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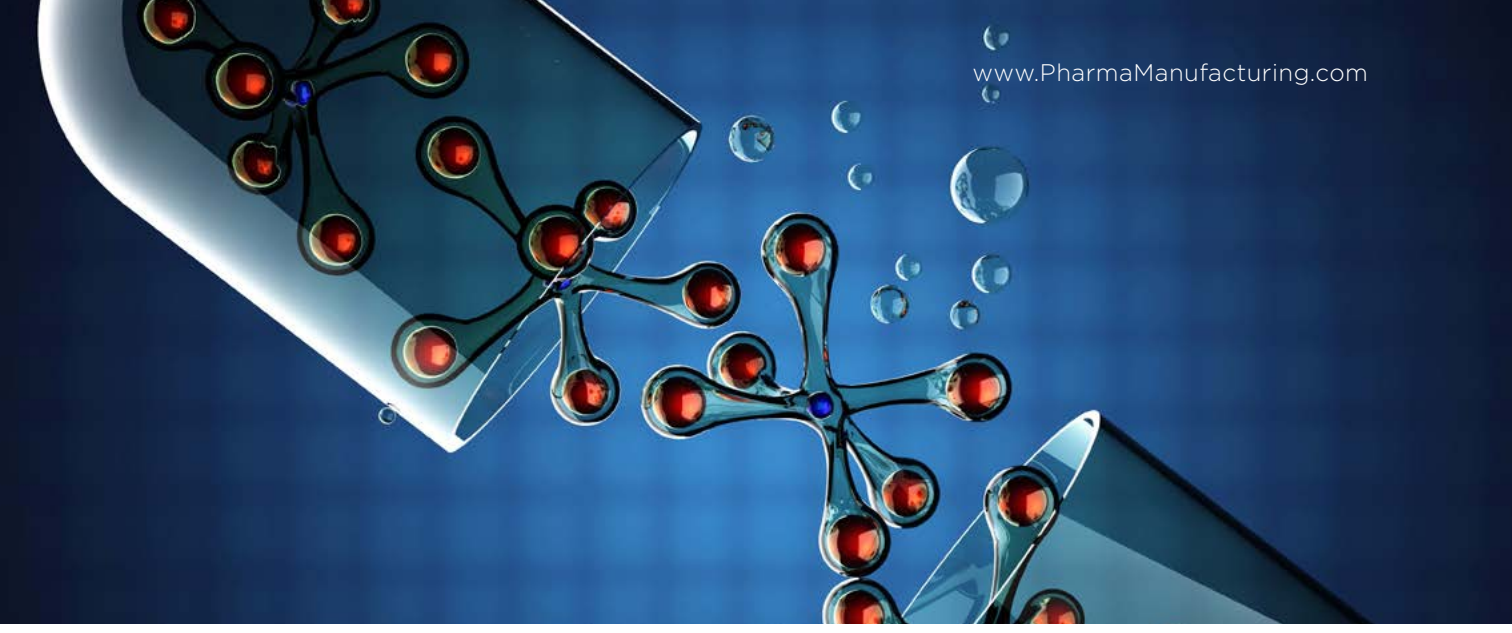

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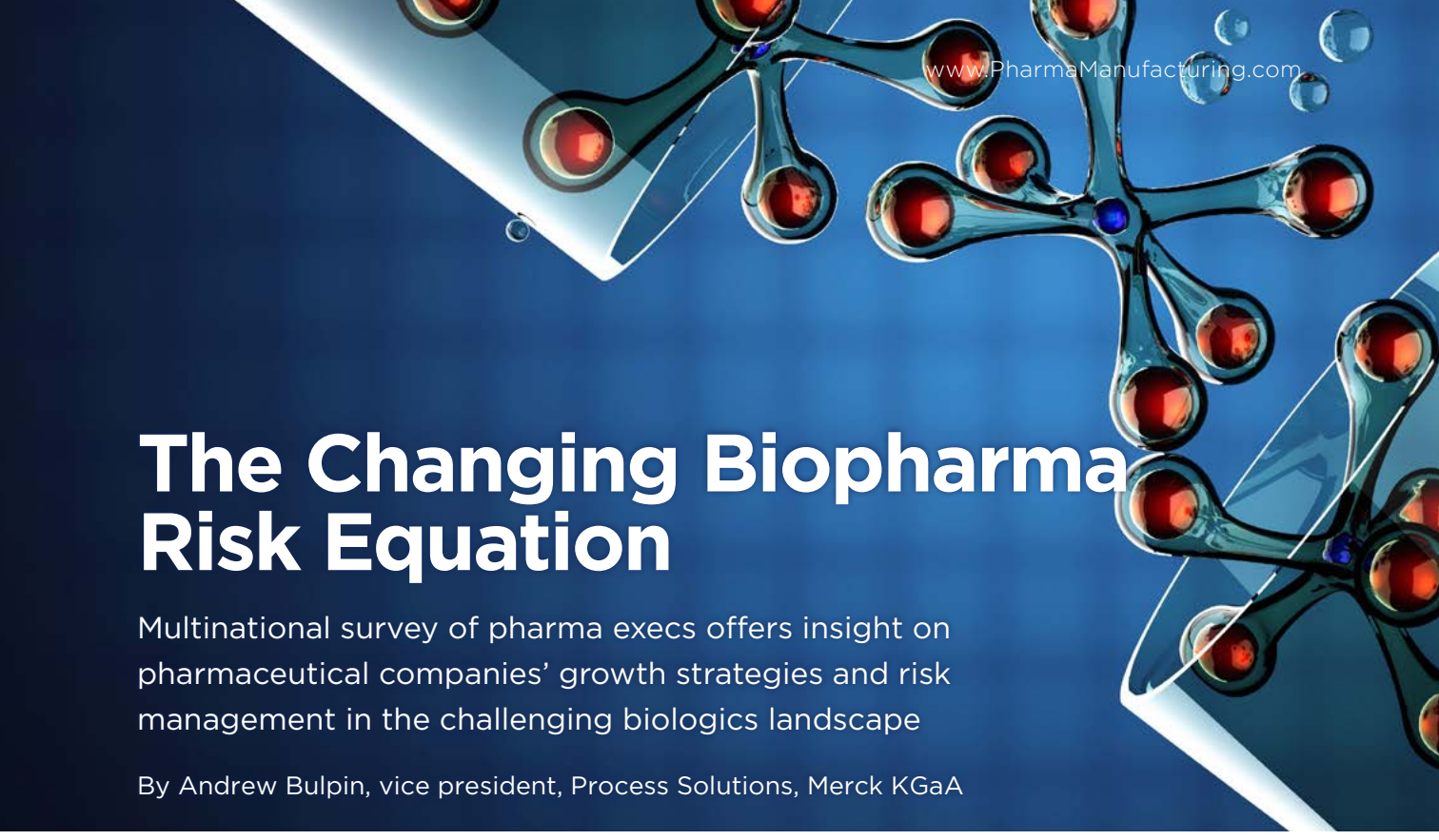


The Changing Biopharma Risk Equation

Multinational survey of pharma execs offers insight on pharmaceutical companies' growth strategies and risk management in the challenging biologics landscape

By Andrew Bulpin, vice president, Process Solutions, Merck KGaA

As pharma companies expand, they are looking more and more to biologics for their next potential blockbusters. However, this class of product — ranging from well-established large molecule drugs to truly novel therapies — poses major challenges because of its scientific complexity and sophisticated development requirements.

Furthermore, expanding the drug pipeline isn't the only growth strategy most companies are pursuing. They are also planning to expand geographically and expect to face various risks doing so, including unfamiliar regulatory environments, shifts in pricing and changes in customers' ability to pay.

All this means that risk management is rising in pharma executives' agendas. To manage risks, companies are developing strategies that involve both building internal capabilities and reliance on external expertise.

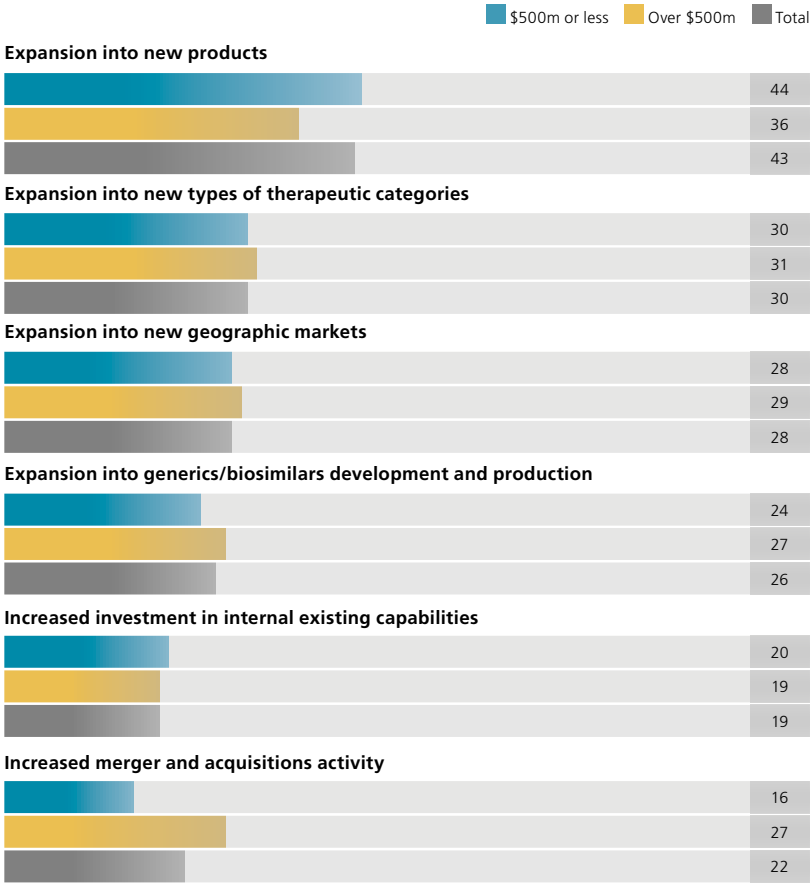
PRODUCT GROWTH

A March 2016 multinational survey from the Economist Intelligence Unit (sponsored by MilliporeSigma) titled, "The Changing Biopharma Risk Equation" of 254 pharma executives found that companies are pursuing different classes of new biopharmaceuticals as part of their expansion.

