Trends to Watch in the Biopharmaceutical Industry:

The Economy, Approvals, Contamination, and Going Animal-Free

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Trends this year continue to indicate that, as we move toward a post-recession environment, the biopharmaceutical industry continues to reflect increasing maturity in its R&D investment, spending, legislative, and operations. For example, spending is cautiously creeping up toward pre-recession levels, but much is directed toward operational efficiency[1]; billions are being spent on investment in R&D sites in the US and Canada; tough decisions are being made on operational strategies, such as contamination problems, and outsourcing; and legislation intended to cut healthcare costs (such as the recently enacted U.S. legislation enabling biosimilar approvals). Some of these trends are likely to affect the biopharmaceutical industry in ultimately positive ways. For this article, we asked our Biotechnology Industry Council™ to weigh in on how trends being seen in the industry are changing strategy.

The Economy

Overall biopharmaceutical R&D appears to be growing, including an increasing number and percentage of the pharmaceuticals in the development pipeline and also product approvals (see below), but the bio/pharmaceutical industry continues to be affected by the global downturn. Companies are increasingly focusing on biopharmaceuticals vs. small molecule drugs[2]; at the same time, economic conditions are causing increasing problems, delays and cancellations of R&D projects. Many companies, particularly the largest international pharmaceuticals that manufacture and market the majority of biopharmaceuticals, have been cutting back—in some cases dramatically. Although staff cutting has slowed, the effect has included laid-off manufacturing and experienced operations staff, and delayed facility expansions. The merging among large companies and other company acquisitions continue to result in the new companies having few products in the R&D pipeline than when operating, presumably less efficiently, as separate entities. Many companies are hoping that their increased investments in biopharmaceuticals, which tend to be more profitable and resistant to generic competition compared with small molecule drugs, will be more attractive to investors and will allow them to grow as they continue to merge and purge. This can deplete knowledge base, resources and infrastructure in the long-term.

Overall, economic conditions and industry cut-backs will continue the focus on cost-cutting. The use and dependence on CMOs and other outsourcing partners is a short-term strategy that most are considering. It often makes sense to outsource more when you have fewer investments in internal resources and infrastructure. The need to cut large capital expenses is also continuing to drive increased use of single-use/one-time (disposable) devices such as bioreactors, purification and other bioprocessing equipment by both developers and CMOs. Dr. T. Hitchcock, Head of Manufacturing Technologies, Recipharm (formerly Cobra Biomanufacturing, UK), a CMO, remarked, "One interesting trend is the desire to develop processes based on single use components, where the receiving CMO would simply reproduce the entire process using the same single use elements as were used in the development studies, the overall aim being to reduce time and cost of the tech transfer process…this has long term implications of the facilities investment and business models for CMO' s in the future." Otherwise, with most companies forced to cut back on staff and investments in new manufacturing facilities, the market for biopharmaceutical manufacture by CMOs is on track to steadily but slowly increase. However, CMOs, themselves, are not immune to broader economic problems, and we may see increased mergers and acquisitions in this area as those with available resources assimilate weaker companies. Also, the recent trend of major (bio)pharmaceutical companies acquiring CMOs will likely continue. Thus, the state of the economy may eventually result in fewer but stronger, more capable and better financed biopharma CMOs. We may also see more niche-focused CMOs capable of supporting narrow technologies, and resolving process development and downstream activities.

More pressure is also being put to industry vendors to resolve technical problems, as well. For example, Dr. J. Martin, Senior V.P., Global Scientific Affairs, Biopharmaceuticals, Pall Life Sciences, noted, "Most early-mid stage companies cannot raise funds to support manufacturing, so more and more clinical batches are outsourced. Big pharma also appears to be outsourcing more testing, training and manufacturing, as well as off-shoring early stage R&D." By doing so, companies are better able to focus on core capabilities, late stage R&D, regulatory submissions and marketing.

Outsourcing Trends

Our 7th Annual Survey of the Biopharmaceutical Manufacturing Capacity and Production [1] confirms that a strategic shift is underway in industry outsourcing, with companies now starting to use outsourcing as a manufacturing strategy, rather than to add flex capacity or to shift out lower value production activities. Larger companies are determining which functions, including manufacturing, can realistically be outsourced, as they now deal with earlier lay-offs and cut-backs. Many areas of R&D are also being considered as options for

outsourcing and the impact of this is being felt on a global basis, with emerging markets ranking favorably alongside established markets as outsourcing destinations. Among 24 areas of outsourcing testing covered in the survey, the primary outsourced activity today was product characterization testing, with biopharmaceutical companies outsourcing an average of 75.6% of this activity. Other areas where the majority of work is now outsourced include toxicology testing (69.2%), validation services (63.5%), analytical testing/bioassays (59.7%) and fill/finish operations (58.5%). While few companies have outsourced all of their manufacturing, this year, nearly one-half (48.2%) of surveyed biopharmaceutical manufacturers expect to increase their budgets for biopharma CMO outsourcing. Also, whether due to concerns about cost-cutting within CMOs or otherwise, industry concerns about outsourcing companies' compliance with quality standards has increased, with 64% indicating quality was a "Very Important" issue, up from 59% last year.

