CPhI Pharma Insights

UBM

Pharma's year of accelerated innovation & convergence

Industry Expert Panel Submissions + Pharma Industry Country rankings for small and large molecules

CPhI Pharma Insights Annual Report

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The CPhI Annual Report is a comprehensive and critically important publication that analyses key trends and innovations forecast by our panel of world class experts. Running as a series of opinions and articles, the CPhI experts call upon their considerable commercial and technical acumen to prophesize the future direction, technologies, opportunities and threats in pharma. It's an essential read for executives who wish to get a head start today on the shape of tomorrow's industry.

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Welcome to the CPhI Pharma Insights Annual Report

Foreword by Orhan Caglayan

It has been a particularly successful 12-months for our industry. We've seen a truly stellar performance from the R&D community, with a record 46 FDA approvals in 2017 and 40 more already in 2018. There are in fact now more products in development than at any other point in history – with 15,000+ in the pipeline. It would not be too bold a claim to say we are entering a 'golden age' of pharma innovation. But as an industry, we can also take great pride in the developments we are seeing across the board – not only in the commercialisation of novel therapies, but in improved techniques and renewed strategies to carrying out pharma manufacturing. We have seen huge innovation in terms of process improvements, whilst advances in flow chemistry, AI and 3D dosage printing are reducing prices and development timelines and increasing patient access. What's more exciting is that innovation is not only being driven by dictates from regulators, but is being created from the ground-up by all types of companies, coming from talented CDMOs, API manufacturers, formulation specialists and generics producers. The industry is, of course, also moving towards large molecules and in response we have launched bioLIVE – our new bioprocessing and manufacturing exhibition, which runs adjacent to CPhI Worldwide. It arrives at a particularly prominent moment, as in the last year we have seen a proliferation of biosimilars and double-digit approvals of biologics – as well as a whole host of investments taking place in contract services. Not to mention ground-breaking innovations, as the EMA approved two gene therapies – Yascarta and Alofise – with a further 1000+ gene therapy products and 600 CAR-T assets under development. In such a dynamic time for the industry, access to insights and analysis are integral to any companies future growth potential and we encourage all pharma professionals to study the CPhI Annual Report closely – both the pharma league tables and our expert contributions. The next year promises huge opportunities and developments.

Orhan Caglayan
Brand Director

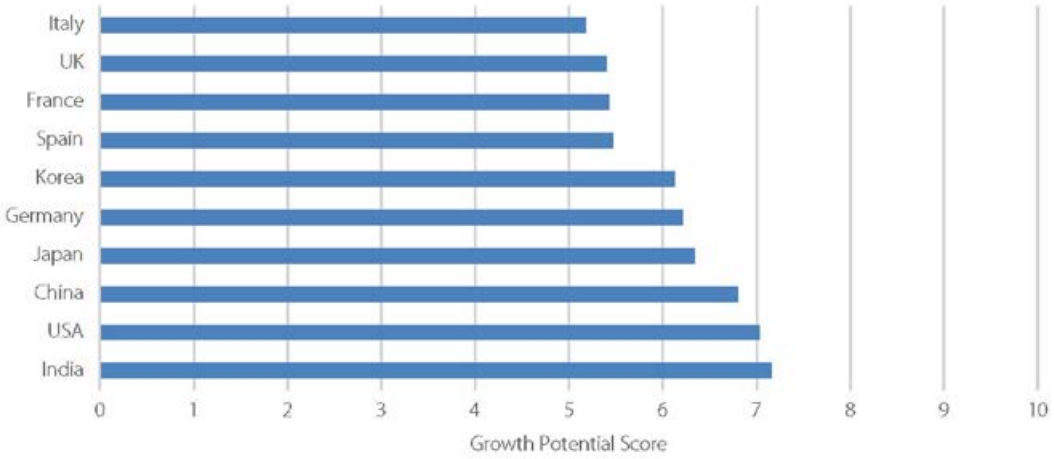
CPhI's Pharma Industry Rankings: **a snapshot of pharma's health**

Reputation matters in a rapidly changing global market and CPhI Worldwide has again surveyed more than 350 of the world's leading pharmaceutical companies and executives to rank the reputations of the most prominent pharma countries. Investment decisions and supply-side arrangements can often hinge on this unspoken influence, particularly when working with new partners. As the world's largest pharma event, with over 45,000 attendees and 150 countries represented, CPhI provides you with a direct window of evidence and analysis on global pharma's overall health. Thanks to our unrivalled industry reach, our survey identifies all the major trends, changes, and developments alongside a 'health-check' on the reputation of each major pharmaceutical economy. The results, as you'll see, include country-specific rankings based on key indicators such as active pharmaceutical ingredient (API) production, innovativeness, market competitiveness, and finished dosage formulations. To celebrate the exciting launch of bioLIVE, our new bioprocessing and biomanufacturing event, this year's anlaysis also explores the ability of countries to meet future bio capacity needs, alongside rankings for bio- innovation and manufacturing quality.

Pharma Market Growth Potential

Unsurprisingly, India (7.16), USA (7.04) and China (6.81) are again the countries executives highlighted as having the fastest growth potential. Respondents cited their high-growth domestic markets and expanding manufacturing exports as the key drivers. The U.S., which has seen a resurgence in the past year, was understandably strong, while Germany was seen as Europe's key growth market. It was notably well clear of France, Spain, the U.K., and Italy. The biggest movers in terms of growth potential in comparison to last year were the United Kingdom, boosting its score by 12.72%, followed by the Italy (+10.94%), USA (+10.63%) and Japan (+9.56%). The big surprise was views of China's growth potential decreasing by 5.34%. This may reflect ongoing trade issues with the US, which is, of course, by far the world's biggest pharma market.

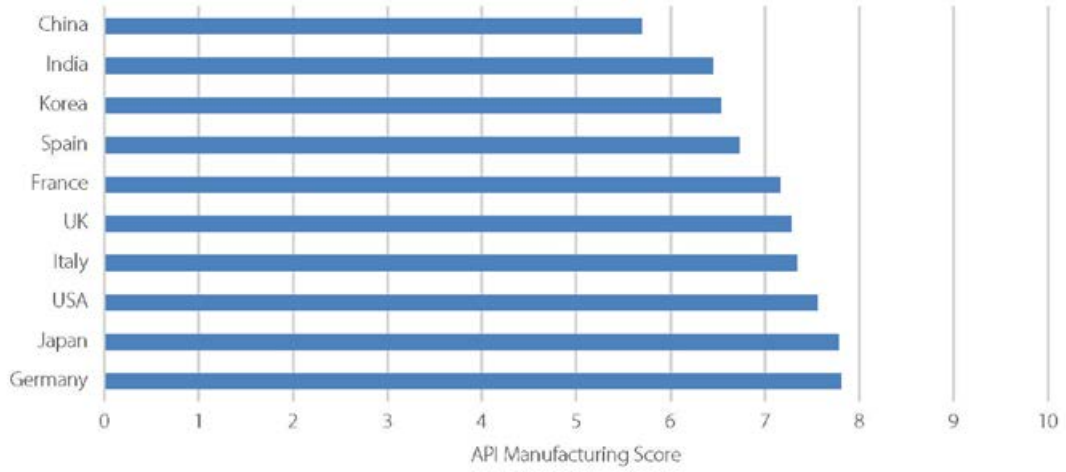
Figure 1: Ranking of countries according to their predicted pharma market growth



Pharmaceutical API Manufacturing

Pharma professionals were asked to rank the quality of pharmaceutical API manufacturing. Germany (7.81) claimed top spot, followed closely by Japan (7.78) and the U.S. (7.55). The research also shows that there is a second tier reputation-wise of well-regarded markets. France and the U.K head this group with Italy just behind. Interestingly, India's recent reputation building efforts may be paying dividends, as its API manufacturing is now seen to be broadly comparable to that of Italy, Spain, and Korea. Italy lead the way in quality of pharmaceutical API manufacturing improvement up 13.54% on last year. China (+10.79%), India (+9.56%) and Korea (+8.91%) round up the top four.