These drugs fall into two distinct categories. First, large-molecule biologics, such as monoclonal antibodies used to treat chronic diseases including, diabetes, cancers and rheumatoid arthritis. Although these complex therapies have been in use for more

than 30 years and are already well established, the category continues to experience significant growth based on scientific and technical innovation. Second, novel therapies that are truly cutting edge, such as gene and cell therapies. The therapies in this category are still largely in experimental phases and not readily available to the market. However, expectations of widespread adoption are at the core of many visions of personalized medicine.

Indicate the most important strategies for growth for your company over the next five years. (% respondents)



Source: Economist Intellegence Unit survey, 2016

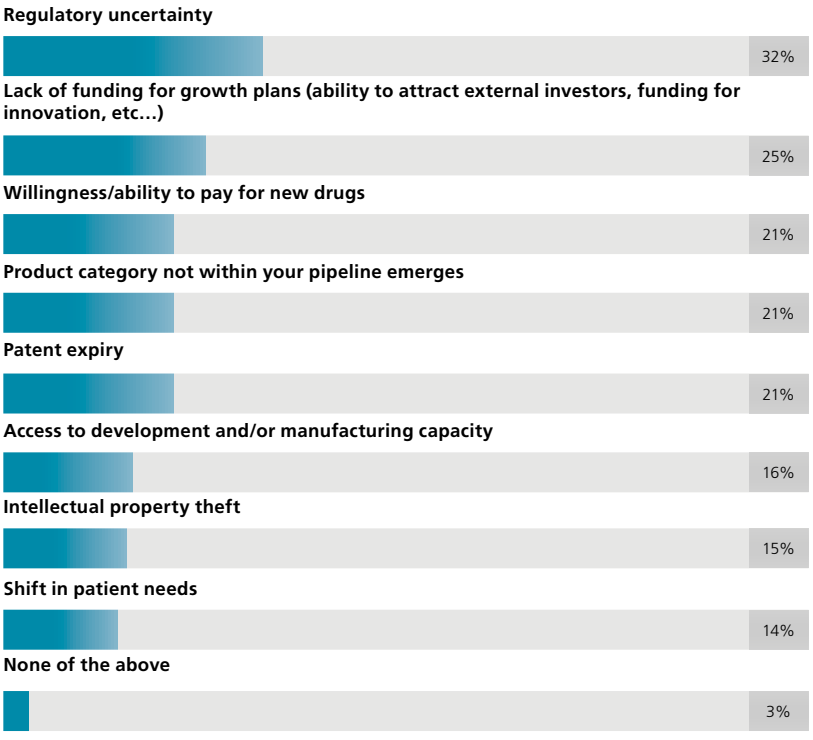
"Strides are being made in rare diseases and orphan drugs, as well as autoimmune disease," says Andrew Baum, managing director of equity research, Citi. "And with Immuno-Oncology, you have a growing number of drugs with known efficacy in multiple indications."

These developments are quickly translating into profits. Sales of biologic products — which employ sophisticated bioprocessing technologies in their manufacture and are used to treat a host of chronic diseases including cancers, diabetes and arthritis — are rising sharply and expected to grow from a $162B market in 2014 to $278B by 2020.[1]

Many of the new therapies help to address conditions that previously had no significantly effective treatments; the demand for such biopharmaceuticals has been so insistent that these new drug therapies have received significantly more U.S. FDA approvals in the 2015 calendar year than the average number approved annually over the last decade. It is not surprising, then, that biologics are a rising priority for most pharmaceutical companies surveyed.[2]

Indeed, the survey shows that stem-cell-derived therapies and gene therapies top

Thinking about other types of risk that might disrupt your company's strategy over the next five years, which of the following, if any, most concern your company? (% respondents)



Source: Economist Intellegence Unit survey, 2016

the list of drug categories deemed likely to disrupt short- and long-term corporate strategies. However, nearly half (48 percent) of survey respondents indicated that they themselves are considering or are already in the process of developing novel therapies. These newer therapies are taking a greater share of production focus than more traditional drug products such as vaccines (38 percent) and blood-derived products (32 percent).

PRODUCT DEVELOPMENT RISKS

Risks of developing entirely new types of drugs are not new to the pharma industry. Since survey respondents highlight cell therapies as the category most likely to disrupt corporate strategy, it follows that the majority (94 percent) of respondents see the development of new and different drug products as increasing the importance of risk management. Those risks include new science and scarce funds for development and revenue.

After regulatory uncertainty (32 percent), a lack of funding for growth emerged as the second biggest concern (25 percent) for survey respondents overall. The inherent complexity of manufacturing diverse types of biologics requires relatively more funding than traditional therapies.

Complicating the funding equation for new drugs and novel therapies are the headline debates over drug pricing in general, which are at their most intense in the U.S., where double-digit drug price rises have been the focus of congressional hearings. "Pricing is the major concern," says Baum in the EIU report, "because that increases systemic risk and creates a lot of bad will — and creating bad will in a heavily regulated industry is not a good thing."

GEOGRAPHIC GROWTH

The survey finds that pharma companies are looking to expand their regional footprint over the next five years across the globe, with higher shares focused on adding capacity or market share in emerging markets.

This focus is notable given emerging markets' somewhat rocky overall economic performance. Asia came up as a particularly attractive region for the pharmaceutical sector in the next five years, with higher shares saying that they expect to be operating in many countries five years from now than say that they have current operations there: Indonesia (34 percent currently operating vs. 40 percent anticipate operating), South Korea (34 percent vs. 44 percent) and Taiwan (30 percent vs. 42 percent).

Indeed, the survey found high levels of optimism for emerging markets' potential overall. For every emerging market that respondents say they anticipate entering in the next five years, at least half of respondents also say that they anticipate return on investment associated with entering emerging markets to increase in the next five years.

GEOGRAPHIC RISKS

Pharmacompanies have been operating to some degree in many countries for decades. The geography-related risks they see now to their favored growth strategies and those they expect to be the most important five years from now largely include regulatory and political concerns.

Among emerging countries, respondents most often indicate they are currently operating in Brazil, China and India — all are nations with somewhat risky regulatory environments that involve various levels of complicated mandates. In China, for example, Ralph Marcello, principal, Deloitte Consulting's life sciences consulting practice, states in the EIU report that he sees a shift away from investment as a result of increased compliance risk, regulatory issues and price pressure on the Chinese national drug formulary.

It's not just existing regulations that can be risky for companies expanding geographically, however — there's also the risk of regulations being changed. A full third of respondents highlight regulatory uncertainty as potentially disruptive to their company's strategy over the next five years. Adding the manufacture of new classes of untested biologic therapies in countries with unfamiliar or changeable regulations presents a high hurdle for companies considering that form of expansion.

But there is reason to be optimistic. Many emerging markets are standardizing their pharma regulations and, in some cases, aligning them with global standards.

MANAGING RISKS

To manage the risks which include regulatory, cultural and funding risks, companies most often say they will be addressing them by building internal capabilities and collaborating with outside experts.

For most, the risk-management strategy will involve building internal capabilities and business units (56 percent), with the second-biggest group pointing to use of outside experts such as contractors and consultants (51 percent). As always, there are major trade-offs to consider in the decisions companies make about whether to focus on in-house resources or to look externally, as well as tasking internal resources to manage and take input from external partners.

In addition to straightforward outsourcing, a range of partnerships is also important to companies; forming local partnerships emerges as the third most popular strategy cited in the survey (42 percent).

"When it comes to product innovation we're seeing a greater willingness to use open innovation, collaborations and partnership with smaller companies, academic institutions or mid-sized companies," says Marcello. "Companies recognize the majority of innovation no longer comes from inside the walls of a large biopharma." And sometimes the more novel the therapy, the more important it is to include a broad range of insights in the innovation process.

Pharmaceutical executives are, on the whole, bullish about the next five years. Most report that they have a balanced portfolio of growth plans and strong confidence that they can overcome the expected risks.

As Baum noted, "in many ways, the industry has never had it so good." However, to earn the returns they expect, pharmaceutical companies will need to build their internal capabilities and manage a range of outsourcing and partner relationships. They will need to learn to thrive in new cultures and ensure that their geographic growth is diversified enough to prosper even if individual countries present economic or regulatory hurdles. And, as always, at the core they will need new science to succeed.

For the full results and analysis of the Economist Intelligence Unit report, please visit www.gobeyondbiopharma.com.