Manufacturing strategies appear to be increasingly driven by the need for specific expertise that may be missing in-house. These niche opportunities appear to be increasing. For example, according to Geoff Hodge, VP Technology at Xcellerex (Marlborough, MA), there is “Considerable interest in vaccines of all types (live/killed virus, VLP, subunit); [as well as] interest from companies looking for help establishing in-house manufacturing capability…This seems to be an unmet need.”

Biopharmaceutical Approvals

Biopharmaceuticals remain a vital and growing subset of the overall pharmaceutical market. These number and percentage of these products relative to the total pharmaceutical market are increasing at a rate significantly higher than that for small molecule drugs[2]. Biopharmaceuticals also generally provide higher profit margins and are less susceptible to generic competition, even with biosimilars a reality in Europe and a new enabling legislation recently enacted in the U.S. Over 500 biopharmaceutical products have now ever received approval in the U.S. and/or European countries, with over 400 currently marketed in these major markets (2). This includes 159 recombinant protein and monoclonal antibody products.

However, many analysts have noted that the number and rate of biopharmaceutical approvals in major markets, particularly the U.S., had significantly decreased in recent years (3). Preliminary indications of a reversal of this trend, with approvals returning to a rate more like that of the earlier 2000s, particularly 2003-2005, have been reported (4). For example, in 2009, FDA granted 18 full approvals (BLAs, NDAs) for biopharmaceuticals products. This was the highest number of new product approvals since 2005, and

considerably more than the 11 and 10 approved in 2008 and 2007, respectively. Looking at approvals in 2010, through mid-September the US FDA had granted 14 full approvals to new biopharmaceutical products (see Table 1). At this rate, we might expect 20 approvals for the year. If this is attained, this will be the largest number approved by FDA since 1998. However, there also appears to be a trend toward increasing delays and even denials of applications by FDA. A large number of applications are pending, including those having been previously rejected or delayed by FDA, e.g., further information requested. So, while it is widely acknowledged that FDA, having been burned by Vioxx and other safety- and approvals-related controversies, is becoming more cautious with more delays and rejections, an increasing number of products reaching the approvals stage is counter-balancing this.

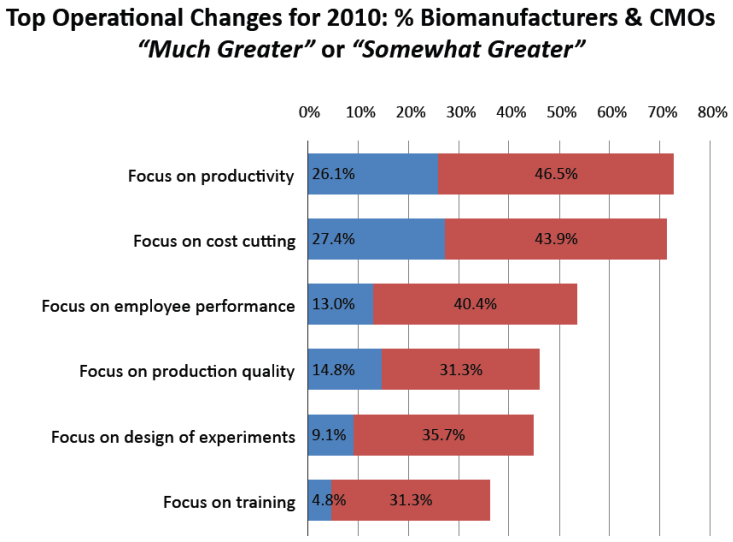
Table 1. Biopharmaceutical Products Approved by FDA in 2010 (as of Sept. 15 2010)