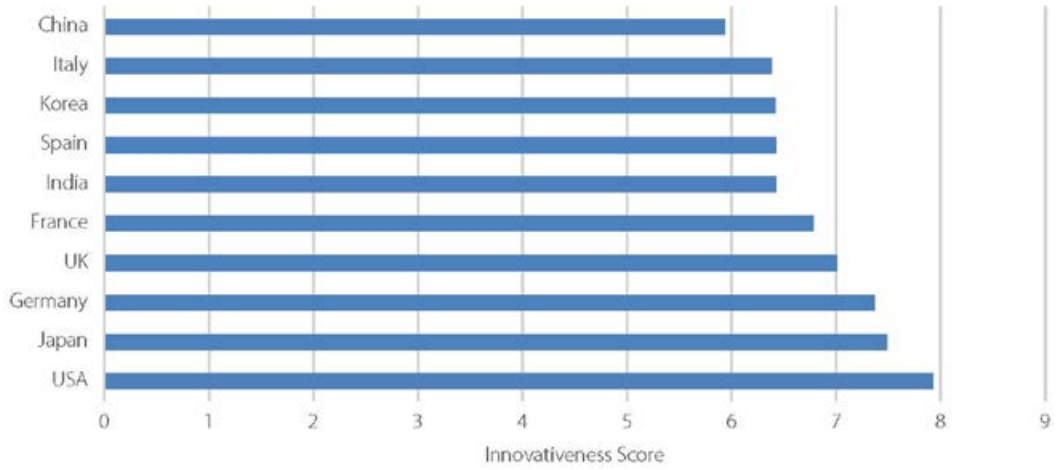
Figure 2: Ranking of countries according to their quality of pharmaceutical API manufacturing



Innovativeness in Small Molecule

Innovation activities are vital for new medicines and the U.S. (7.93) is again the highest-ranking country in this sector. Japan (7.49) comes in second, owing to its historic patent-centric drugs market, excellent reimbursment, and a large number of innovative pharma companies. Germany and the U.K. also scored extremely well. Spain, host of CPhI Worldwide in 2018, was the big mover with a 16.38% increase in comparison to last year. The continuing evolution of the biotech industry in Madrid and Barcelona seems likely to be having positive effects. Italy (+10.80%), India (+10.02%) and France (+8.12%) completed the top four sector movers.

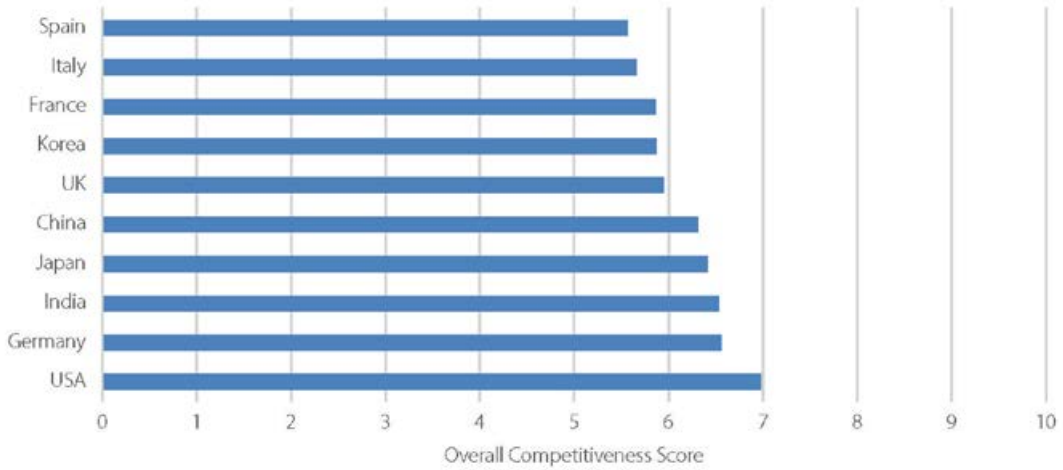
Figure 3: Ranking of countries according to their innovativeness in the pharma industry



Competitiveness

To guage overall competitiveness respondents were asked to evaluate cumulatively each country's tax environment, quality of employees, infrastructure, research potential, labor costs, accessibility, and access to funds. The U.S. (6.98) again topped the pile ahead of Germany (6.56). A strong second tier of countries included India, China, and the more mature economies of Japan, France, and the U.K. Korea also featured prominently because its mix of overall growth and expanding biologics sector. Korea (6.21%) too led the way in improvement on 2017 followed by Italy (6.02%), France (5.50%) and Japan (5.44%).

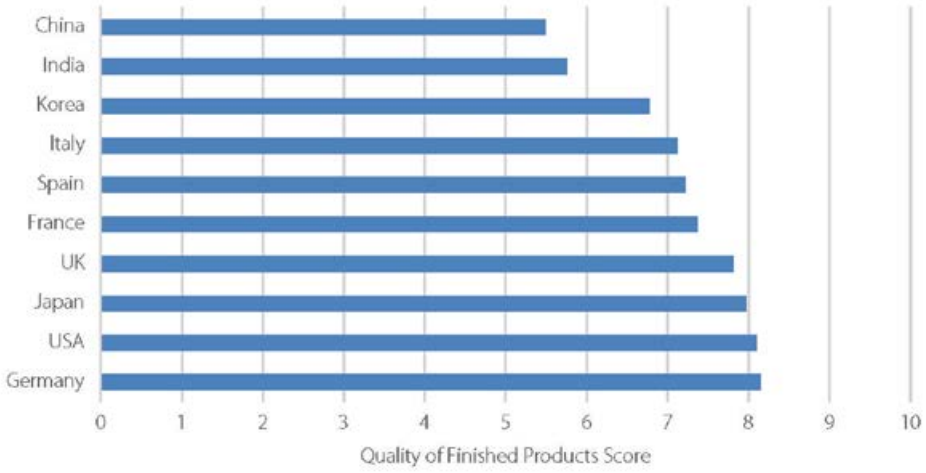
Figure 4: Ranking of countries according to their overall competitiveness



Pharmaceutical Finished Product Manufacturing

Mirroring 2017, Germany (8.07), the U.S. (8.01) and Japan (7.95) are again above all other major pharma economies in terms of the quality of finished formulations driven by the strong standing of their manufacturers and regulators. The second tier includes the U.K., France, and Italy, while India and China were regarded as having lower-quality finished products. The latter's comparable status to India is somewhat surprising given India's more substantial finished product industry. India leads the way in growth improving by 14.72%, but it was closely followed by China, which saw its score increase by 13.74%. Italy (11.90%) and Korea (8.88%) complete the top 4 movers. These findings indicate a a wider trend of perceptions around quality gradualy harmonising as India and China climb to western standards.

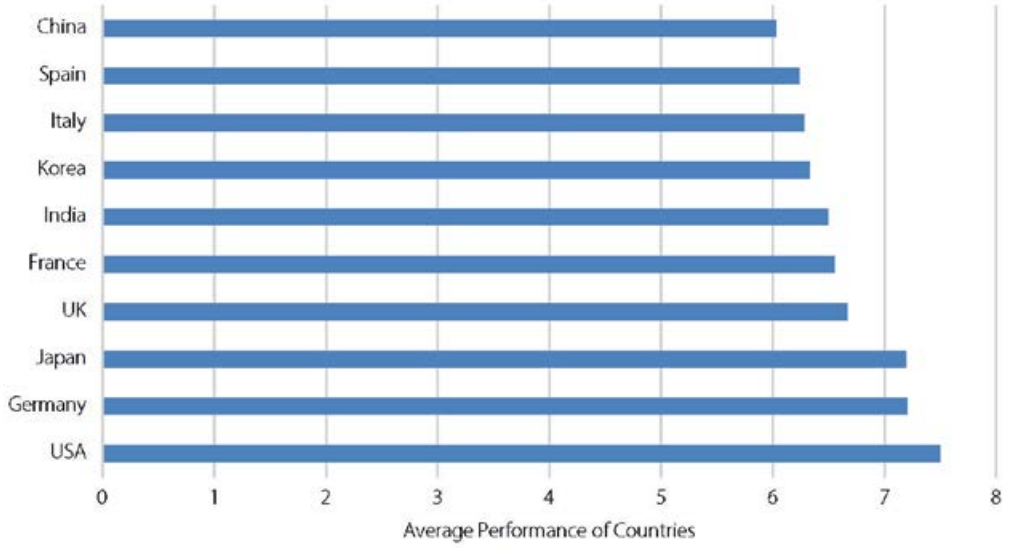
Figure 5: Ranking of countries according to the quality of finished product manufacturing



Country Reputational Ranking

The overall reputation rank of each country is based on an average score across all five categories. The U.S. (7.50) once again claimed first place, thanks to its strong performances across multiple categories. Germany (7.21) and Japan (7.19) followed closely behind. China fagain finished bottom despite leading the growth potential category.

Figure 6: Overall reputation rank of each country

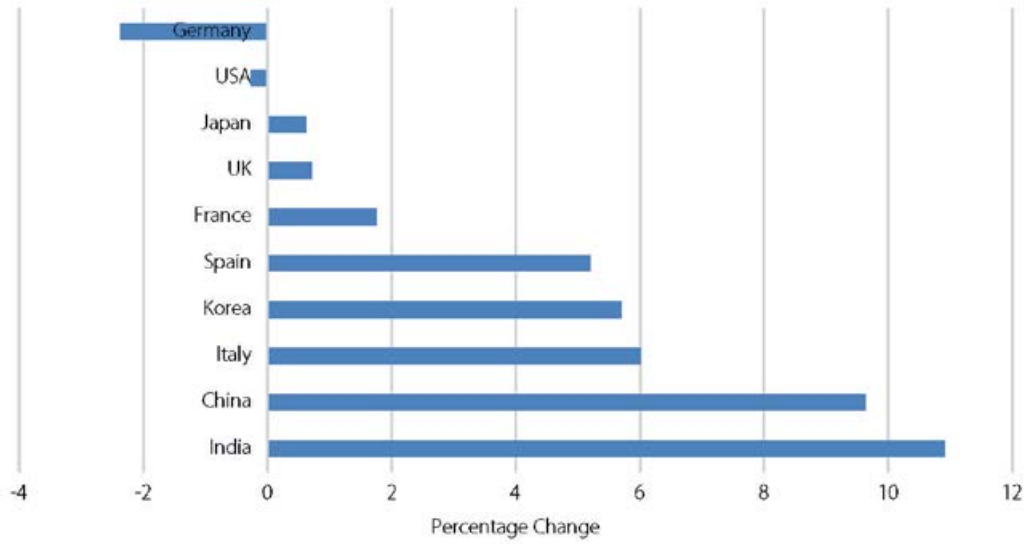


As shown in figure 7, India (10.92%) and China have both made huge strides improving the perceptions with an impressive 9.64% increase in overall score on 2017. This reflects probably an easing of negative news around Indian manufacturing, and China's considerable efforts to impove quality over the last year. In particular, the commitment to harmonise standards with The International Committee of Harmonization (ICH) has been a huge catalyst for improving quality all across the country.