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CATALENT EXPANDS TO MEET COMMERCIAL BIOMANUFACTURING DEMANDS

Catalent Pharma Solutions, the leading global provider of advanced delivery technologies and development solutions for drugs, biologics and consumer health products, recently celebrated its ground breaking for a new $34 million extension to its state-of-the-art Madison, Wisconsin biologics manufacturing facility. When completed, the additional 22,000 square feet of space will accommodate a new 2 x 2,000 liter single-use bioreactor system, allowing the company to support late-phase clinical and commercial production of up to 4,000 liter batches. The new footprint will also support expansion of analytical and process development laboratories, as well as additional office space.

The ground breaking ceremony, led by Lieutenant Governor of Wisconsin Rebecca Kleefisch and Catalent President and Chief Executive Officer John Chiminski, marks the beginning of construction at the site that will eventually create more than 100 new jobs.

"*I want to thank the company for its continued commitment to Wisconsin by deciding to grow here*," said Lt. Governor Kleefisch. "*This expansion will further enhance the Madison region's leadership position in the pharmaceutical and health industries*."

The Wisconsin Economic Development Corporation (WEDC) has awarded Catalent with up to $1 million in state tax credits over the next three years. The actual amount of credits the company will receive is contingent upon the level of capital investment in Madison during the three-year period.

"*Our continued investment in biologics capabilities is in direct response to market demand, where underlying growth for large molecules is expected to exceed that for small molecule drugs*," commented Barry Littlejohns, Catalent's President of Drug Delivery Solutions. "*We are immensely proud of our facility, and the people here in Madison who have helped achieve our customers' program milestones and move toward larger commercial programs*," he added.

Opened in April 2013, Catalent's Madison facility is the home of the company's proprietary GPEx® cell line technology, used to create high-yielding mammalian cell lines. Catalent provides development, manufacturing and analytical services for new biological entities (NBEs) and biosimilars from the Madison facility. It was designed for flexible cGMP production, from 10 liter up to 1,000 liter scale, and non-GMP production up to 250 liter scale, and features extensive use of single-use technologies and unidirectional flow to maximize efficiency. Manufacturing is supported by integrated analytical, process and formulation development capabilities and separate microbiology and quality control functions. Work to extend its integrated analytical capabilities was completed in January 2016, and Catalent has also completed investments to expand process development capability at the site, including integration of an Ambr® 15 microbioreactor system into its cell line and upstream development process, providing overall reductions in timelines and increases in expression levels.

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Manufacturing Costs Will Be Critical to Biosimilars' Success

Attaining low costs is critical for biosimilar manufacturers to support discounts and defend against competition

By Ronald A. Rader, BioPlan Associates Inc.

Biosimilars have finally entered major markets, including the U.S., and are starting to have an impact on the current approximate $200 million biopharma products market. This includes four biosimilars approved in the U.S., while the European Union (EU) has already approved over 20 biosimilars, including some that are capturing big market share from their reference products.

Big (Bio)Pharma companies — those with the most number of biopharmaceuticals for whom filling out portfolios with biosimilars is not a major challenge, are the early leaders in biosimilars development, manufacture and approvals, particularly in Europe. However, while a small number of current major players dominate these earliest product launches, there are hundreds of companies worldwide developing biosimilars targeting diverse markets, ranging from major Western market countries to the poorest developing countries[1,2]. More biosimilars competition, more products, will becoming in most every country and biopharmaceutical market niche.

But many companies developing biosimilars ultimately targeted for Western markets are slow with their product development. Some are letting others blaze the regulatory trail with analytical, clinical trials, regulatory approval and marketing. The biosimilars pioneers are also spending substantial resources on biosimilars-related patent disputes. Others are waiting for more approvals and finalization of regulations, especially by FDA, or want more regulatory guidance concerning interchangeability.

These biosimilars are very attractive, because they will essentially be A-B generic drug products with full interchangeability and substitution at the prescription/pharmacy level. These products will not require marketing as branded products, as most generic equivalent drugs are sold with no brand marketing at all.

VERY HEALTHY PIPELINE

Despite the delays, many more biosimilars, and new players, will soon be entering markets worldwide as more legacy reference products go off-patent.

The biosimilars pipeline is healthy. BioPlan's Biosimilars/Biobetters Pipeline Database (www.biosimilarspipeline.com) currently reports more than 750 biosimilars in various stages of development[1]. The number of biosimilars for major reference products are shown in Table 1. Soon enough, we can expect the number of marketed biosimilars to exceed the innovative biopharmaceuticals. At present, the largest portion of biosimilars are cancer therapeutics, with 482 different biosimilars in the pipeline. More than 100 biosimilars are now in clinical trials. In addition, 277 are either mAbs or fragments. Gaining major market biosimilar approvals is proving to not be too difficult and with negligible development failures so far, a higher percentage of these products in the pipeline can be expected to enter world markets compared to innovative biopharmaceuticals.

Table 1: Biosimilars in the Pipeline Targeting Specific Reference and Classes of Products

REFERENCE PRODUCT	# BIOSIMILARS
Humira	34
Remicade	17
Epoetin alfa	85
Neupogen	58
Neulasta	25
Enbrel	32
Rituxan	52
Herceptin	42
Lantus	10
Avastin	30
PRODUCT CLASSES	**# BIOSIMILARS**
Cancer indications	482
mAbs/mAb fragments	277
TNF inhibitors	91
Interferons (alfa)	59
Insulin and analogs	51
Somatropins	34
Interferons (beta)	26

Even removing from consideration as 'biosimilars' about 200 lower-end (non-GMP) 'biogenerics' targeted to lesser- and non-regulated international markets, there are a large number of products in development, with the vast majority targeting the U.S market. This includes biosimilars for nearly every current biopharmaceutical product.

CURRENT LOWEST COSTS FOR BIOSIMILARS APIs

Having low(er) costs for biosimilars manufacturing will be critical. The point of biosimilars is to provide cheaper alternatives to off-patent innovative reference products. Biosimilars must be priced at a discount relative to their reference

products, currently ≤30 percent, in Europe; but likely to increase to 50 percent or more, eventually, in the U.S. Biosimilars must also compete with other biosimilars, with 10 or more for each major reference product likely in major markets. Plus they must compete with biobetters and other innovative products targeting the same indications. So there will be a lot of competition, much of it on the basis of prices. Pricing of biosimilars may not always be rational (by conventional biopharma standards). Some developers are expressing intentions to low-ball their prices to capture market share. Others will be interested in protecting or growing their product portfolios and may bundle sales. Competition on prices could well become more extreme as interchangeable biosimilars enter world markets, with these competing directly with the earlier branded biosimilars.

BioPlan Associates recently evaluated costs associated with biosimilars API manufacturing. Bioprocessing professionals with biosimilar developers pre-qualified as knowledgeable concerning bioprocessing costs were interviewed regarding their views on costs currently attainable with biosimilars API manufacturing, particularly monoclonal antibodies. We also evaluated types of manufacturing approaches and facilities most suitable for low costs commercial manufacturing; and what that cost would be for a "typical" mAb biosimilar. As a basis, we presumed that a minimum of 100 kg/year of mAb is required once manufacturing has ramped-up, such as 3-5 years after launch.

Today, biosimilar manufacturing facilities include:

- Big (Bio)Pharma 10,000+L bioreactor-anchored facilities
- Smaller, flexible single-use facilities
- Stainless-steel facilities, mid-scale
- Stainless-steel facilities, very large-scale; and
- New facilities in developing regions

Table II: Summary of Interviewees' Most Efficient Facility Manufacturing Cost Estimates*

FACILITY TYPE	EST. LOWEST COSTS/GRAM
Smaller (e.g., 2,000 L) single-use	$175-$225/gram
Emerging Market GMP	$160
Legacy, stainless-steel reference product manufacturers	$95-$100
Major new Stainless Steel facilities (e.g., Korea)	$100 - $120

*Assume minimum biosimilar mAb manufacture of 100 kg/year.

Table II shows general consensus data collected from interviews. Not unexpectedly, the very lowest costs for biosimilar mAb GMP manufacture were reported for facilities operating the very largest scales using stainless steel. This particularly includes Big Pharma legacy facilities with multiple 10,000 L bioreactors. These are followed very closely by the new super-sized facilities coming online — Samsung Biologics

and Celltrion, both in S. Korea. The very lowest costs attainable at Big Pharma facilities were reported to be about or slightly below $100 for legacy large-scale facilities. Costs are reported to be just a few percent more for the totally new Korean super-sized facilities.

Despite these low numbers, any facility attaining ≤$500/gram is likely to remain competitive. We note that we have not addressed overall industry average ranges of cost. However, many manufacturers likely will be manufacturing at costs in the $1,000/gram region. As noted, much of the variations in cost for manufacturing are based on scale, but as aspects such as titer improve, the need for massive scale production decreases.

Interviewees noted that even $1,000 or more per gram is still very workable, providing acceptable profits for most biosimilars selling for multiple thousands per dose. For many biosimilar players, it will be of relatively limited impact whether their costs for manufacture are $50 or $500/dose, with their selling prices often in multiple $1000s/dose. Contrary to expectations, best cost/gram for microbial commercial manufacturing were found to be similar to those for mammalian mAbs, while the cost per dose is generally significantly less, with many microbial products substantially more potent than most mAbs.

Essentially, $100/gram appears to be the current lowest cost attainable with GMP biosimilar mAb manufacture. This is attainable by some products at some of the largest facilities, whether old or new. Samsung and some legacy Big Pharma facilities were cited as having these very low costs, while some other legacy facilities likely have costs 20-30 percent more, generally viewed as a trivial increase. Costs at the new Korean facilities were expected by interviewees to continue to decrease further, below $100/gram, in coming years as efficiencies are attained and 100s of expensive onsite staff and consultants required for start-up, leave. Although there are few good examples, many presume that new commercial scale single-use biosimilar mAb facilities optimized for a company's products can reduce costs to be very competitive with even the lowest costs facilities (keeping in mind that costs below $500/g are considered by the industry as still rather competitive).

