards adoption of single-use equipment continues, with continued rapid growth in this market projected (2). As confirmed by survey data, single-use equipment, particularly for upstream manufacture (e.g., bioreactors), now thoroughly dominates pre-commercial, i.e., small- to mid-scale R&D and trials supply manufacture, while fixed stainless steel equipment continues to thoroughly dominate commercial-scale manufacturing. Many technological improvements are needed, particularly including single-use bioreactors above 1,000 L and downstream equipment and technologies need many improvements. This included the need to move beyond the current predominant paradigm or approach involving dropping plastic liners into stainless steel bioreactor and other equipment. This is simply not optimal or even suited for many applications. For example, microbial (bacterial, yeast, etc.) manufacturing is typically performed at much higher extremes of mixing/agitation, temperatures, media/nutrient content, etc. compared to mammalian cell culture, but current single-use upstream equipment is simply not robust and physically strong enough to handle this.
Bioprocessing Continues to Improve: The slow but steady increase in expression yields continues, with incremental improvements in host cell lines, cell line engineering, expression systems, vectors, promoters, etc. But other improvements are also coming and nearing industry adoption. This includes large-scale (≥1,000 L) single-use systems being increasingly being adopted for commercial manufacturing, with hardly any biopharmaceuticals yet commercially manufactured using single-use vs. fixed stainless steel upstream equipment. Also, new downstream technologies are approaching adoption for commercial manufacturing, including single-use, highly-flexible simulated moving bed purification systems and new membrane filtration systems. More and better sensors and control equipment are also becoming available, with this remaining an area still needing much improvement. In the next few years, likely pioneered by biosimilars manufacturers, we can expect to see more biopharmaceuticals being approved and their markets supported by commercial manufacture using fully upstream and, perhaps, also downstream single-use bioprocessing systems. Increased mergers and acquisitions among single-use developers and vendors can be expected, as companies prepare to go after the much larger commercial (vs. current precommercial/R&D-supporting) single-use systems markets. This is where incredible growth in single-use systems can be expected in coming years, as these systems start to be used for commercial manufacture. Many future facilities, such as for monoclonal antibody manufacturing, will likely involve multiple trains of single-use bioreactors and other equipment operating in parallel, rather than traditional use of one or a few very large stainless steel-based bioreactors and other equipment.

Biopharmaceutical R&D Outpacing Drug R&D: Much of the industry, particularly the largest pharmaceutical companies, is increasing its investment in biopharmaceutical R&D at the expense of drug (chemical substance-based) R&D. It is widely accepted that 40% or more of pharmaceutical industry R&D funding is now going for biopharmaceutical vs. drug development. This trend is continuing, and within a matter of years, likely 50% or a majority of pharmaceutical R&D could well be devoted to biopharmaceuticals. Despite the advent of biosimilars (discussed below), biopharmaceuticals provide better and more opportunities for longer IP/patent protection than small molecule drugs, along with much higher profits from lower sales volume. Also, many classes of biopharmaceuticals, e.g., monoclonal antibodies, involve inherent high specificity and selectivity in their activity and efficacy, with about their only major downside, after efficacy is shown, being potential immunogenicity, which can increasingly be predicted and avoided. Thus, biopharmaceuticals, in many respects, offer a simpler and more direct path to licensure. Recent studies support this, with biopharmaceuticals vs. drugs having entered Phase I trials having a higher likelihood of eventually attaining regulatory approvals.

Downstream is Becoming Less of a Problem: Although downstream purification remains the most challenging part, in the sense of still struggling to keep up with improved yields and higher output from upstream processing, this year’s survey results indicate that these problems are lessening and that industry is adapting and finding ways to increase downstream productivity. Purification is no longer an increasing or worsening bottleneck for much or most of the industry. However, downstream processing remains much more of a challenge and bottleneck-prone than upstream, where incremental improvements continue to contribute to improved yields and product quality.