Korea's overall reputation went up by 5.71% due to its mixture of growth and expanding of their biologics sector. The top tier countries saw much more modest gains and Germany's fortunes suffered a notable decline.

"China is issuing new guidelines at a feverish pace and will be harmonised with ICH very quickly. The result is that over the next two to three years poorer qality manufacturers will drop out of the market and China's manufacturers will look to compete in international markets as well as domestic" CPhI Annual Report Expert, Bikash Chatterjee

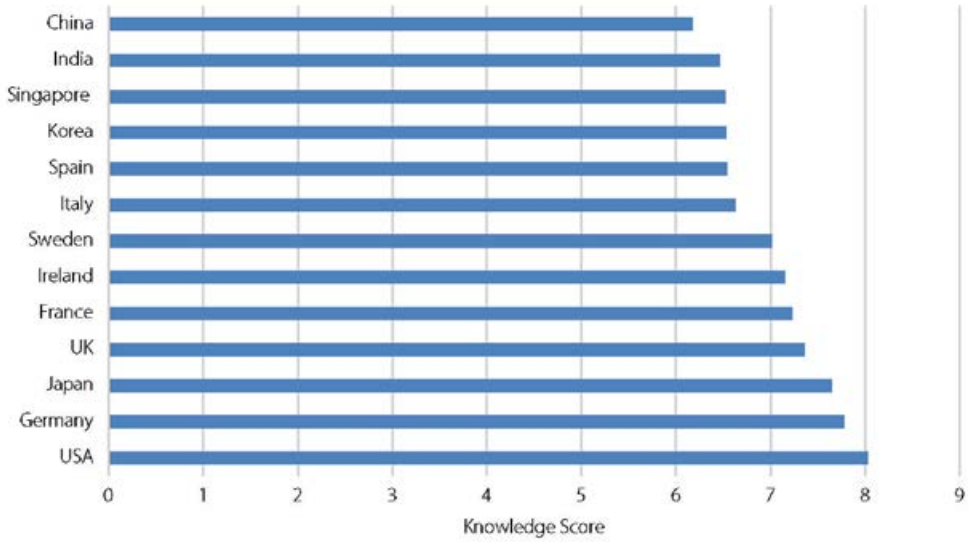
Figure 7: Percentage annual change in overall reputation rank of each country



Country Bio Processing and Manufacturing Knowledge of Biologics Professionals

The U.S. (8.03), Germany (7.79) and Japan (7.65) score the highest for the knowledge of their biologics professionals. The second tier includes the U.K. (7.36), France (7.23) and Ireland (7.16). Ireland's high score in this category can be explained, in part, by new training initiatives brought in by Ireland's National Institute for Bioprocessing Research (NIBRT). China (6.12) and India (6.46) were ranked last and second last reflecting the immaturity of their respective industries. China in particular is experiencing high demand for biologics professionals as its industry continues to grow quickly.

Figure 8: Ranking of countries according to the knowledge of their biologics professionals.

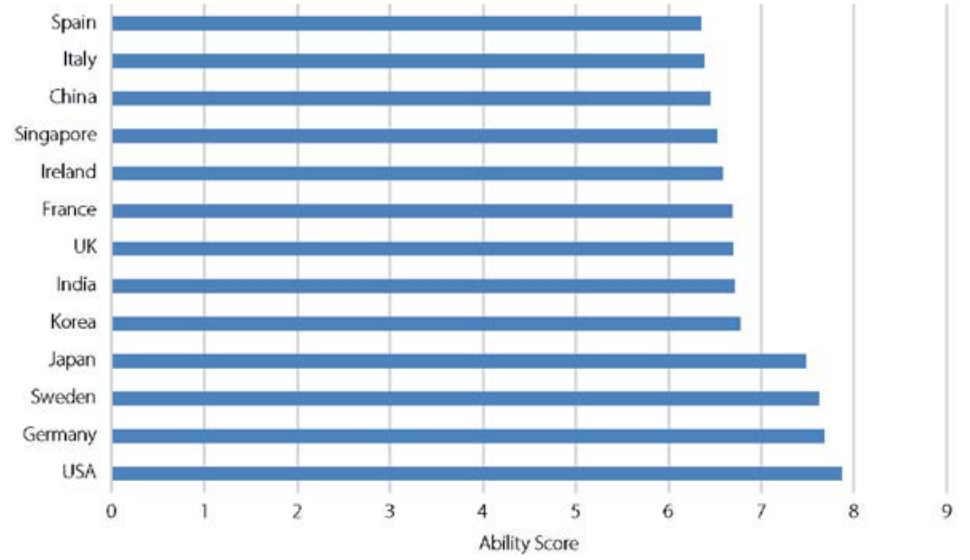


Ability to Meet Future Bio Capacity Requirements

The U.S. (7.87), Germany (7.67), Sweden (7.63), Japan (7.48) led the standings among respondents in terms of their ability to meet future capacity requirements. Below these tier one nations, scores were broadly comparable; from Korea (6.78) to Spain (6.35) at the bottom. These results are interesting as there have been a number of investments made from big pharma and CDMOs, particularly those in Asia in recent years. For example, Sanofi plans to invest around €600 million euros annually for the next few years, BI's €230m development centre, the $240m in capital by WuXi Biologics for a new biologics centre in Northern China, and Samsung BioLogics' recently completed $740m facility in South Korea. Yet, despite the latter two investments, China and Korea scored relatively low. This suggests either perception lacks behind reality, or a belief that demand will increase even faster than the facilities can be completed and/or that there is an existing need for greater capacity in these countries.

Interestingly, The U.S. trails Asia in terms of investment, but still ranked the highest in this category, suggesting that respondents believe that The U.S. already has a surplus of capacity to deal with both current and future industry demands.

Figure 9: Ranking of countries according to their ability to meet future capacity requirements.



Innovativeness of Biologics industry and Quality of Biological Processing

For innovativeness of biologics industry, The U.S. (7.95), Japan (7.62) and Germany (7.37) were, once again, the highest scorers, while China (5.82) and India (6.00) were the lowest. This mirrors their rankings in small molecules for percepetion of pharma innovation.

For quality of biological processing, The U.S. (8.01) ranked highest, closely followed by Japan (7.72) and Germany (7.59), with European countries largely making up the second tier. China (5.61) and India (6.02) finished bottom of the table.

These results reflect the fact that The U.S., Japan and Germany all have established biomanufacturing industries whereas China and India are still developing. Dawn M. Ecker of BioProcess Technology Consultants and bioLIVE expert commented: "If we look at quality and innovation – both important attributes for advancing bioprocessing technologies – the US, Germany and Japan are ranked highest, followed by several other European countries, where biomanufacturing is a mature industry. China and India, both burgeoning markets for biologics, were not ranked as high for innovation. This perception may relate to the still developing biologics and bioprocessing industry in these regions, coupled with the knowledge of their existing reputations for mass production of generics."

Figure 10: Ranking of countries according to innovativeness of their biologics industry.