BEST VALUE VS. LOWEST COSTS

Optimizing biosimilars manufacturing costs is critical for all biosimilar players and, as more products enter the market, costs will increasingly become a determinant in setting price floors. Essentially every interviewee noted that developers are seeking maximal manufacturing cost-effectiveness (within their size/scale and other limits), including adopting current or

future-looking, rather than legacy, manufacturing technologies.

Companies that have long manufactured biopharmaceutical reference products were also concerned about their manufacturing costs. With their big vats, and long-established manufacturing platforms, they expect to achieve long-term cost savings.

But most every interviewee noted that having optimized, best fit, manufacturing for products is more critical than simply attaining low costs/gram for APIs. Nearly every interviewee qualified their reporting of lowest costs with biosimilar mAb manufacture by noting that the cost-related variables that really matter most in the long-term involve having a "right-sized" and outfitted facility with optimal scheduling to maximize capacity utilization. If the facility, its processes and scheduling are optimally integrated with cost-effectiveness as the goal, low costs for that type/class of facility will generally follow.

As noted, single-use manufacturing, if done right, can be very competitive, such as attaining costs below $200/gram, along with the inherent flexibility, lower capital expenses, faster turnaround, smaller footprint and other benefits of single-use bioprocessing (but with these operational benefits not usually included in cost calculations). On the other hand, costs in this Single-use range can also be attained using optimally designed, mid-sized stainless-steel facilities, such as the 8,000 L facility Oncobiologics (Cranbury, NJ) designed to support its biosimilar mAbs through initial product launches. It was significant that no interviewees mentioned new stainless-steel facilities as having lowest costs, other than the few new super-sized Korean facilities.

New large-scale facilities in developing countries, notably India and China, were cited as likely having lowest costs averaging around $160/gram. In this context, most interviewees saw no benefits and some downsides involving hidden costs associated with GMP biosimilar manufacture in developing countries. No interviewee presumed manufacture in those countries would be the cheapest. Manufacture in developing countries entails many added costs and difficulties with communications, management, travel, language/translators, shipping delays, unexpected scheduling problems, import duties, safety, costs of foreign consultants, fears of IP/proprietary technology losses, etc., besides the current risks associated with the quality of manufacturing in emerging regions.

Costs of goods/manufacturing, at least as commonly calculated, does not include all of the real costs involved with biopharmaceutical manufacturing. Many interviewees noted that lowest API costs/gram are much less important than total manufacturing

operations efficiency, in the context that many aspects critical to bioprocessing and companies are not taken into account in costs calculations. This includes single-use facilities adding considerable value or even being invaluable, such as providing increased flexibility and speed-to-market, factors not included in direct cost calculations. For many, single-use facilities can be preferable and more cost-effective vs. large-scale stainless steel facilities or hiring a CMO. In some cases the increased speed-to-market or lower initial capital investments compensating for somewhat higher calculated costs of manufacturing.

As biosimilars enter major markets, including the U.S, large biopharma companies with the most number of products are the early leaders. However, there are hundreds of companies worldwide developing biosimilars. More biosimilars competition, more products, will coming in most every country and biopharma market niche. The biosimilars pipeline, what is in development, is healthy, with over 750 biosimilars in various stages of development[1]. Soon we can expect the number of marketed biosimilars to exceed the innovative biopharmaceuticals.

Competition will increase, and attaining low costs, generally involving using current vs. older legacy bioprocessing technologies, is critically needed by biosimilar manufacturers to support discounts and defend against the considerable expected biosimilars competition. Lowest costs are generally associated with the very largest scale stainless-steel manufacturing. However, calculated manufacturing costs are just part of the real or total costs of manufacture, which include many hidden costs of simply being a manufacturer.

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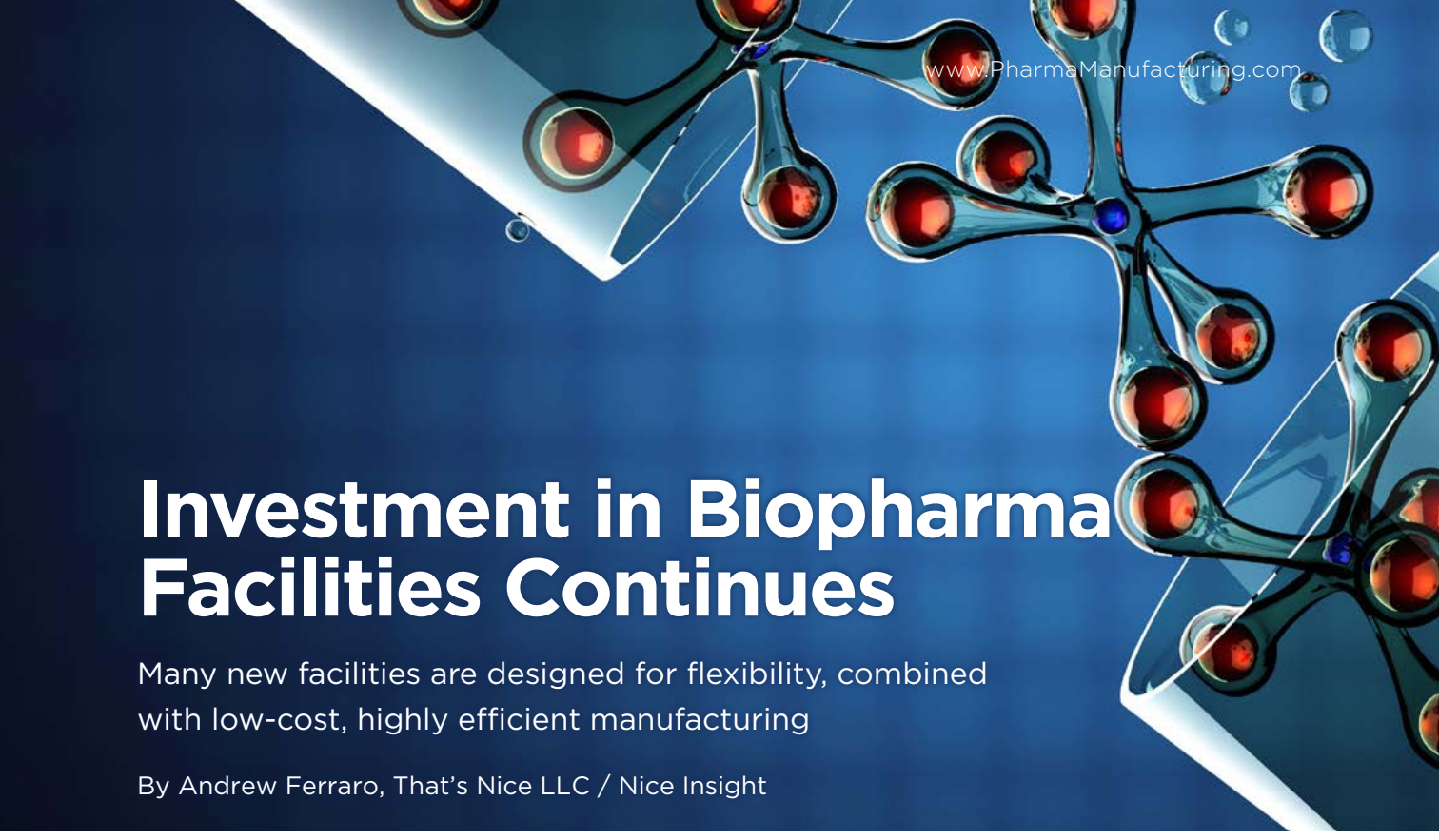


Investment in Biopharma Facilities Continues

Many new facilities are designed for flexibility, combined with low-cost, highly efficient manufacturing

By Andrew Ferraro, That's Nice LLC / Nice Insight

The ability of biologic drugs to treat chronic and other challenging diseases has led to a steady increase in the demand for these medicines around the world. Both investment in innovation by large and small bio/pharma companies and the number of biopharmaceutical drug approvals have also increased. Expanding pipelines have led to a significant growth in investment activity, as both sponsors and contract manufacturers seek to add production capacity designed to enable commercialization of the most advanced, complex large-molecule drugs. Many new facilities are designed for flexibility, combined with low-cost, highly efficient manufacturing.