Mammalian Manufacturing is Crowding-out Other Platforms: An increasing number of companies, particularly larger ones (including many industry leaders), are now standardizing their in-house bioprocessing to be solely mammalian based, usually selecting a single or few CHO and perhaps other cell line-based manufacturing platforms. The former truism or presumption that microbial manufacture is generally cheaper and simpler than mammalian manufacture (where the product allows) is obviously no longer true. Higher mammalian cell
culture yields and improved technology have made mammalian manufacture more cost-effective and easier. Also, as discussed above, mammalian manufacturing has proven much more adaptable to use of single-use equipment, while microbial manufacturing remains largely unsuited for use of current single-use equipment. Companies clearly prefer the flexibility and cost-savings single-use systems provide, and have little interest in using microbial platforms that continue to require use of fixed stainless steel bioreactors and other equipment. With mammalian single-use equipment now nearly universally used for routine in-house pre-commercial manufacturing and companies naturally preferring to scale-up using the same manufacturing platform, microbial and other non-mammalian platforms are now only being used where required or cost-effective for a specific product. This sideling of microbial manufacturing may change, as more suitable robust and larger scale single-use equipment becomes available and as new product classes more suited for microbial manufacture, such as single-chain and antibody fragments, become more common. But for the near future, mammalian will become even more dominant for both pre- and commercial-scale biopharmaceutical manufacturing.

**Modular Bioprocessing Facilities are Coming:** Multiple bioprocessing equipment and technology developers and vendors are developing modular approaches to bioprocessing. This involves hooking-up of prefabricated bioprocessing modules or suites, with these often integrated and installed within their own portable trailer- or shipping container-based clean rooms. Companies will be able to assemble bioprocessing systems using off-the-shelf or customized modules ready for plug-and-play with other modules (from the same company). GE is among the leaders in developing these technologies, and its acquisition in 2011 of Xcellerex, the prior largest unaffiliated single-use systems manufacturer, will likely only speed this up. Much as we are now talking about single-use systems having become incredibly common, in a short as 5 or 10 years, we may comparably be talking about industry widespread adoption of flexible bioprocessing modules. Construction of new bioprocessing facilities, even for commercial manufacture, could well be completed in days or weeks. This modular approach will likely accelerate worldwide proliferation of commercial manufacturing, including to lesser-developed countries. Many foreign countries can be expected to increasingly demand local product manufacture, particularly once modular facilities become commonplace.

**Biosimilars are Coming, Including Finally to the U.S.:** A recent report shows a very healthy pipeline of biosimilar (and biobetter) products in development targeted for the U.S., EU and other major markets (see [www.biosimilars.com](http://www.biosimilars.com)). This report shows well over 400 biosimilars and over 350 biobetters in development. The biosimilars (and biobetters) development pipeline and the impact of biosimilars on biopharmaceutical developers and manufacturers are discussed below.

**FDA and Industry are Getting Ready for Biosimilars:** Although still moving at its usual slow or glacial pace, in later 2011 FDA finally issued its first installment of biosimilars filings guidance documents, and is reported to finally be starting to meet with prospective biosimilar applicants regarding what needs to be in their applications. However, well over 2 years after passage of enabling legislation, FDA still has not yet accepted its first biosimilar license application. At least the guidance documents are reassuring, in the sense that they contain few surprises and are unlikely to disrupt ongoing development activities. This includes a biosimilar required to have its active agent have the same primary (amino acid) sequence as its reference/comparator product; and beyond that, all types of molecular modifications are allowed, e.g., different glycosylation, appendage/conjugation with other molecules, etc. The main goal that biosimilars must attain is lack of significant differences compared to a currently-approved reference product. This is actually much different than with generic drugs, where the sponsor must prove equivalence or being essentially the same product, for all practical purposes. In many respect, developing
a biosimilar is harder than developing an innovative product involving full approval, since it will likely be harder to closely match many aspects of analytical data and clinical and safety. Many biosimilar developers will likely run into problems with their candidate products, with most biosimilars/biobetters being manufactured using current vs. decades-old technology and equipment. Ultimately, many of these product could well be significantly better in some or many respects, including safety and efficacy, than their usually several decades-old legacy reference product, with this negating biosimilar approval.