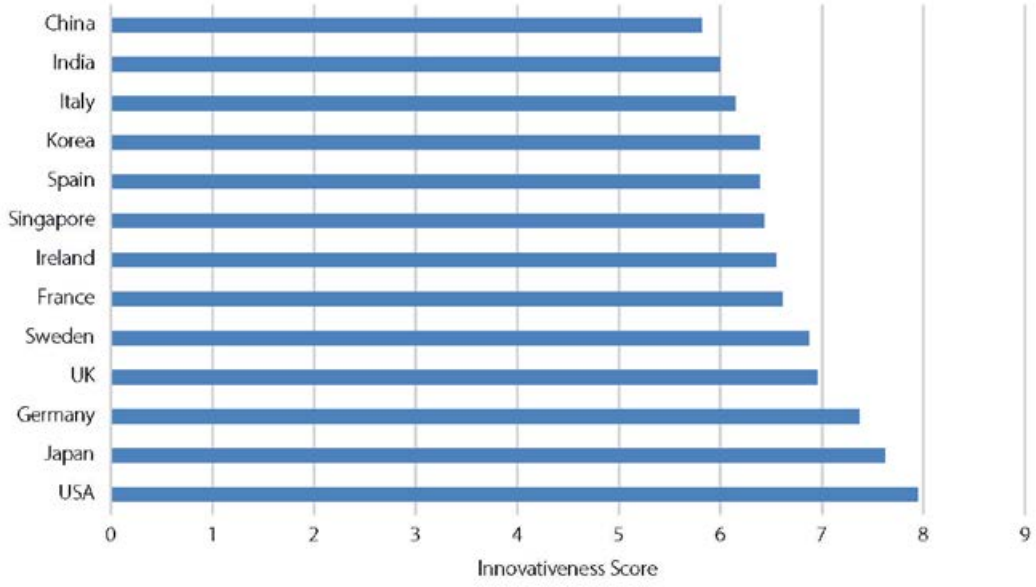
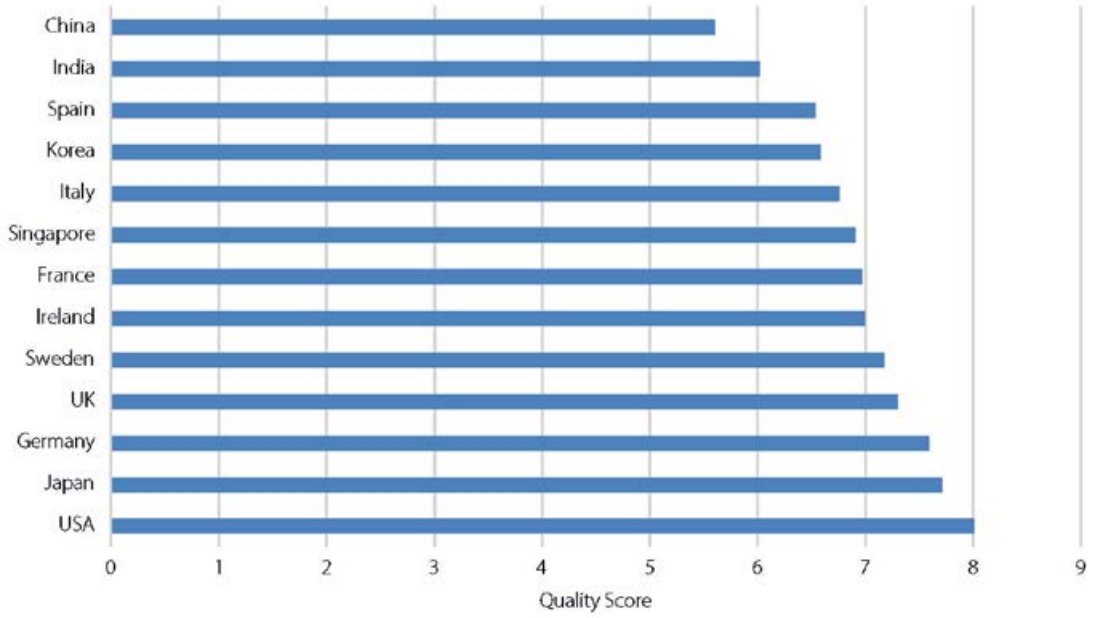


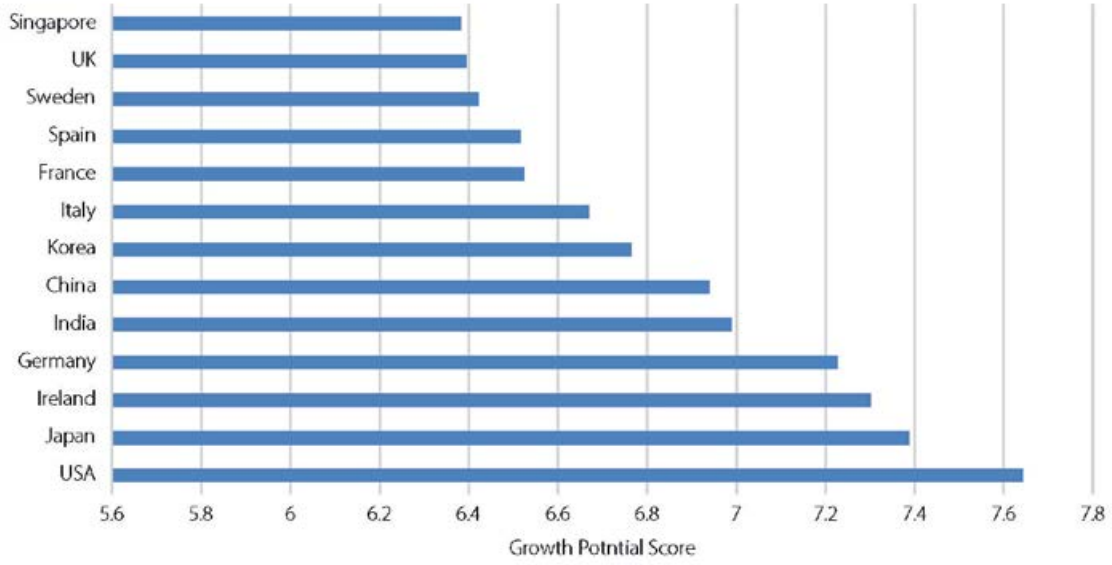
Figure 11: Ranking of countries according to the quality of their biological processing.



Growth Potential of Biologics Manufacturing Industry

The U.S. saw the highest score for growth potential for biologics manufacturing industry. The most interesting result in this category was Ireland (7.30), which was ranked third, placing it above Germany (7.23). The envisaged addition of significant new capacity in biomanufacturing facilities is likely to be a key driver; e.g. WuXi Biologics recently committed to a €325 investment to create the world's largest biomanufacturing facility using single-use bioreactors here. Singapore (6.38) and The U.K. (6.40) were ranked the lowest by respondents in terms of their growth potential. It has been suggested that perception could be lagging behind reality as many of the Asian countries, such as Singapore and China, performed poorly in spite of their rapid development as bio hubs. These nations have a lot more capacity for potential growth compared to countries with mature and well established biologics manufacturing industries like The U.S. However, the perceived growth potential could be a reflection of the opportunity for drug development and reimbursement systems for innovative medicines in the U.S. and Japan. High profit margins, coupled with the strong FDA pipeline (a record 46 FDA approvals in 2017, with more than 15,000 products currently in development), suggest The U.S. market still represents the biggest and best options of many bioinnovators.

Figure 12: Ranking of countries according to the growth potential for their biologics manufacturing industry.



Overall BioRanking

Overall, when an average over all 5 categories is analysed, the USA (7.90), Japan (7.57) and Germany (7.53) emerge as the top nations. This is the same result as seen in small molecule manufacturing. China (6.20) and India (6.44) trailed the field. Surprisingly, other Asian players, Singapore (6.62) and Korea (6.61), did not perform significantly better. Reviewing these results, Dan Stanton, editor of BioProcess Insider said:

"Unsurprisingly, the established American, Japanese and German markets top nearly all the tables, while other Western European countries are also well represented. (Note the UK's low growth potential is likely to relate to the business uncertainties surrounding Brexit, something the Irish market is and will capitalize on.) Unexpectedly, there are some Asian countries which seem low on the list. Singapore has historically been a hotbed of biomanufacturing, talent and quality but may be being held back by high costs and limited expansion space. South Korea, led by biomanufacturing giants Celltrion and Samsung Biologics, is vying to be a major player, and has been active in increasing presence in the space. And China, through ongoing regulatory changes and demand for innovative biologics, is going through a biomanufacturing revolution which seems to have been undervalued in these stats."

As China and its neighbouring countries continue to rapidly develop their biologics industries, perceptions, particularly those centred around these countries' bioinnovation, growth potential and ability to meet future capacity requirements, are likely to change and we could potentially see these countries start to climb in the rankings quickly in the years ahead.

Figure 13: Overall bio ranking.

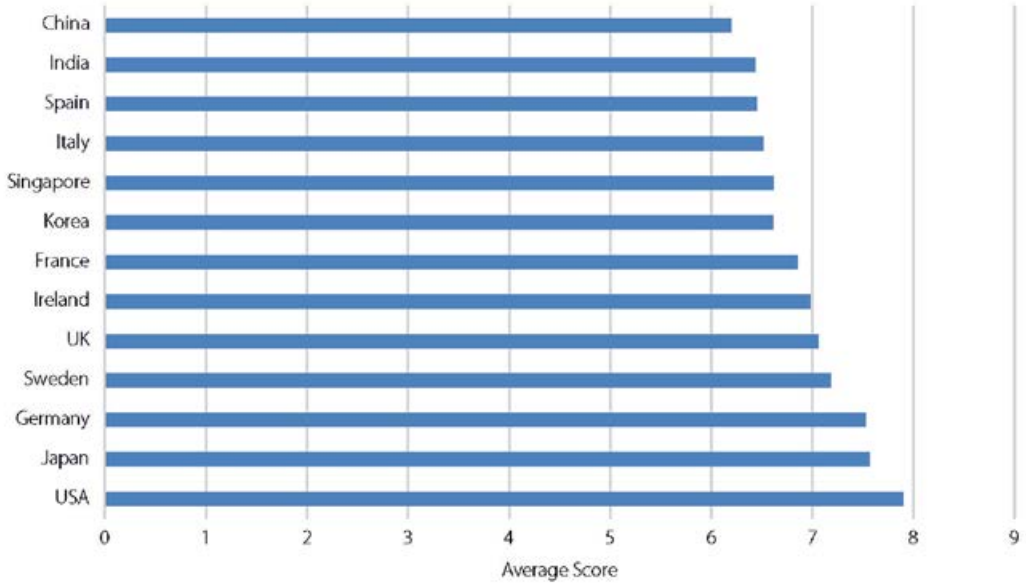


Figure 14: What type of company respondents work for.