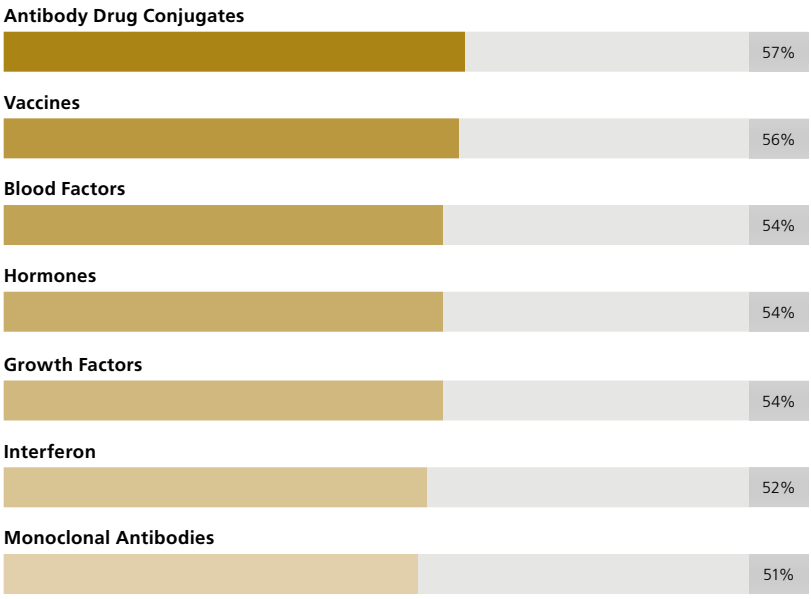
REAL GROWTH

The biopharmaceutical market in 2015 was valued at $200 billion and growing at ~14 percent annually, according to BioPlan Associates.[1] The top 15 biopharma products each have annual revenues of greater than $2 billion and some (e.g. Humira) generate sales of more than $10 billion per year.[2] The clinical pipeline is robust, with 10 to 15 new biopharmaceutical therapies expected to receive approval each year, and greater numbers of biosimilars also are expected to reach the market.[2]

Indeed, the current and future product pipelines of 66 percent of the bio/pharma professionals responding to the 2016 Nice Insight CDMO Outsourcing Survey include large-molecule new biological entities (NBEs), which is significantly higher than the 57 percent indicating that their pipelines include small-molecule APIs.[3] Similar fractions will have small-molecule generics

and biosimilars in their pipelines (53 percent vs. 50 percent). Furthermore, at each phase of development from discovery through Phase IV/post-launch, 75-80 percent of survey respondents that are active at these stages indicated that they have biologic candidates under evaluation. The top types of biologic drugs being developed by respondent companies include antibody-drug conjugates (ADCs), vaccines, blood factors, hormones, growth factors, interferon and monoclonal antibodies.

Biopharma Investment: Types of Biologics



The global biopharmaceutical contract manufacturing market is, consequently, also very healthy. In June 2015, HighTech Business Decisions (HBD) predicted that the market for biopharmaceutical contract manufacturing services would reach $3 billion in 2015[4], while Roots Analysis estimates the market is growing at an annualized rate of 8.3 percent.[5] HBD also predicted that the biopharmaceutical contract manufacturing sector will increase its capacity for mammalian cell culture production by 14 percent and for microbial fermentation production by 16 percent by the end of 2016.[4]

DRIVING INVESTMENTS

The strong growth in demand, combined with globalization of the biopharmaceutical industry, is driving significant investment in the expansion of existing and the addition of new capacity in many established and emerging markets. Some of this capacity belongs to international bio/pharmaceutical companies looking to establish a presence, as individual governments increasingly require in-country manufacturing of medicines and vaccines.

Indeed, according to BioPlan Associates, bioprocessing-related budgets were higher in 2015 than the year before across all areas, including capacity expansion, equipment expenditures, process design, new personnel hiring, and facility construction, although a significant portion of current investments are targeted at

MANY OF THE NEW PLANTS UNDER CONSTRUCTION ARE BEING DESIGNED TO TAKE ADVANTAGE OF SINGLE-USE SYSTEMS.

improving productivity through enhanced process development capabilities and the implementation of new technologies, particularly for downstream processing.[1]

NEW LOOK FOR FACILITIES

Constructing conventional, large-scale biopharmaceutical manufacturing facilities typically costs $200 to $500 million (vs. $30 to $100 million for similar-scale, small-molecule plants) and takes four to five years, according to McKinsey.[2] It is not surprising, then, that many of the new plants under construction are being designed to take advantage of single-use systems, which are now suitable for commercial production of mAbs and other proteins given the 10+-fold increase in titers achieved today. A 2000-L disposable bioreactor can now replace a 20,000-L stainless-steel vessel, allowing for significant reduction in the necessary scale for biopharmaceutical manufacturing facilities. When compared to traditional stainless-steel equipment, single-use technologies have been shown to reduce capital and operating costs by 40-50 percent and 20-30 percent, respectively, and time-to-build by 30 percent.[6]

Biopharmaceutical manufacturers are also leveraging modular technology to reduce the time and cost of constructing new facilities. In November 2015, JHL Biotech's pre-fabricated KUBio plant manufactured by GE Healthcare Life Sciences was assembled from 62 containers in Wuhan, China, in 11 days.[7] KUBio facilities are based on single-use technology for rapid switching between processes and include all necessary components, such as clean rooms, piping and HVAC systems, and are designed to meet FDA and EMA GMP standards. GE also consulted with China's Food and Drug Administration. According to the company, the cost of a KUBio plant can be as much as 45 percent lower than a comparable, traditional facility.

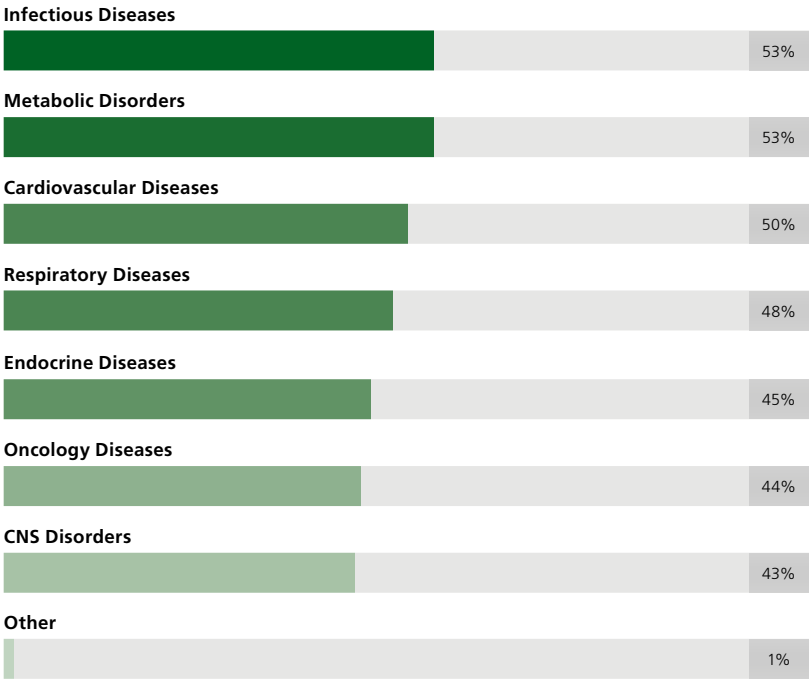
Other features and technologies being incorporated into many of the newest facilities include capabilities for continuous upstream (USP) and downstream (DSP) bioprocessing, and for the production of highly potent biologic APIs and drug products.

LOTS OF SPONSOR ACTIVITY

Investments in biologics facilities by sponsor companies cover all aspects of biologics drug development and manufacturing, including API production, fill-finish and packaging operations. In addition, not only

international, big pharma/biotech firms, but also developing start-ups are making these investments. Ireland and Singapore are two hot spots for recent biopharma investment, but dollars are being spent around the globe. Many announcements have been made as recently as December 2015/early 2016.

Biopharma Investment: Therapeutic focus of drug development pipeline



Recent big pharma/biotech investments include:

- Expenditure of approximately $550 billion by Boehringer Ingelheim to expand its biopharmaceutical production capabilities in Vienna with the construction of a large-scale manufacturing facility for biologic APIs manufactured using cell cultures.
- Bristol-Myers Squibb is planning to build a new state-of-the-art, large-scale biologics manufacturing facility in Dublin at a cost of ~$900 million that will produce multiple therapies. The company is also expanding its recently opened $500 million biologics production site in Devens, MA.
- Novartis has broken ground on a new $500 million biologics plant in Singapore. Its generic pharmaceuticals business, Sandoz, recently inaugurated its new, nearly $165 million, state-of-the-art BioInject biopharmaceutical manufacturing facility in Austria.
- Biogen plans to invest $1 billion to triple its biologics capacity with the construction of a fourth manufacturing plant in northern Switzerland.
- AstraZeneca acquired a high-tech biologics bulk manufacturing facility in Boulder, Colorado, from Amgen in September 2015 that it is refurbishing. The site is expected to be operational in late 2017. The purchase followed announcements that AstraZeneca is investing $285 million in a biologics facility in Sweden and expanding its Frederick, Maryland, site. The new Swedish facility will focus on filling and packaging of protein therapeutics and, from 2018, supplying

medicines for the clinical trial programs of AZ and its MedImmune subsidiary.

- Pfizer is spending $100 million to upgrade its biologics plant in Ireland.
- Genzyme is investing $80 million at its recently approved facility in Framingham, MA, adding more downstream processing capabilities for Fabrazyme, its treatment for Fabry disease.
- Eli Lilly is completing a $450 million biologics facility in Ireland. In 2013, the company also announced nearly $1 billion in planned plant expansions for the production of its insulin products, including API and cartridge manufacturing capabilities.
- Amgen opened in August 2015 a $300 million facility including a syringe filling facility and a cold chain warehouse in Singapore. The facility uses disposable technology, continuous processing and real-time analytics, has a replicable and flexible modular design with a small footprint for reduced energy and water consumption and waste generation. It was also constructed in half the time required for a conventional plant, according to the company.
- Baxter opened its first biologics facility in Asia in 2014. The $370 million facility in Singapore produces ADVATE and will also manufacture treatments for hemophilia B once a second expansion suite opens in 2017.
- Roche announced in 2013 that it is investing $880 million in biologics manufacturing capabilities, including an ADC manufacturing plant in Switzerland and expansion/upgrades of sites in California and Germany. Its Japan-based subsidiary Chugai Pharma is also investing $310 million in antibody production capacity at a plant in Tokyo. An additional $125M investment in an expansion of a Genentech fill/finish facility in Oregon was announced in March 2015.
- Smaller biotech firms have not been idle, either:
- Regeneron will be investing an additional $350 million on top of its initial $300 million investment to create a pharmaceutical plant at a former Dell computer manufacturing site in Ireland.
- Alexion Pharmaceuticals plans to construct the company's first biologics manufacturing facility outside of the United States. The nearly $500 million investment in Ireland will take four years to complete.
- Allergan is spending $350 million on a new biologics facility in Ireland to expand its manufacturing capacity for Botox and develop a manufacturing base for the next generation of biologic products currently in the Allergan pipeline.
- Jazz Pharmaceuticals is constructing its first plant in Ireland at a cost of $68 million.
- Grifols is investing $85 million in a purification plant for protein albumin at its biologics plant at Grange Castle, Dublin, earlier than planned in order to meet growing demand.