Cost-containment and Controls:
2011 was a rather quiet year in the U.S. in terms of new calls for and implementation of cost-containment measures or cost controls for pharmaceuticals, including biopharmaceuticals. With an election coming up, these issues did not progress far in Congress, and the Centers for Medicare & Medicaid Services (CMS) didn’t issue any studies on the topic, which would have been highly controversial whatever they may have concluded. But in 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) consider the most appropriate. As biosimilars become available, much as with generic drugs, insurers will surely be forcing physicians, pharmacists and consumers to use these rather than more expensive innovator products. But the situation in the U.S. could change radically, if the Supreme Court throws out the large omnibus health care reform bill passed several years ago by Congress, with previously unthinkable cost-control and other options potentially being considered. And if this entire legislation is negated, this includes key biosimilar approvals-enabling legislation; and the years of intense debate over biosimilars, data exclusivity and related topics could well start all over again.

Internationalization of Biopharmaceuticals:
Perhaps, indicative of a trend, FDA granted the first approval in 2011 for a biopharmaceutical (biologic) manufactured in Latin America - Anascorp, the first approved therapeutic for scorpion stings, from a Mexican company. With the U.S., by far, the largest and most receptive market for biopharmaceuticals, we can expect many other companies in lesser-developed countries to launch their products in the U.S., EU and other major markets. Many of these companies will likely enter the U.S. and other major biopharmaceutical markets through development of biosimilars and biobetters, with the primary challenges here involving manufacturing and gaining market share against considerable competition. For many biosimilar/biobetter developers, actually capturing significant market share in the U.S., EU and other major markets will likely not be a serious goal. Rather, many foreign companies look upon U.S. product approval, even if only a biosimilar, as validation of that company and its product, facilitating wider sales and at higher prices in lesser-regulated markets worldwide. Similarly, many foreign companies will view U.S. biosimilar/biobetter approval as validating their company, its management, facilities and bioprocessing capabilities, e.g., with the cost of obtain U.S. biosimilar approval probably recovered many times over in increased stock value after product approval.
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 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 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.

Conclusions: Overall, 2012, like 2011, will 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.
1-3 MARKET POTENTIAL

The biopharmaceutical market will continue to expand. There are currently many 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 sales (cost more) and profits per sale, and with their often requiring more complex detailing and other sales support, increasingly fit well with the resources and marketing-oriented 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 US Medicare for older patients, the major US 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, with expensive biopharmaceuticals being an easy target for elimination or reduction.

However, since most biopharmaceuticals are used for indications for which there are few alternatives, the overall market is rather protected from widespread cost-containment and controls. Those countries that have imposed cost controls, so far, are 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 $145 billion/year. This continues to grow worldwide at about 15%-18%/year, making biopharmaceuticals a fairly recession-proof, growing and profitable industry. The market for recombinant proteins now exceeds $100 billion, having attained this milestone in 2011. Much of this growth in biopharmaceutical revenue is due to an increasing number and sales of recombinant monoclonal antibodies, now a $45 billion market or about 45% of the recombinant protein and 31% 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.
Biosimilars will increase in number and importance. Currently, the markets for approved biosimilars in Europe remains small, only about $300 million for a dozen products, generally no more than 10% of the market for the established reference product. The uptake and market penetration of biosimilars will slowly increase in 2012 and beyond in Europe, as European Union member and other countries slowly implement their own cost-controls and recommendations for biosimilars use, and as these countries’ health care systems adopt these products. However, unlike Europe, uptake and market penetration by biosimilars in the U.S. will likely be more rapid, upon approval, with private sector insurers expected to rapidly adopt and require use of biosimilars wherever possible. It is reasonable to expect that biosimilars will have a worldwide market of several billion dollars over the next 3-5 years.

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 2012. 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 is 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 are 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.

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 manufacturing 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 2011 and early 2012. Its intent is to provide a quantitative 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 Pipeline

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 5,300 products having entered development (up from about 5,000 last year and 4,500 in 2009). [Note, these data represent the cumulative (over time) biologics pipeline, not the currently active pipeline, and is useful to show the industry’s concentration on specific indications]

Fig 1.1: Investigational Drugs: Large Molecule (Protein Therapeutics), Worldwide, January 2012 vs March 2010