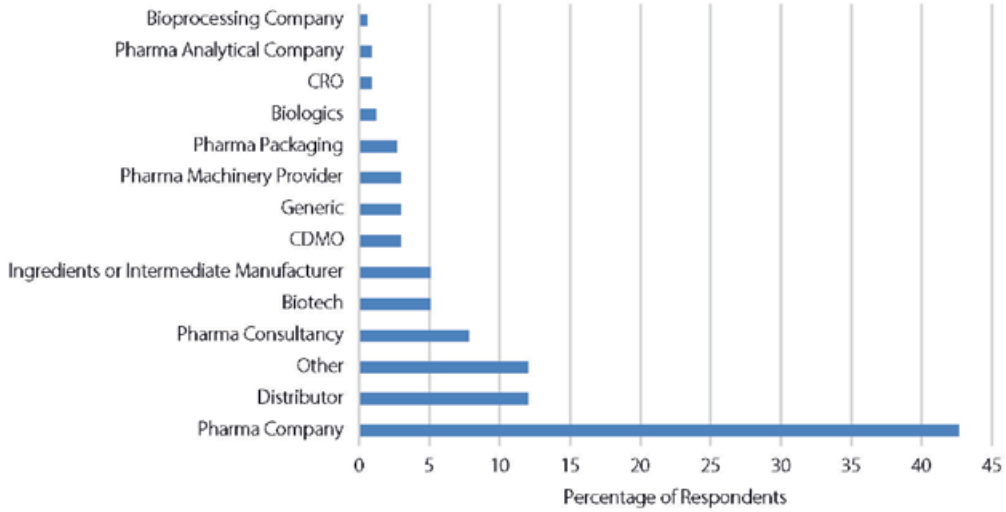


Figure 15: To which markets respondents export.

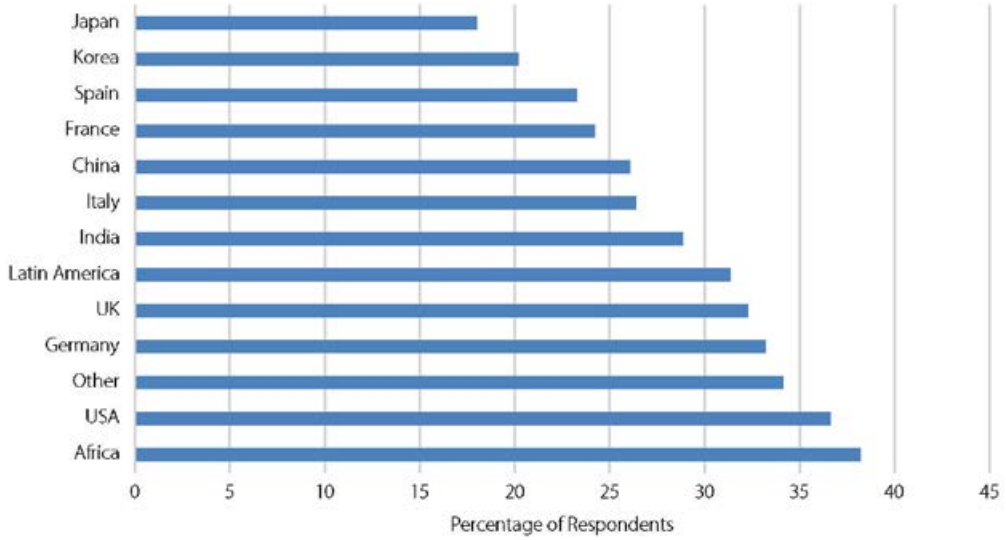


Figure 16: Will Pharma Production/Manufacturing increase over the next five years

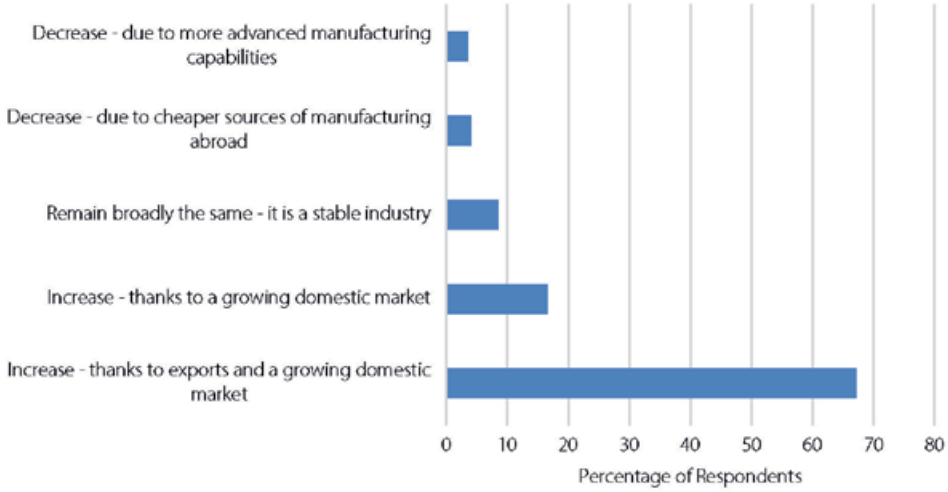


Figure 17: Transparancy index, regulation robustness and corruptness of pharma industry

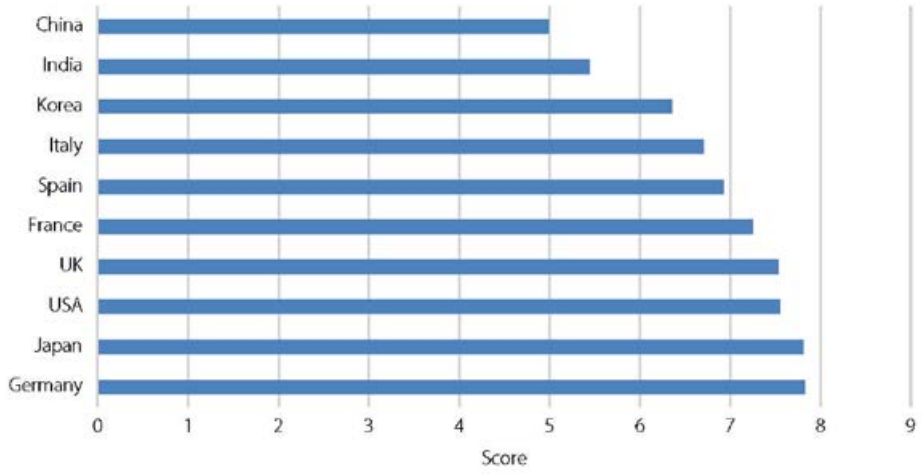


Figure 18: Are respondents looking to work with any foreign partners in the next year

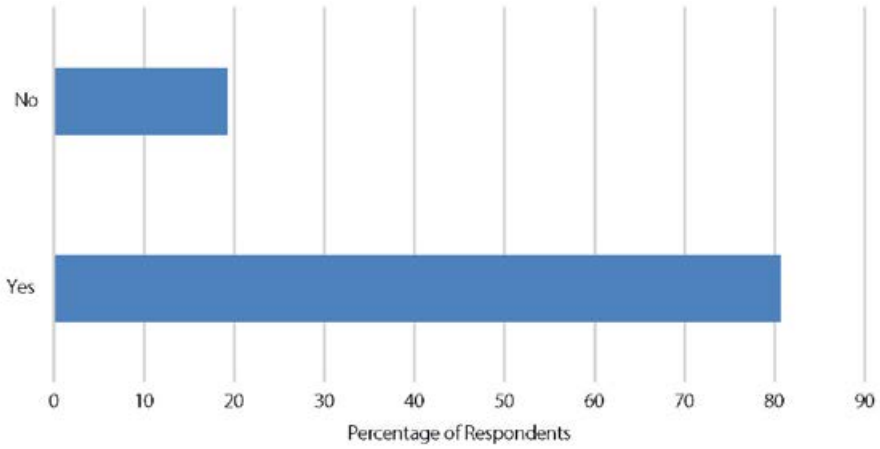


Figure 19: Are respondents currently looking for investment or capital sources

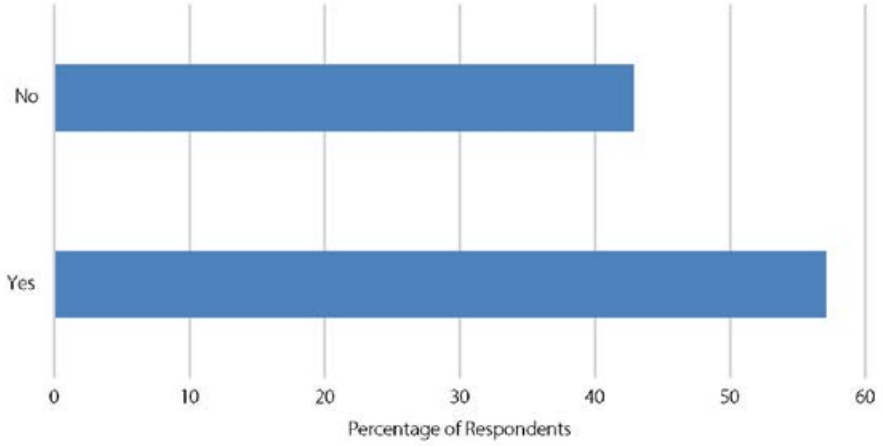


Figure 20: Is it important for the pharma industry that the UK stays in the EU customs union, or has a trade deal with the EU