- ShangPharma plans to establish a subsidiary in the Qidong Biopharma Industrial Zone as part of a multistage expansion project for its biologics service portfolio, with $60 million invested in the first phase to build pre-clinical research and biologics manufacturing facilities. The latter should be operational in 2018.

CONTRACT BIOPHARMA MANUFACTURERS SPENDING, TOO

With the high level of in-house investments being made by sponsor companies, it might at first glance be surprising that biopharmaceutical contract manufacturers have also been expanding their capacities. Notably, most of these investments are being made by larger contract development and manufacturing organizations (CDMOs) offering full support to biologic drug manufacturers from discovery to commercial manufacture.

Many of these firms are leaders in the industry and are investing now in order to meet anticipated increased demand for their services. Others are focused on offering contract development and manufacturing services for advanced and next-generation technologies that require highly specialized capabilities, and in some cases the development of new technologies and processes to enable commercialization (such as for cell and gene therapies).

Recent and ongoing biopharmaceutical CDMO investments include:

- Samsung Biologics is investing $740 million in a new biologics manufacturing facility that will double its production capacity. The plant is located in South Korea and expected to be onstream in 2018.
- Brammer Bio, which was formed in late March 2016 when Brammer Biopharmaceuticals merged with Florida Biologix to create a cell and gene therapy biologics CDMO, now has 45,000 ft^2 of process development and phase I/II clinical manufacturing space in Alachua, FL, and is developing a 50,000 ft^2 facility in Lexington, MA, with plans to build-out large-scale, phase III/commercial-ready viral vector manufacturing suites and segregated cell and gene therapy suites for clinical and commercial launch services.
- WuXi PharmaTech is constructing its third cGMP facility for the manufacture of cell therapy products. When operational in mid-2016, the Philadelphia plant will produce cell therapies that contain viral vectors, such as chimeric antigen receptor T cell (CAR T cell) therapies. The second facility for autologous cell-based therapeutics was completed in 2015. The company is also building a state-of-the-art integrated biologics solution center at its headquarters in Shanghai to support biologics discovery, development and clinical manufacturing.
- Catalent Pharma Solutions opened its new, state-of-the-art biomanufacturing

Center of Excellence in Madison, WI, in April 2013.

- Abbvie is investing $320 million to build a facility in Singapore for the production of both small-molecule and biologic APIs. The company will also spend $30 million to expand its Barceloneta, Puerto Rico, site.
- Patheon Biologics is adding capacity at its sites in the U.S. and the Netherlands.
- KBI Biopharma is expanding its mammalian and microbial API production capacity.
- Fujifilm Diosynth Biotechnologies acquired Kalon Biotherapeutics in 2014 and has since made additional investments to increase its bioreactor capacity and expand its process and analytical development capabilities, which are coming online in 2016.

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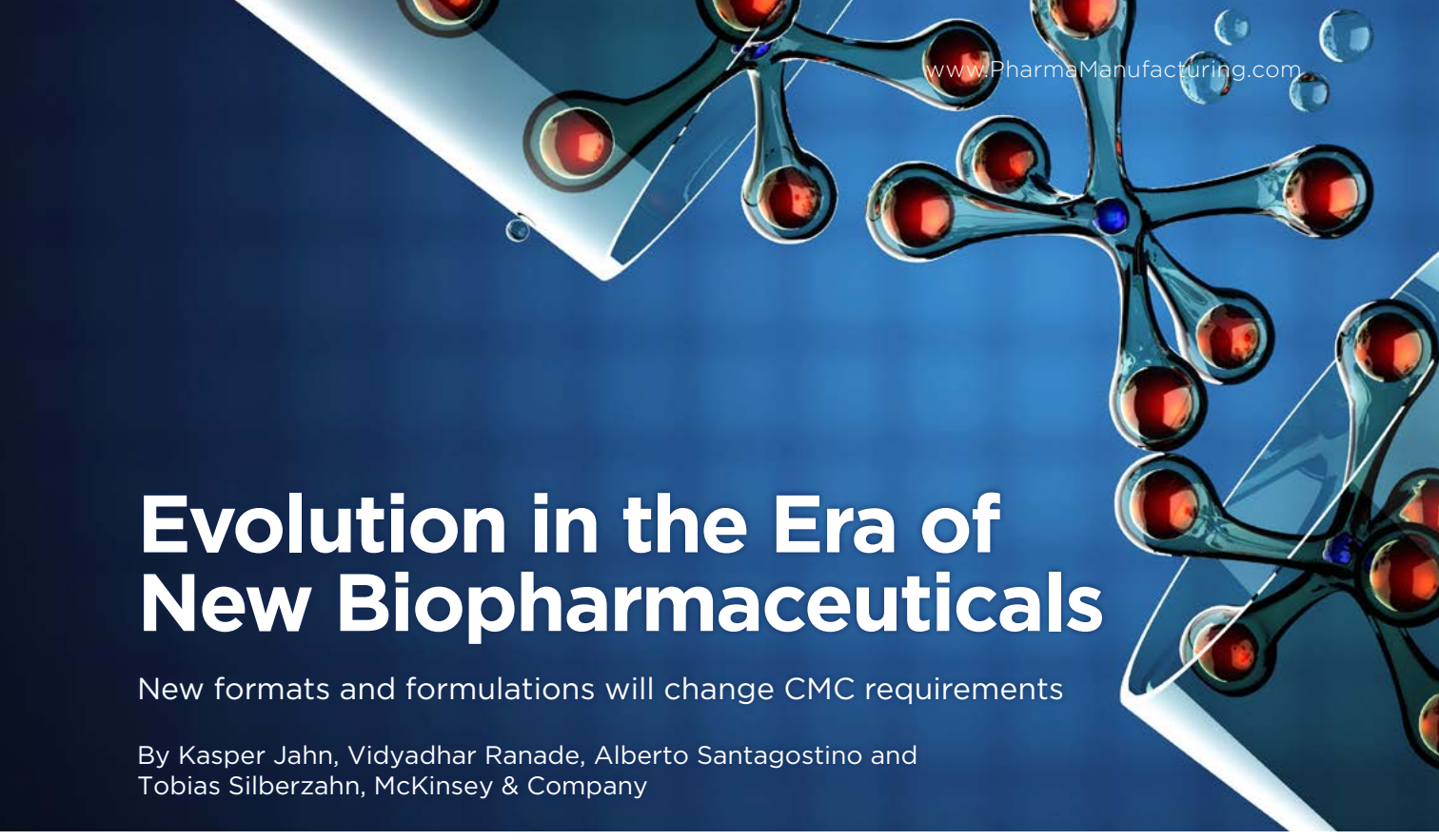


Evolution in the Era of New Biopharmaceuticals

New formats and formulations will change CMC requirements

By Kasper Jahn, Vidyadhar Ranade, Alberto Santagostino and Tobias Silberzahn, McKinsey & Company

In the already diverse field of biopharmaceuticals, chemistry manufacturing and control (CMC) is about to get more complex. New formats and formulations will change CMC requirements, dictated by the need to characterize products of increased complexity and the expectation of authorities that companies will keep pace with the latest technologies so as to minimize quality risks.

The potential implied changes required for an effective CMC include: more extensive information handoffs, greater cross-functional cooperation and a greater focus on relationships with regulatory agencies. These trends will demand a rethinking of the CMC setup and an appraisal of its capabilities based on a company's product pipeline.

OVERARCHING REQUIREMENTS

Chemistry manufacturing and control, also called technical development, is the process that takes a molecule from research and turns it into a product that can be manufactured in a large-scale facility. In the course of its work, the CMC function is charged with satisfying all the necessary quality and regulatory requirements as well as delivering the product at the right cost (Exhibit 1).

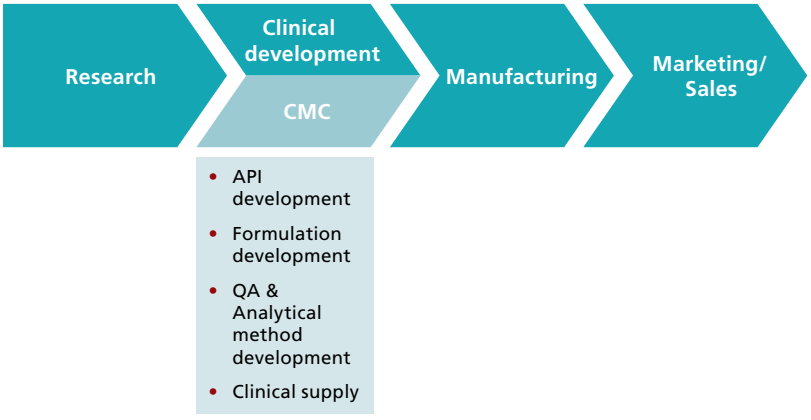
As a multidisciplinary, highly technical process, CMC encompasses a significant amount of risk. Ensuring that the function's setup is tailored to the company's pipeline is crucial in mitigating some of the risks, particularly those incurred through either delays in launch or increases in production cost.