## Table 1.1: Biologics (Large Molecule), Worldwide, through January 2012

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Investigational Drugs, 2012</th>
<th>NDA / BLA Filed</th>
<th>Phase III</th>
<th>Phase II</th>
<th>Phase I / IND Filed</th>
<th>Pre-Clinical / Discovery</th>
<th>Number of Product Launched</th>
<th>Status Unclear</th>
<th>Investigational Drugs, 2011</th>
<th>Investigational Drugs, 2010</th>
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<td>Cancer</td>
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<td>71</td>
<td>543</td>
<td>1,513</td>
<td>1,125</td>
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<td>293</td>
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<td>Infectious Diseases</td>
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<td>45</td>
<td>115</td>
<td>305</td>
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<td>979</td>
<td>373</td>
<td>51</td>
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<td>1194</td>
<td>96</td>
<td>455</td>
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<td>Immune System</td>
<td>1090</td>
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<td>Hormonal Systems</td>
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<td>246</td>
<td>225</td>
<td>25</td>
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<td>701</td>
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<td>Central Nervous System</td>
<td>826</td>
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<td>59</td>
<td>114</td>
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<td>410</td>
<td>90</td>
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<td>Cardiovascular</td>
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<td>14</td>
<td>89</td>
<td>164</td>
<td>109</td>
<td>248</td>
<td>103</td>
<td>27</td>
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<td>962</td>
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<td>Musculoskeletal</td>
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<td>142</td>
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<td>HIV Infections</td>
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<td>18</td>
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<td>Dermatology</td>
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<td>76</td>
<td>9</td>
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<tr>
<td>Respiratory</td>
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<td>83</td>
<td>59</td>
<td>95</td>
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<td>Gastrointestinal</td>
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<td>100</td>
<td>40</td>
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<td>Diagnostic / Imaging Agents / Delivery</td>
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<td>15</td>
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<td>Eye and Ear</td>
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<td>27</td>
<td>44</td>
<td>46</td>
<td>112</td>
<td>23</td>
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<td>59</td>
<td>37</td>
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<td>172</td>
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<tr>
<td>Genitourinary</td>
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<td>8</td>
<td>31</td>
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<td>15</td>
<td>31</td>
<td>61</td>
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<tr>
<td>Nephrology</td>
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<td>9</td>
<td>29</td>
<td>19</td>
<td>28</td>
<td>19</td>
<td>0</td>
<td>101</td>
<td>190</td>
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<td>Total</td>
<td>16,599</td>
<td>345</td>
<td>1,269</td>
<td>3,157</td>
<td>2,725</td>
<td>6,339</td>
<td>1,890</td>
<td>874</td>
<td>14,927</td>
<td>14,305</td>
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</table>

Source: BioPharm Insights, www.biopharmainsights.com

Note: A number of products had unclear status but are included in the product totals.
A major difference in recent years is 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 conventional recombinant monoclonal antibody manufacture, held by Genentech/Roche, expire in the U.S. later this decade, and as other monoclonal antibody-related patents similarly expire. A large and growing portion of cancer and, to a somewhat lesser extent, infectious disease therapeutics involve recombinant monoclonal antibodies or antibody fragments, further indicating that the number and percentage of marketed monoclonal antibodies will increase in coming years.

Figure 1.2 shows the breakout of the cumulative pipeline for large molecule biologics in the various stages of development and launched (on the market). Typically, only about 10% of the total number of products in early development actually make it to the marketplace.

Fig 1.2: Current Worldwide Pipeline & Launched Products, Large Molecules, January 2012
(Note: Cumulative Worldwide Pipeline, Large Molecules, Having Attained Various Stages of Development)

### Fig 1.3: Cumulative Worldwide Pipeline & Launched Products, Large Molecules, January 2012

![Cumulative Worldwide Pipeline & Launched Products, Large Molecules, January 2012](image)