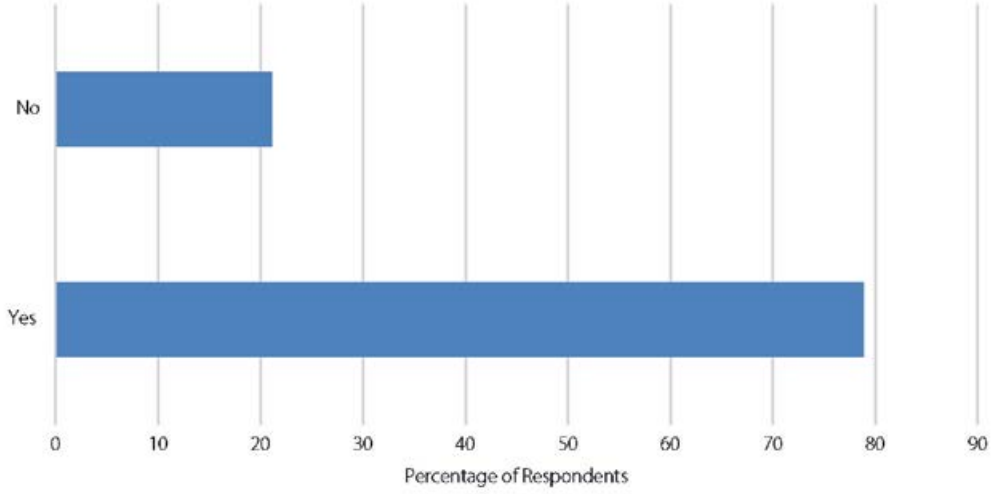


Figure 21: Will leaving the EU increase the cost of pharma production in the UK

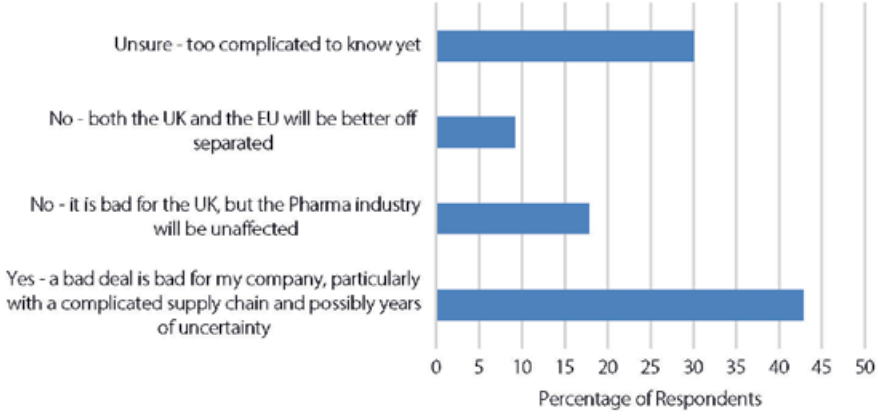
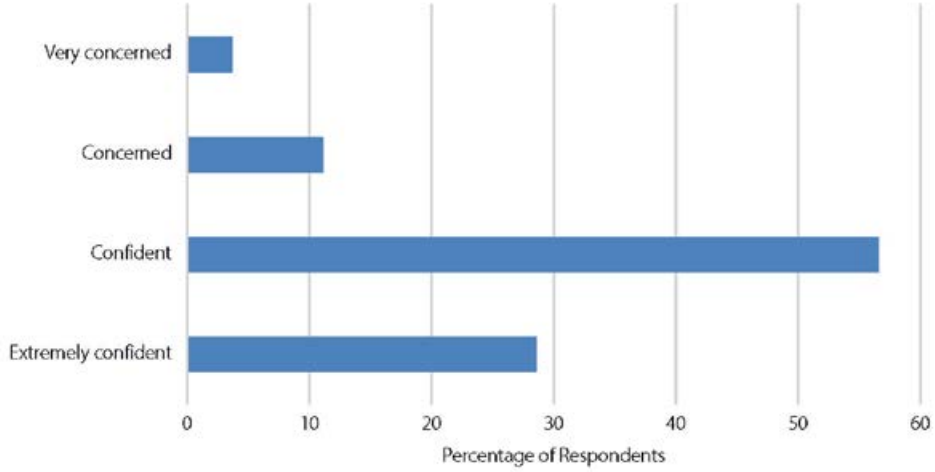


Figure 22: Quality and knowledge of solid dose pharmaceutical professionals

Figure 23: How confident is your business outlook for domestic market in 2018?



CPhI Pharma Insights

Part 1.

Preventing innovation inertia

PANEL MEMBER
Girish Malhotra, President at EPCOT International

Pharma's future is putting innovations in the hands of innovators

Introduction

Pharma's future is putting innovations in the hands of innovators, not regulators – but we need to end the inertia before it's too late

Market Predictions:

- In the next few years we will lose valuable process advances if regulators don't stop dictating approaches.
- The development of a 'cultural dogma' in pharma companies where their approach is only to meet regulations and companies become devoid of process advancements.
- If given freedom by forward thinking pharma companies, CDMOs may have the incentives to innovate new process and manufacturing improvements and be a key part of the solution.
- Is hopeful that if the regulators are listening in the next few years they will enable a manufacturing technology innovation environment by shortening approval time to three months. That way commercial and financial considerations can dictate innovations – e.g. continuous manufacturing is an ongoing case in point

Who is Responsible for Manufacturing Technology Innovation: Product Developer/Producer or the Regulator or the Equipment Supplier or the Contract Manufacturer

Sometimes answer to a question exists and everyone is aware of the answer but is ignored for one self's convenience. However, it is good to ask the question again to refresh and reinforce the existing and an established answer. We all know the answer to the question 'Who is responsible for the product quality and manufacturing process technology innovation for any product?' The answer has been in front of us since the Stone Age. It is 'the manufacturer and manufacturing process developer who is the creator of the product'. Other entities can, and do, assist in the process. But, I am revisiting the question and the answer to ensure that we all are on the same page. It is my perspective and not intended to question the creativity and imagination of any individual or entity.

Since the Stone Age humans have innovated and created products and processes that improve life and lifestyle. Time after time human creativity and imagination has delivered and transformed our understanding through the Stone age, the Industrial Age to the Information Age. Remarkable contributions have been made. As the products and processes developed with time, innovators also realized that every useful product and/or process may and may not be safe for the consumers and workers. However, over time product quality, consistency and process safety

gained importance. Since many products impact human life, regulatory bodies were created to safeguard consistent product quality, integrity and safety. They achieve this by using robust and reliable processes, as a result product quality consistency became critical for the survival of businesses. Regulatory bodies were also created to assure environmental preservation for generations.

Product producers even with the best processes and product quality "at times" live at the edge to maximize their profits. This is true for most enterprises. This is not a bad thing, so long as producers can maintain product quality, their safety and profits.

If we focus on the chemical industry – and that includes pharmaceuticals as its subset – the manufacturing philosophy is to maximize profits whilst retaining product quality and their safety. This is economics 101 and the basic building block of every business. Competitive pressures keep companies on their toes for product quality and safety through manufacturing process technology innovations and continuous improvements. Again, every manufacturing technology innovation has to come from the product manufacturing organization[1,2]. In addition, their incorporation in every process has to be justified. Companies have to make sure that they do not run afoul of the regulatory requirements. If they do, they deserve to be penalized with no exceptions.

Following entities participate in making sure that each manufacturing process and product follow certain norms. Focus here is on pharmaceuticals.

1. Process Developers, Designers and the Commercializers
2. Equipment suppliers including CMOs (contract manufacturing organization)
3. Regulators

Process Developers, Designers and Commercializers

Design of type of process for chemical synthesis and formulation depends on product demand. Generally manufacturing processes fall in two categories batch or continuous. Their definitions are well established[3,4] and accepted for over two hundred years. Chemists and chemical engineers manipulate chemical synthesis steps, unit processes and unit operations, to create an economically viable process. Same happens for the formulations. Understanding and exploitation of physical and chemical properties of chemicals have a significant role in process development, design and commercial operations[4].