Product	Company	Indication(s)
Xeomin (Botulinum Toxin A)	Merz Pharmaceuticals	cervical dystonia or blepharospasm.
Glassia (alpha-1 antitrypsin)	Kamada Ltd.	alpha1-antitrypsin deficiency
Prolia (RANKL Mab, rDNA)	Amgen	osteoporosis
Lumizyme (glucosidase alpha)	Genzyme	Pompe disease
Provenge (cellular vaccine)	Dendreon Corp.	prostate cancer
Pancreaze (pancreatic enzymes)	Johnson & Johnson	pancreatic insufficiency
TachoSil (Fibrin Sealant Patch)	Nycomed Austria GmbH	control bleeding
Vivaglobin (Immune Globulin Subcutaneous)	CSL Behring	primary immunodeficiency
Glucocerebrosidase, rDNA (velaglucerase)	Shire Pharmaceutical	Gaucher disease
Prevnar 13 (13-antigen pneumococcal vaccine)	Pfizer/Wyeth	pneumonia prevention
Menveo (Meningococcal vaccine)	Novartis	meningococcal disease prevention
Collagenase (enzyme)	Auxilium Pharmaceuticals	Dupuytren's disease
Victoza (Glucagon-like peptide-1,	Novo	type 2 diabetes
Actemra (Interleukin-6 receptor Mab, rDNA)	Amgen	rheumatoid arthritis (RA)

Quality Problems:

The trends toward cutbacks in experienced staffing may have an impact on product quality, which is showing up in our annual study, and may, in fact be showing up in recent contamination events,

This year, the industry's primary focus was on "productivity" and "cost cutting". These areas were among the top four where companies are getting more from existing resources: productivity, cost-cutting, employee performance and production quality. We found that 73% of biopharmaceutical manufacturers are focusing on 'productivity' to a 'Much Greater' or 'Somewhat Greater' extent. But less than half (46%) are focusing on production quality. Can productivity realistically be boosted without a detrimental effect in product or service quality, as manufacturers are forced to do more with less? With limited resources, there may be a trade-off.



Source: 7th Annual report and Survey of Biopharmaceutical Manufacturing and Capacity, BioPlan Associates, Inc.

Over the past year, multiple major microbial contamination problems have affected the biopharmaceutical industry. In most cases, advancing analytical testing technology has allowed identification of previously undetected animal virus contamination. Luckily, the viruses found in marketed products are not known to be human pathogens. The absolute critical importance of avoiding microbial contamination and the difficulties in facilities recovering from contamination are illustrated by Genzyme, which may be acquired through a hostile take-over, the outcome of which may be partially related to manufacturing problems. The potential for a major nightmare health crisis is illustrated by recent reports of years of contamination of pediatric rotavirus vaccines from two different companies.

In March, FDA imposed a consent agreement on Genzyme's U.S. manufacturing facilities, with a 3rd party now overseeing bringing these facilities back to GMP compliance. The company's problems began with a halt in manufacturing in mid-2009 after finding porcine (pig) vesivirus 2117 contamination of multiple Chinese hamster ovary (CHO) cell lines being cultivated in bioreactors used for manufacture of multiple recombinant protein products. Contamination was reported to have been introduced through a cell culture nutrient, due to a porcine-sourced component. Luckily, vesivirus 2116 is not known to infect humans and is not presumed to be hazardous (although this will likely not stop related liability suits). The company's manufacturing facilities remain closed, with this increasingly causing financial problems for Genzyme, loss of $100s million in revenue, all overshadowed by take-over efforts.

Also earlier this year, the two marketed rotavirus vaccines, Rotarix from GlaxoSmithKline (GSK) and RotaTeq from Merck, were found to be contaminated with porcine viruses. Rotarix was reported to contain porcine circovirus (PCV). Porcine (pig)-derived trypsin, an enzyme used to separate individual cells for cell culture, used in the original development of the Vero host cell line used for manufacture, was identified as the likely source. Shortly after this, RotaTeq was found to be similarly contaminated with PCV, obviously also from use of a porcine-derived material. Luckily, PCV is not known to infect humans, post-marketing surveillance has shown no safety problems with the vaccines, and these needed vaccines are now back on the market, while the companies take corrective action. In both cases, the contamination involved the Master Cell Bank (MCB) and the vaccines have been contaminated from their very initial development. With well over 100 million infants worldwide having received these vaccines since their approval in recent years, the potential for a major public health disaster from unidentified pathogen contamination is evident.