### Table 1.2 Worldwide Pipeline, Large Molecules, 2012

<table>
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<tr>
<th></th>
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<tr>
<td>Pre-Clinical/Discovery</td>
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<td>49.3%</td>
<td>5,779</td>
<td>39.7%</td>
<td>7,052</td>
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<td>560</td>
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<td>-18.05%</td>
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<td>Phase I / IND Filed</td>
<td>2,725</td>
<td>17.3%</td>
<td>2,608</td>
<td>17.9%</td>
<td>2,156</td>
<td>15.2%</td>
<td>117</td>
<td>4.49%</td>
<td>452</td>
<td>20.96%</td>
<td>1,821</td>
<td>14.8%</td>
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<tr>
<td>Phase II</td>
<td>3,157</td>
<td>20.1%</td>
<td>3,008</td>
<td>20.7%</td>
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<td>16.9%</td>
<td>149</td>
<td>4.95%</td>
<td>607</td>
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<tr>
<td>Phase III</td>
<td>1,269</td>
<td>8.1%</td>
<td>1,155</td>
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<td>114</td>
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<td>10.63%</td>
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<td>NDA / BLA Filed</td>
<td>345</td>
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<td>308</td>
<td>2.1%</td>
<td>249</td>
<td>1.8%</td>
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<td>59</td>
<td>23.69%</td>
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<td>1.9%</td>
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<tr>
<td>Product Launched</td>
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<td>11.7%</td>
<td>1,287</td>
<td>9.1%</td>
<td>186</td>
<td>10.92%</td>
<td>417</td>
<td>32.40%</td>
<td>1,034</td>
<td>8.4%</td>
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**Source:** BioPharm Insights, www.biopharmainsights.com, January 2012

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1-5 U.S. AND WORLD BIOPHARMACEUTICAL AND RECOMBINANT PROTEIN/MAB MARKETS

There is increasing consensus among analysts in terms of estimating the worldwide market for biopharmaceutical products. Wide disparities reported in the past have generally been related to how analysts defined biopharmaceuticals, with some variably excluding products such as vaccines, blood/plasma, cultured cell/tissue and other non-recombinant products. And many sources simply use FDA's most prominently-reported approval data, which commonly includes only those biologics that happen to be reviewed by the FDA's drug (CDER, which maintains this portion of the the FDA Web site) and excludes those biologics reviewed by its biologics division (CBER).

This year, we assess the worldwide biopharmaceutical drug market at $145 billion, including ≥$100 billion for recombinant proteins and antibodies.(1;  Rader, R.A., BIOPHARMA: Biopharmaceutical Products in the U.S. and European Markets, BioPlan Associates, online database at www.bioplanassociates.com/es/). The biopharmaceutical market constitutes about 15% of the world's total pharmaceutical market, which is now approaching $1 trillion revenue/year. The growth in the biopharmaceutical markets is about twice that experienced by non-biopharmaceutical products. Biopharmaceutical markets will continue to grow relatively rapidly as a result of new product approvals, expansion of indications and markets for current products, as lesser-developed countries become increasingly affluent, and as the population ages in the U.S. and other major pharmaceutical markets. Aging populations need treatment for various chronic and acute conditions, including cancer and arthritis, with these diseases increasingly being treated using biopharmaceuticals.

As discussed below, biosimilars (and biobetters) will result in many more products and companies entering the market, but the markets (total revenue) for reference products and their biosimilar/biobetter competition will decrease, and biosimilars/biobetters will each only attain much smaller markets compared to their reference products. Thus, biosimilars/biobetters will fracture the markets for successful biopharmaceuticals coming off-patent.

As of April 2012, there were over 435 biopharmaceutical products approved in either the U.S and/or European markets, including 166 recombinant proteins and 43 monoclonal antibodies. There were 283 biopharmaceuticals currently approved in both the U.S. and Europe, including 117 recombinant proteins and 33 monoclonal antibodies. There are at least 50 products with FDA applications either pending or expected within coming months.

The U.S. continues to be the leader in biopharmaceutical development and manufacture. It accounts for about half of worldwide biopharmaceutical sales (revenue). Thus, U.S biopharmaceutical sales can be assumed to be in the range of $70-$75 billion annually. Biopharmaceuticals can be expected to have a somewhat lesser market penetration in other countries, even including Western Europe and other major pharmaceutical markets. The U.S. continues to be the source for invention, development and manufacture of biopharmaceutical products. Associated with this, the U.S. economy and health care system, more than any other major pharmaceutical market, continue to support adoption of new biopharmaceuticals. In the U.S. there continues to be a distinct preference or bias in favor of new, innovative products, as long as they provide clinical improvements relative to existing products. The same cannot be said for other major market countries, where cost-conscious centralized government control of pharmaceutical markets, e.g., U.K., can lead to refusal to adopt certain therapeutics. While the U.S. and other major biopharmaceutical markets tend to grow
by rapid adoption of new products and new indications for existing products, growth in most of the rest of the world tends to be driven more by overall economic improvement, including the development of a middle class, and other broad economic and social trends supporting improved health care in these countries.