Creativity and imagination play a significant part in selection/manipulation of unit processes and unit operations in development, design and commercialization of an innovative and economic process. The resulting innovations can many a time stump even the equipment manufacturers. They, after justification, may be incorporated in the manufacture and formulation of chemicals; pharmaceuticals being a subset of chemicals. Each process especially continuous processes are chemistry, formulation and demand specific. Thus, the philosophy of batch process, that many products fit the same equipment, does not apply for continuous processes.

In the design of a pharmaceutical process and/or product like in any chemical synthesis or formulation process, chemists and engineers are assigned the task of creating the most economically viable process that produces quality products from the get go using safe processes and practices. Actually, instead of being assigned, it is expected they will create and commercialize such processes. They follow what is normally taught in their curriculum and hands-on training. If the commercialized process does not produce quality product the first time, it suggests all of the necessary process design considerations have not been incorporated in the process. Every "t" has not been crossed and every "i" has not been dotted. It could point to

lack of experience and also suggest short comings in their education. If the expected norms are followed, product quality is built in rather than tested in. Harsh words, but shortcomings ultimately lower profits.

However, if an external enterprise suggests/tells a manufacturing enterprise that it has to build quality in their products, the manufacturing organization is essentially being told that it has failed to do what is expected from them – i.e. design and produce quality products from the start. With this lack of a quality culture, long-term viability of enterprises can be in jeopardy. By having outside guidances/directives on process design, quality and manufacturing methods or technologies, I believe our universities are also being indirectly told that they have failed to teach process developers and designers value of innovation and creativity in process design.

As stated earlier product demand and volume dictates the type of process (batch or continuous) that will be used. Investment and profits of the company depend on the process selected. Process type, batch or continuous, have established definitions[3,4]. One cannot and should not ignore these established definitions and misrepresent realities. In addition, one should not, and cannot, create their own definitions to suit their objectives.

Since discussion and use of continuous process pharmaceuticals has become the latest fantasy, it is necessary to acknowledge and differentiate between a batch and a continuous process. Batch processes operate part time during the 8,760 hours that are available per year. Batch campaigns can be done multiple times during the year to satisfy the product(s) demand if the demand is not large enough to operate 8,760 hours per year. A continuous process[5] means an 8,760 hours per year production of a single product with minimal or no downtime. Downtime means the time when the product is not being produced. It includes time for preventive maintenance, generally pre-designated, or time due to fix un-expected process upsets. Downtime for a continuous process is accounted in the product standard cost.

Ironically many drug formulations have the demand to be produced using continuous processes but the producers have opted not to do so. Reasons and rationale are not known. Could it be internal reluctance or tradition? My conjecture "it is the combination". The majority of the APIs, except for less than ten, are produced using batch processes even if they could be produced using a continuous process.

Equipment Supplier and CDMO (Contract Developer/Manufacturer Organization)

My definition of equipment supplier is much broader than the generally accepted definition. I have included contract/developer manufacturer and the equipment supplier in the same category. My basis is that each is a vendor that loans or sells their equipment to a company that needs to produce a product. CDMO can facilitate process development as discussed earlier.

Equipment suppliers provide relevant machineries for different unit processes and unit operations that are used in a batch or a continuous chemical synthesis or formulation process. Each innovates equipment and associated process methodologies to gain edge over competitors. The process developer (client) has to be sold on the efficacy of the equipment or the process. Process economics plays a vital part in equipment/process selection. Financial justification has to be made by the client. It is to be noted that the same processing equipment can be used in a batch or a continuous process. Determination of how the equipment is used is made by the process developer/designer and is based on product demand and is not made by the vendor or the regulator.

Contract manufacturer (CMO) uses client company's process and fits it in their equipment to produce the desired quality product. CMO personnel can be a facilitator and innovator, but they still have to sell their innovations to the product developer. Again, everything has to have financial justification.

The role of regulators

It is my understanding that the primary task of the regulators is to assure consistent and repeatable quality product is available independent of type of manufacturing (batch or continuous) process or for that matter any and every manufacturing process. Regulators have established cGMP practice guidelines that need to be followed. They have the obligation to approve the manufacturing process and the final product rather than endorse type of manufacturing method. As indicated earlier, process selection and product quality assurance are the responsibility of the manufacturing company.

Regulator's endorsement or suggestion of type of processes/methods that should be used, in my estimation, is unethical or is tantamount to favoritism for a type of process and is synonymous to interference in manufacturing company's decision-making process or the equipment supplier's business. It is also, as stated earlier, questioning the competence of chemistry and chemical engineering curriculums of our universities who have trained the best of the best worldwide. If the chemists and chemical engineers at the companies are not continuously creative then our universities and companies have not trained them adequately and our educational institutions as well as the companies have not crafted an environment for continuous innovations and improvements.

FDA's recent blog[6] gives the impression that investing in continuous process will lower costs and produce quality products. This could happen if the process meets the demand and operating criterion outlined earlier. Each continuous process design and equipment configuration are product and demand specific. The blog does not recognize that unlike batch process equipment where many products can be produced in the same equipment, continuous process design cannot be used to produce other products unless the chemical synthesis and formulation needs are exactly the same or are similar. It seems that this is a critical differentiation is not understood by the blog author.

Regulators as well as the product producer, developer and equipment supplier cannot change science based established definitions without due process and public review, which applies to create new or change established definitions. Lately this has been done without any explanation.

Since the regulatory bodies are making suggestions about "how and what" of manufacturing processes, a question needs to be asked is "are these suggestions/ recommendations being made by the personnel with actual hands on experience in process development, design, commercialization and operations of chemical or pharmaceutical plants that produce salable products? Have they justified such investments?" If they have not, I wonder about the credibility and authenticity of their suggestions.

I would also like to ask the regulators "how much effort they have made to simplify the drug filing and approval processes which could immensely lower cost to the approval filing costs[7]?" I believe recently some effort has been proposed, but how long it will take to become a reality is anyone's guess.

More than ten years ago regulatory bodies suggested that the companies should move from Quality by Analysis (QbA) to Quality by Design (QbD). Companies should have questioned this suggestion as QbD is the basic building platform for every commercial process. It is ironic that many companies diverted significant attention to this suggestion as if they were not practicing QbD. It is well accepted that to produce a quality product every company has to have repeatable command of the process, which is QbD. My conjecture is that significant monies has been spent by the companies whether they follow QbD practices. It could have been better spent elsewhere. Did the companies get any return on the monies spent? Most likely none.

I equate such regulatory suggestions to like telling a master chef how to slice and dice onions who practices the art to perfection every day. Since quality issues still persist, my conjecture is that the companies still do not have absolute command of the processes or are not following good manufacturing practices. It is interesting to note that with QbD fervor fading and another fervor (continuous manufacturing) as discussed earlier that needs to meet the established definition and has to be economically justified is taking hold. Continuous manufacturing in pharmaceuticals is a long way from reality[8].

How Manufacturing Technology Innovation Can Become Routine?

Brand and generic pharmaceutical companies due to combination of short patent life after new drug discovery, long regulatory approval times and their ability to secure the demanded selling prices have no desire or incentive to innovate manufacturing technologies. They believe and practice well-known and best processes and methods to manufacture their products.

CMOs, CDMOs and equipment manufacturers have a significant manufacturing role in manufacturing technology and method innovation. However, adoption has to be financially justified.

Regulators have to create manufacturing technology innovation environment. One of the ways I see that happening is to shorten the approval time to three months. This will give companies the freedom and the incentive to innovate and compete on cost and quality basis and allow them to capture bigger market. They will have higher profits. Drug affordability will improve and shortages could reduce also. In addition, regulators have to stop suggesting what and how of the methods and processes companies should use. Companies, as stated earlier, have to justify their investment on the basis of product demand, a fundamental of every business.

I also believe that companies are lost in excessive regulatory guidances and directives that are a distraction to the companies. Regulators are suggesting manufacturing companies to practice continuous improvements for what they practice. Question needs to be asked to the regulators "are they practicing 'continuous improvements also'. If they did costs and time associated with dealing with regulators could be significantly lowered.

Regulators will resist and hedge in giving companies the freedom that would come with short approval times. They still have ultimate control over the companies if they do not produce quality products. It is to shut the manufacturing at the facility down if quality deviations exist and cGMP practices are not followed[9]. Loss of profits alone should be enough incentive to maintain quality and follow good manufacturing practices.