Outsourcing strategy and quality initiatives may converge here. These and prior incidents suggest that companies recognize the need continue to exercise caution to ensure products and manufacturing facilities are not contaminated. Both in-house manufacturing facilities and CMOs hired to manufacture clinical or commercial biopharmaceuticals are now seeing the financial impact of these events. Companies providing biosafety testing and pathogen detection may benefit from this trend. Companies should also consider testing their GMP Master and Working Cell Banks, cell culture media and other materials used in biopharmaceutical manufacture for potential pathogens, including using state-of-the-art PCR and other testing for newly-identified pathogens. Such due diligence testing will likely become expected and a standard part of all biopharmaceutical development and manufacturing efforts.

Risk-Reducing Production Strategies

In the context of recent incidents of animal virus contamination of biopharmaceutical products, manufacturers are increasingly considering how to reduce production risks. One of the most long-lived trends is going animal-free, i.e., eliminating all use and exposures to animal-derived materials in the development and manufacture of their products. For many decades, and well before recent reports of animal virus contamination, there has been a definite trend in the industry to reduce or eliminate the use of animal-derived materials. In many cases, this is simply not technically possible, but when the opportunity to reduce exposure opens up, most manufacturers are evaluating the use of defined media, and recombinant replacements for animal-derived products used as excipients. Some of the products being evaluated include the widespread use of human serum albumin (HSA) to stabilize protein formulations, animal-derived products used in culture media, such as fetal bovine serum (FBS) and bovine serum albumin (BSA). Besides animal viruses, potential hazards associated with animal-derived materials include prions, such as bovine spongiform encephalopathy (BSE), which can form protein deposits in the brain leading to severe neurological disorders and death; and human retroviruses remain significant potential hazards. Even using the latest pathogen inactivation/killing and removal technologies and taking other precautions, it remains difficult or impossible to completely eliminate the potential risk. Efforts are continuing to concentrate on careful sourcing and testing to prevent exposure to any contaminated animal-derived materials.

In addition to contamination issues, other regulatory approval problems when using animal-derived materials include the difficulty in fully characterizing these materials, i.e., determining all of their individual components and their concentrations. For example, it is impossible to characterize complex mixtures, such as fetal bovine serum (FBS). This is one reason companies try to avoid using FBS. Much as the recent major contamination incidents were only identified through use of new testing technologies, it is possible that more new viral, prion and other hazards will be identified in future. In this context, use of animal-derived materials is a long-term liability for any manufacturer.

FDA, EMEA and other regulatory agencies have all expressed a preference for products lacking animal-derived excipients in product formulations and manufactured using culture media free of any animal-derived components. Animal-derived materials for use in biopharmaceutical manufacture are not considered unsafe by regulators. In fact, many of currently marketed biopharmaceuticals are manufactured using human serum albumin as a stabilizer or are manufactured using culture media containing FBS, BSA or other animal-derived

growth factor supplements. FDA and other major market regulatory agencies in the future can be expected to increasing prefer the avoidance of animal-derived materials in biopharmaceutical manufacture.

Thus, one now commonly sees discussion and marketing of serum-free media (which only means it does not contain serum; it may contain other animal-derived components, such as BSA). Many serum-free culture media formulations are now composed totally of synthetic or other pure, characterizable chemical substances. If a cell line does not grow well in such simple nutrient formulations, it is common to supplement these with one or more animal protein growth factors.

New, recombinant versions and substitutes for animal-derived excipients and culture media components, particularly culture media protein growth factor supplements, are rapidly becoming available. Sooner or later, these will come to dominate biopharmaceutical manufacture. A variety of new, recombinant products are becoming available, with these specifically targeted as replacements for animal-derived materials. For example, companies such as Invitria and Novozymes are now offering recombinant human serum albumin (HSA) for both formulation excipient and culture media use. Bioprocessing vendors are gearing up to support a switch to animal-free culture media and other products. For example, Becton-Dickinson recently opened a new world-class, totally animal products exposure-free culture media manufacturing facility to serve this growing market.

In the mean time, despite the long-term trends, BSA, FBS and other animal-derived components will continue to be used in biopharmaceuticals and their culture media for many years, perhaps decades. With these products universally recognized as safe (although safety is a relative and constantly-shifting parameter), manufacturers in the U.S. and other major markets, are actively evaluating their sourcing of animal-derived materials from countries such as New Zealand that remain BSE free, have well-regulated meat animal husbandry and processing industries and have reputations for quality and reliability; or from the few "closed herds" of cattle and other animals in the U.S.

References:

1) 7th Annual Survey of the Biopharmaceutical Manufacturing Capacity and Production, BioPlan Associates, Inc. 2010, Rockville, MD www.bioplanassociates.com

2) Rader, R.A., BIOPHARMA: Biopharmaceutical Products in the U.S. and European Markets, online database at www.biopharma.com.

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