The major class of biopharmaceuticals with the greatest growth in market revenue continues to be recombinant monoclonal antibodies. Worldwide monoclonal antibody (mAb) revenue in 2011 was about $45 billion, up from about $40 billion in 2010 and $36 billion in 2009. Monoclonal antibodies are increasingly perceived as a relatively secure investment, with antibodies being very targeted/specific, relatively non-toxic, and an increasing number of antibody design and genetic engineering/expression system platforms becoming available. These products tend to be well established in the marketplace, having proven to be viable therapeutics candidates since the mid-1990s. A disproportionate high number of mAb products are blockbusters (>1 billion revenue/year), with many of these used for cancer treatment. Despite mAbs becoming a mature class of products and technologies, recombinant antibody treatment remains generally rather expensive, with some products costing over $100,000 per year or course of treatment. Much of this high cost is related to the high amounts of protein required for antibody-based treatment, e.g., 100 mg vs. micrograms, with repeated, frequent, e.g., weekly, doses required.

Recombinant mAbs place very high demands on bioprocessing, with large amounts of antibodies needed due to their relatively low potency and short half-life. Patients often need grams of a protein for each course of treatment. Thus, the >40 recombinant mAbs on the market account for >90% of the world’s mammalian cell culture capacity, with major mAb products often requiring multiples of 10s of 1,000s of liters of bioreactor capacity. Production increasingly involves multiple sites serving different worldwide markets. For example, manufacture of the blockbuster (≥$1 billion/year in sales) biopharmaceuticals (see Table XXX, below) each typically requires the use of multiple dedicated 10,000 L stainless steel bioreactor-based systems, often at multiple sites. In contrast, most recombinant protein therapeutics can have their annual world supply produced by much smaller bioprocessing systems, such as operation of one or more 1,000 L or smaller bioreactor-based systems. Today, 500 liters is often cited as the most optimal or cost-effective bioreactor size for commercial-scale manufacture using single-use/disposable equipment. But single-use equipment has not yet been adopted for commercial product manufacture. Fixed stainless steel equipment continues to dominate commercial manufacture.

No mainstream biopharmaceutical product is yet manufactured using a fully single-use/disposable upstream bioprocessing system. However, this will likely change over the next few years as products that are currently in development are manufactured using single-use systems. To get there, FDA and regulatory agencies in other developed countries will need to be shown that single use devices are at least as safe as products manufactured in stainless systems. Once this happens, much of the industry can be expected to further accelerate its adoption of single-use systems for commercial manufacture.
1-6 BIOPHARMACEUTICAL APPROVALS TRENDS

New biopharmaceuticals continue to enter the market, although the rate in the U.S. has slowed, presumably reflecting R&D cutbacks in prior years, with biopharmaceuticals typically taking about a decade to reach the market. As shown in Fig XXXX [below], there is a recent trend towards fewer FDA biopharmaceutical approvals. FDA approved 12 biopharmaceuticals in 2012. However, only 4 of the 12 (33%) approvals were for recombinant proteins, a low number and percentage. This included 3 monoclonal antibody-based products.

FDA approvals of biopharmaceuticals in 2011 were even fewer in number and will have lower economic impact than in recent years (see http://www.biopharma.com/approvals_2011.html). Twelve biopharmaceuticals received full approval in 2011, a number even lower than the poor results in the past few years. Considering that 40% or more of pharmaceutical industry R&D and revenue, particularly among the large international (Big Pharma) companies that sponsor about 90% of all pharmaceutical R&D, now involves biopharmaceuticals (vs. drugs), if recent trends continue, there could well be an insufficient rate of approvals to support the industry in the long-term. But the current decline in approvals is likely a by-product of less investment in R&D 5-10 years ago, so approvals can presumably be expected to pick up in coming years, reflecting industry’s renewed investments in biopharmaceutical development.
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