For innovator drug substances, the cell line expressing the molecule and any development of pre-formulation needs to be handed over from research to the CMC function. This handoff must be a smooth transition to ensure that all of the information on drug substance, drug product and analytical development is transferred without knowledge loss. The CMC function then needs to build on this base to experimentally prove the purity of the molecule and the robustness of the production process, while increasing the scale toward commercial production levels.

The biopharmaceutical industry has graduated from synthesizing small peptides to generating full-fledged protein therapeutics routinely on a large scale. The industry is familiar with recombinant proteins that mimic endogenous agonists (interferon, insulin, growth hormones and so on). It is equally familiar with the big wave of monoclonal antibodies (mAbs). Both of these recombinant protein types have become common science in CMC's standardized development processes with the introduction of platforms such as optimized expression systems and vectors.

Exhibit 1

TASKS CARRIED OUT DURING THE CMC PHASE



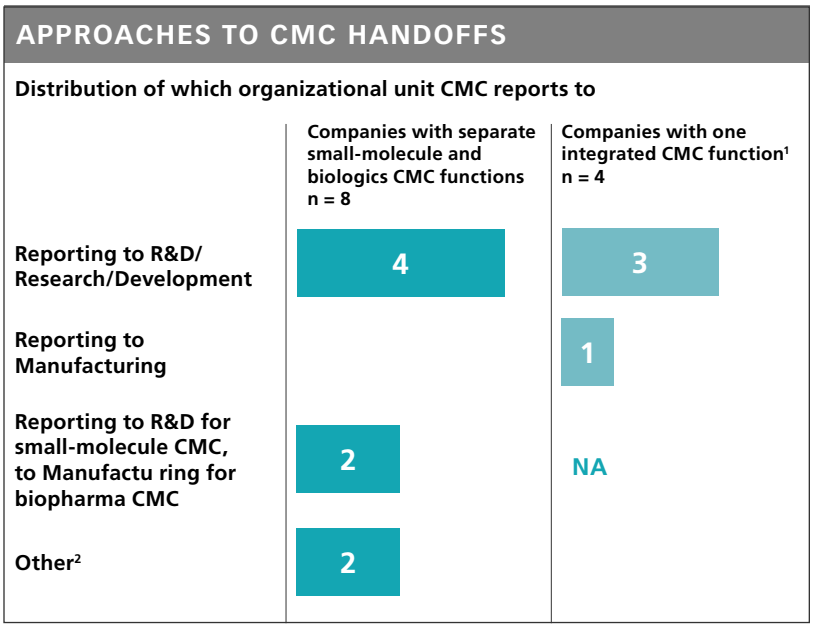
But the landscape is quickly changing. Many new protein therapy formats are being developed and entering the market. From 2006 through 2013, the share of these new formats reached 11 percent of the pipeline and grew 33 percent year over year. Examples of these new therapeutics include the following:

- Biosimilars, sometimes called "follow-on biologics," growing in number because high-revenue biopharma molecules are going off patent
- Innovative formats/ formulations
- Advanced-formulation products, which have a complex drug delivery formulation and are intended to improve pharmacodynamics and target the drug substance to specific areas
- Covalently modified biopharma-ceuticals, which are recombinant proteins modified to enhance their pharmacokinetics (PK) and PD; these formats are complex and require new capabilities that are

at the interface of chemistry and biologic processes

- Antibody-drug conjugates, a subclass of covalently modified biopharmaceuticals that are gaining particular importance; in this case, the covalent modification redefines the mechanism of action of the mAb, creating the opportunity for a new level of drug potency (less drug is needed as it is delivered right to the place where it is intended to be active).

Exhibit 2



1 Small-molecule plus biologics CMC in one function
2 E.g., regional reporting line

Source: McKinsey CMC Benchmarking

These emerging categories of therapeutics will place new demands on CMC. In this article, we will take a close look at the factors that biopharma CMC organizations need to master in order to succeed.

NEW THERAPEUTIC MOLECULAR FORMATS

Advanced-formulation products and biosimilars exemplify the new protein therapy formats that require an appraisal and rethinking of the CMC setup and capabilities.

Advanced drug formulations demand a high knowledge of the drug product, the drug substance and the interplay between the two. The added layer of complexity of these novel formulations increases the variability of the final product and the parameter space that needs to be controlled. CMC's responsibility is to create data that clearly demonstrates the safety of these products in the light of the altered PK and PD.

The CMC process will have to be much more focused on the simultaneous codevelopment of drug product and drug substance as the interplay between the two becomes much more extensive than in more traditional biopharmaceuticals. Not only does the transition of knowledge from research have to be flawless for CMC to have the right starting point, but the capabilities to develop the novel formulations and characterize the formulations are more challenging.

In the same way that CMC must more tightly align with research, so must it sustain

CODEVELOPMENT OF DRUG SUBSTANCE AND DRUG PRODUCT IN THE RESEARCH PHASE ADDS A NEW DIMENSION TO KNOWLEDGE TRANSFER COMPLEXITY.

closer dialogues with regulatory agencies in order to confidently know what scientific evidence will be demanded prior to approval of novel products. In new areas, where regulators are often seeing a given drug delivery system for the first time, the approval process can be expected to be even more cautious and conservative than usual. CMC must be prepared to satisfy unusually extensive demands for scientific evidence.

Biosimilars must show low variability of the product, robustness of the processes, and true biosimilarity beyond any reasonable doubt. This requirement demands much more capacity for analytical testing. Because the "ask" for biosimilarity is rightfully high to avoid approval of products of inferior quality, many players shoot for having smaller variances than originators for critical process parameters and product specification.

Respecting these narrow boundaries adds significant complexity in terms of excellence of execution and technical competence and poses a direct trade-off with development lead-time and cost. It is relevant in this context to underscore that cost is of considerable importance for biosimilars because of the likely price pressure that will result as multiple players enter the market and compete to replace the high-revenue molecules losing patent protection. But, more importantly, CMC also needs to enable speed-to-market in biosimilars development. Speed is even more crucial than for innovators — if the biosimilar molecule is not first or second to market, it will capture minimal market share.

TAILORING THE CMC SETUP

Because novel drug delivery formulations and biosimilars have different requirements than conventional originator biopharmaceuticals, CMC units must be set up to develop those precise molecular formats. We will examine which considerations need to be made for the CMC setup along the following four dimensions:

1) Contact with regulatory agencies

Why is it important? While continuing dialogue with regulatory agencies is needed for all molecular formats, the relative novelty of both biosimilars and complex drug product formulations mandates an even closer relationship than normal. The uniqueness of these formulations implies that the regulatory agencies are likely not to know

at the outset exactly what kind of scientific proof is needed for a product to be "good enough" to ensure patient safety. Companies should expect agencies to be exceedingly cautious in granting approvals, making it imperative that the CMC unit stay informed throughout the development process about what evidence will be needed so that it won't be blindsided by unexpected requirements.

The original guidelines for biosimilar development regulation came from the European Medicines Agency in 2005 and the abbreviated pathway for biosimilars included in the U.S. Affordable Care Act in 2010. The rules, however, are still new, and more biosimilars need to enter the market before better clarity will be established regarding the requirements to prove biosimilarity.

Drug delivery systems pose a different concern for health authorities because many of these systems add an extra layer of complexity regarding product formulation that is difficult to characterize fully. So that no time is wasted in CMC, frequent communication with health authorities will be needed early in the process to ensure that the analytical development satisfies regulatory needs.

A key point, emphasized by the FDA, is that the evidence needed for approval of either biosimilars or complex drug delivery formulations may differ on the basis of the pharmaceutical drug. There will be a core set of analytical data expected in the CMC filing and additional analysis on a case-by-case basis that differ significantly among assets. In proving biosimilarity, safety or efficacy, however, the sufficiency of the additional analyses needed is assessed on a case-by-case basis by the specific regulator. A good example is the evidence burden needed to prove biosimilarity between a relatively simple insulin molecule consisting of 51 amino acids not glycosylated versus proving biosimilarity between a mAbs consisting of approximately 1,300 amino acids with multiple glycosylations. The latter will clearly need more evidence to prove similarity. Ensuring that the experimental setup is robust enough through early and frequent dialogue with the health authorities can potentially reduce the need for further clinical trials.

How to do it? Early dialogue with the regulator, specifically on CMC of an asset, helps ensure that the right input is available in a timely fashion. It is important that the regulatory representative responsible is an expert in CMC and quality issues, and not just in clinical development. Regulatory inputs need to be worked into the CMC strategy for the product, necessitating ongoing interaction between the regulator and the CMC representative. This can be best facilitated through a CMC project team.

2) Quality by Design

Why is it important? Biopharma manufacturers have conventionally defined a manufacturing process and sought to perform that process consistently in order to ensure that critical parameters are kept within a narrow range of specifications. This approach has produced safe and efficacious biotechnology products. Any variability, however, in raw materials, environmental controls and so on will result in variability of the product that can potentially lead to batch failure. QbD is an approach to control these problems. Initially advocated by the FDA in its process analytical technology guidance, QbD is intended to yield a better understanding of how variability in process parameters ultimately affects product quality. Ultimately, QbD provides insights into the process parameters that matter most. Having this knowledge builds comfort that the process and the product quality can be effectively controlled. QbD has implementation costs, but its long-term business potential in terms of cost savings and faster time-to-market is very significant (T. Fuhr, 2010).

For complex drug delivery formulations and biosimilars, the advantages of QbD become even more pronounced.

The parameter space for a complex drug delivery formulation is much more complex than for a simpler biopharma product. Liposomes or other nanoparticles, for example, have many process parameters determining shape, size and distribution of the particles, such as formulation temperature profile and stirring speed. Given the vast number of process parameters, it is critical to understand which process parameters have the greatest effect on product quality so as to ensure low variability of the finished product's characteristics. There's another big benefit to QbD: having the parameter space analyzed for quality effect on the product will ease the process of persuading the FDA to approve the product even though only a few previous cases are available for comparison.

For biosimilars, QbD will be critical in ensuring that production costs are low and that time to market is fast by avoiding quality issues that appear in the scale-up process. Having a set of well-known cell lines that serve as "platforms" for biosimilar development could prove to be a viable strategy. With platforms, knowledge of critical parameters affecting product variability and yield can be built in upfront, independent of the molecule being developed, thus easing the task of creating needed QbD data.

In both cases, the arguments for implementing QbD are strong with respect to quickly gaining in-depth knowledge and control over of the drug substance and drug product development.

How to do it? It is important to have the right mindset when implementing QbD. It should be seen not as an extra burden mandated by increasing regulatory requirements but rather as an opportunity to learn, ensure smooth scale-up and simplify future manufacturing operations.

The first step in effectively implementing QbD in biopharmaceuticals is to ensure that the expertise is available and being continuously developed within the organization. To ensure such expertise, a CMC organization needs the right talent and to proactively manage knowledge sharing and training. Secondly, it is necessary to develop a tailored QbD approach to each asset. Completely standardized QbD approaches are likely to be too expensive and not acceptable for all assets, although introduction of tech platforms and standardization will significantly simplify efforts.

3) More analytical capabilities

Why are they important? Relative to originator drugs, biosimilars will typically be produced in different cell lines or under different environmental conditions. They thus may be expressed with subtle but important differences. The FDA believes that three protein properties are highly relevant to these potential differences and must be analyzed: post-translational modifications, three-dimensional structure and protein aggregation. The challenge, however, is that they cannot be measured effectively enough to provide proof of similarity beyond legitimate doubts. Hence, the quest for a continuous analytical method improvement continues.

Using liquid chromatography-mass spectrometry (LC-MS) methods, the primary sequence and the presence and identity of post-translational modifications can be determined. Characterization of the glycosylation present on recombinant proteins is particularly important because the carbohydrates attached to the molecule can modulate the stability and ability of the molecule to elicit its desired effector response.

But slight, nondetectable differences in molecular composition may lead to significant changes in higher-order structure. In fact, many of the forces holding the structure together are weak, noncovalent interactions. To analyze higher-order structure, similarity methods such as circular dichroism, fluorescence, differential scanning calorimetry, analytical ultracentrifugation, and size exclusion chromatography can be used. These analyses, however, do not provide information on which locus on the molecule may give rise to a difference between biosimilar and originator molecules. Protein structural analysis using advanced experiments such as hydrogen-deuterium exchange MS has begun to yield greater insight as to where on the

molecule changes do exist and hence to make a real case regarding similarity.

A different set of analytical capabilities are needed for more complex drug delivery formulation because the formulations typically will comprise a distribution of particle sizes and composition. As a result, the focus is on proving a narrow distribution of the formulation and reproducibility from batch to batch versus proving a unique identity with a high purity. To investigate the size distribution, ensemble techniques such as dynamic light scattering and circular dichroism and single-molecule techniques, such as electron microscopy, are powerful tools to master in order to show that the distribution is narrow and consistent.

How to do it? As regulator expectations will progressively increase; companies will be expected to constantly have products and processes that are characterized by the best possible levels that gold-standard analytical technology will allow.

The imperative is to remain at the forefront of the analytical technology evolution. The implication is the need for an explicit strategy on how to nurture internal, and access external, capabilities. Comprehensive levels of intelligence about which analytical methods exist and are being developed must be mapped against the product pipeline. Given the number of pipeline assets demanding a certain analytical capability, a decision should be made regarding internal development or outsourcing. A contract manufacturing organization is a good choice for noncore technologies. In-house analytical capabilities are the right choice for the analytical technologies in which the CMC organization may have scope to build internal expertise given the pipeline size and composition.

4.) Seamless handoffs and the use of CROS/CMOs

Why are they important? In conventional biopharmaceuticals, there is a handoff of knowledge on the drug substance from the research unit to the CMC functions. This information is built up through a process of target screening, selection and cloning.

When novel drug delivery formulations make the drug product more complex, however, considerable drug product development must be performed in the research phase because formulation is a key driver of both efficacy and safety. In other words, drug substance and drug product will be codeveloped. This may be a challenge because capabilities are generally fragmented among different parts of the organization, with research leading the expertise on development of the biopharmaceutical's active pharmaceutical ingredient and CMC holding the expertise on biopharmaceutical formulation.

Conversely, in the case of biosimilars, the bulk of the formulation development will typically be done in the CMC unit, so the knowledge transfer for generating the drug product will not be that extensive.

Codevelopment of drug substance and drug product in the research phase adds a new dimension to knowledge transfer complexity because it is vital that information about the interplay between drug "substance" and "product" is flawlessly coordinated. High performers take the radical approach of organizing around projects so that they bring to bear all relevant competencies and functions; some, even more radically, create a merged organizational unit that specializes simultaneously in both drug substance development and drug product development.

At the other end of development, with the handoff to production, there must be an equivalently seamless knowledge transfer. The manufacturing organization needs to be involved early to ensure manufacturability of the product. There are added reasons for early involvement with novel formulations, like the imperative to know the effect of scale, which will have a large impact on choices that need to happen in early CMC. Similarly, because many of the technologies will be new, manufacturing needs to be educated by CMC on such technologies and the related processes.

Because many of the technologies needed for these novel formulations are not always available in-house, CROs/CMOs might be involved in developing some aspects of the final product. Taking some of the development outside of the company puts high demands on both parties in the collaboration. For example, the CRO/CMO will be required to carefully document the experimental evidence in development, so that when the molecule is handed back to manufacturing, the right knowledge will be in place to ensure manufacturability. The point is particularly critical when outside resources are used, because manufacturing cannot reach out to the development team as easily as with an in-house development.

For biosimilars, the handoff challenge is different. Because the drug is already known, the research organization does not perform many of the typical activities done for innovative drugs. The main tasks prior to CMC are determining the primary sequence and modification pattern of the originator molecule and cloning that sequence into a suitable host to produce the molecule. In cloning, it is preferable for the host to be one with which the company has previous experience, so as to allow faster analytical characterization and more rapid scale-up. In biosimilar R&D, the research part is limited and does not require the share of work related to product innovation. Hence, the full focus is on the CMC, making the case for pure biosimilar players to integrate into the CMC organization the few

CMC capabilities that are generally anchored in the research part of the organization.

How to do it? An organizational decision must be made about whether the unique skill set needed to develop drug delivery formulations requires the drug product development team to follow the molecule into the CMC process. The handoff/no-handoff choice will be influenced by the number of these "unique skill set" molecules going through the pipeline. If the number is small, the drug product team should follow the molecule to ensure capability continuity in the technically difficult area of drug delivery formulation. If not, when there is a handoff, it will be more extensive than usual. This is because the knowledge of the drug product development is much more complex, demanding a differentiated approach compared with conventional handoffs. A formal handoff of responsibility linked to development milestones does exist, but it is coupled to the commitment of research, CMC, and manufacturing to remain substantially involved throughout the molecule's development journey.

An example of how companies can strengthen handoffs to or from CMC is by having the CMC report in to either R&D or manufacturing, depending on where the most crucial handoffs are seen and where the CMC function can best leverage the existing skill set.

SETTING UP THE CMC FUNCTION FOR SUCCESS

In summary, the new biopharmaceutical era presents challenges and opportunities to CMC units. To succeed, CMC organizations need to focus on three things:

- Improve capabilities throughout the function with respect to regulatory relationships, QbD and analytical technologies
- Ensure that tightly integrated teams are working in organizational setups that guarantee seamless handoffs between research and CMC, and between CMC and manufacturing or that are organized on the basis of product-focused cross-functional teams
- Integrate regulatory input and QbD early in the process of defining CMC strategies and plans

The question facing company leaders is, how can we accomplish these things in an efficient, effective manner?

The solution is to approach CMC like a project organization. The right mix of competencies is important, but even before that comes planning and adequate resource commitment. In this respect, CMC is no different from any engineering or product development project organization. But there is an additional complication: the risk of clinical development failure.

Given the unpredictability of clinical development success, CMC organizations are exposed to fluctuating workloads. Resource needs will be difficult to forecast, all the more so if the unit is pursuing several different molecular formats that require specialized technologies, capabilities and processes. The situation gets worse for those organizations whose pipelines do not have sufficient scale in the pursued molecular formats.

The mark of the effective, well-managed biopharma CMC unit will be its ability to flexibly optimize resources: to power up the right resources to swiftly develop biopharmaceuticals when the pipeline is full and to shed extraneous resources to avoid waste when it is not. CMC will be "living the trade-off" in a space where risk is coupled to critical fast-to-market requirements.

Success will depend on having the right organization setup and resources to finely balance those choices.

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