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References

1. Malhotra, Girish: Innovation in Pharmaceuticals: What Would It Take & Who is Responsible? Profitability through Simplicity, November 28, 2017 Accessed July 10, 2018
2. Malhotra, Girish: Pharmaceutical Manufacturing Technology Innovation: Does Reading the Tea Leaves Matter? Profitability through Simplicity, December 22, 2017 Accessed July 15, 2018
3. Batch Production, https://en.wikipedia.org/wiki/Batch_production, Accessed June 20, 2018
4. Continuous Production, https://en.wikipedia.org/wiki/Continuous_production, Accessed June 20, 2018
5. Malhotra, Girish: Chemical Process Simplification: Improving Productivity and Sustainability John Wiley & Sons, February 2011
6. Gottlieb, M.D. Dr. Scott, FDA Budget Matters: Investing in Advanced Domestic Manufacturing, FDA Voice, July 13, 2018 Accessed July 13, 2018
7. Malhotra, Girish: Can the Review and Approval Process for ANDA at USFDA be Reduced from Ten Months to Three Months? Profitability through Simplicity, March 25, 2017 Accessed July 10, 2018
8. Malhotra, Girish: The Good, The Bad, The Ugly (1) Complexities of Pharmaceutical Manufacturing, Profitability through Simplicity, April 9, 2018 accessed July 10, 2018
9. When E.F. Hutton talks, people listen. https://www.youtube.com/watch?v=wd7gC_IZmMM Accessed July 18, 2018

CPhI Pharma Insights

Part 2.

The impact of global regulation, data integrity and convergence

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IPRs in Trade Agreements & Access to Medicines

5-year trend summary

- Global trend towards patent term restoration/extension, e.g. Regional Comprehensive Economic Partnership (RCEP) text seeks to redefine protection period to 20 years from the *date of marketing approval*.
- 'Patent linkage' under Comprehensive and Progressive Trans-Pacific Partnership Agreement (CPTPP) will require [generic company] to gain consent from patent holder prior to use of data in (generic) marketing approval.
- CETA between the EU and Canada has similar patent restoration as does EU-Japan economic partnership agreement.
- The net result of these patent regulations is that patients may need to wait 5-10 years longer for access to generic medicine.
- This will significantly increase the overall cost of healthcare in developed and developing countries by as much as $100 Bn over the next five 5 years[1].
- Unintended consequences: In the medium-term, the pharma industry will likely face a sizeable backlash from the government, health activists, and wider society that may see a fundamental reform of how companies are reimbursed for innovative medicines globally.

Introduction

The new trade regime unleashed by President Trump has heightened trade tensions. The two major trading partners, the US and the EU, are at loggerheads. Trump has frequently attacked the EU for alleged unfair trading practices. His Administration's *Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs* has highlighted "foreign governments free-riding off of American investment in innovations". His focus is on "addressing price disparities in the international market", particularly among the countries that are part of the Organization for Economic Cooperation and Development (OECD). his blueprint states that "U.S. consumer and tax payers generally pay more for brand drugs than consumers do and tax payers in other OECD countries. In effect, other countries are not paying an appropriate share of the necessary research and development to bring innovative drugs to the market and are instead free riding off U.S. consumers and tax payers"[2].

UN Declaration on TB:

As is evident from the fate of UN Declaration on TB, the barriers to access will grow because of many country's reluctance of adding new fronts of conflict with the US. Thus, even without a formal bilateral treaty, the new trade regime unleashed by the US is having its impact on the access to medicines. The draft text of the Declaration[3] shows that it is stripped of the language about the use of TRIPs flexibilities to reduce drug prices under pressure from the US.

Special 301 Report:

The 2018 Special 301 Report released in April 2018 had already indicated a top priority of the Trump Administration "to use all possible sources of leverage to encourage other countries to open their markets to U.S. exports of goods and services, and provide adequate and effective protection and enforcement of U.S. intellectual property (IP) rights"[4]. The report classified Canada, China, Colombia, India, Indonesia and Russia on the Priority Watch List among a list of 12 countries. Their folly:

China
Trade secret theft, online piracy and counterfeiting, high-volume manufacture and export of counterfeit goods, technology transfer requirements imposed as a condition to access the Chinese market, the mandatory application of adverse terms to foreign IP licensors, and IP-ownership and research and development localization requirements.

Canada
The only G-7 country identified in the Special 301 Report. Its downgrade to Priority Watch List reflects a failure to resolve key longstanding deficiencies in protection and enforcement of IP. Counterfeit, pirated goods, weak patent and pricing environment.

India
For lack of sufficient measurable improvements to its IP framework include those which make it difficult for innovators to receive and maintain patents in India. An outdated and insufficient trade secrets legal framework, skepticism about whether India is serious about pursuing pro-innovator and creativity growth policies.

Colombia
Lack of meaningful progress warrants its elevation to the Priority Watch List.

One can go on listing many countries. The common refrain among all of them is "inadequate" IP protection and enforcement. The USTR action on these observations by itself is sufficient to create barriers to access in developed as well as developing economies. The US has been continuously trying to distance countries from any reference to the TRIPs flexibilities: be it Special 301, UN Statement, World Health Assembly or any other forum.

It is against this backdrop that the new trade agreements are taking shape. A preview of some of the key trade agreements indicate hardening of stance on the intellectual property rights (IPRs). This article examines a few of them (CPTPP, RCEP, CETA, EU-JAPAN) to understand how access to medicines will be impacted. The examination is limited to five areas, namely, patent term extension, patent linkage, border measures, protection of undisclosed test data, and use of TRIPs flexibilities for compulsory licensing.

Trade Agreements:

Comprehensive and Progressive Trans-Pacific Partnership Agreement (CPTPP):

The countries have agreed to suspend several IP obligations negotiated earlier under the Trans-Pacific Partnership (TPP). However, there are measures which would have profound impact on the access to medicines. These are:

- **Patent Linkage:** The patentee will be notified of anyone seeking to rely on that drug's clinical trial data prior to granting marketing approval. The agreement provides for adoption of a system that precludes the issuance of marketing approval to a third person, unless consented by the patent holder.
- **Border Measures:** Empowering competent authorities to initiate border measures ex officio[5] with respect to goods in transit that are suspected of being counterfeit trademark goods or pirated copyright goods.
- **IP – An Asset in the Investment Chapter:** Enabling private investors to have the right to use the Investor-State Dispute Settlement (ISDS) mechanism to interpret the IP chapter of the CPTPP and also the TRIPs Agreement.

Regional Comprehensive Economic Partnership (RCEP):

- **Patent Term Restoration:** The RCEP text seeks to redefine the protection period as 20 years from the date of marketing approval. The TRIPs Agreement grants protection of 20 years from the patent filing date. Thus, RCEP proposal could end up granting patent monopoly for more than 30 years.
- **Data Exclusivity:** The RCEP seeks inclusion of Data Exclusivity provision over and above Patent Term Restoration. This would extend monopoly for innovators and delay the launch of generics.
- **TRIPs Plus Enforcement:** It provides for disproportionate damages. It includes any measure of value (lost profits, sales) that the right holder may provide to the judicial authority. It creates obligation on an alleged infringer to provide information about the origin and distribution network of the infringing goods, putting onerous responsibility on a legitimate generic manufacturer.
- **Border Measures:** Border Measures empowers customs authorities to seize goods suspected of infringing patent or trade mark, without the need for a complaint by the rights holder. The TRIPs Agreement empowers competent judicial authorities and not customs officials and also provides for exception in case of goods in transit.
- **IP – An Asset in the Investment Chapter:** The RCEP Agreement may include IP as an asset in its Investment Chapter. It will enable private investors to use the Investor-State Dispute Settlement (ISDS) mechanism to interpret the IP Chapter in RCEP as well as the TRIPs Agreement. There is no such provision in the TRIPs Agreement.

Canada-EU Comprehensive Economic and Trade Agreement (CETA):

- **Patent Term Restoration/Extension:** CETA requires the parties to provide a period of "sui generis" protection to pharmaceutical patents to cover the period between the filing date of the patent application and the date on which the pharmaceutical product was granted authorization to enter the market. This sui generis protection confers the same rights as conferred by the patent and is subject to the same limitations and obligations. It is essentially a patent term extension or restoration for some of the time lost between the filing date of the patent application and the date when the pharmaceutical product was granted market authorization. Though the agreement prescribes certain limitations and exceptions, this provision will allow extended period of patent protection, denying access to affordable generics.
- **Patent Linkage:** CETA provides a "patent linkage" mechanism. Thus, marketing authorization for a generic version is linked to the patent status, thereby denying access to affordable generics.
- **Protection of Undisclosed Test Data:** The Agreement provides six to eight years of protection against generic entry. The only exception is obtaining approval/ authorization from the originator of the data, which rarely works. This clearly goes much beyond TRIPs Agreement and could delay entry of generics beyond expiry of patent.
- **Border Measures:** The CETA provides for suspension or detainment of goods in transit on mere suspicion of infringement of some form of IPRs. This could be done suo moto by the "competent authorities" or on a request of the right holder.

EU-Japan Economic Partnership Agreement:

- **Extension of the Period of Protection for a Patent:** The Agreement provides for "compensatory term of protection" to cover the time taken for marketing authorization. The compensatory term being limited by statute to five years, the extension will deny entry of generic by the extended protection period.
- **Border Measures:** A provision very similar to the CETA ensures suspension or detainment of goods in transit on mere suspicion of infringement of an IPR. This could be done suo moto by the "competent authorities" or on a request of the right holder.

Other Recent Developments:

- Among other developments that would have major bearing on the access to medicines are the outcomes of EU-Mexico negotiations and the NAFTA. The EU-Mexico Agreement in making seems to suggest that it will have "high standards of protection and enforcement beyond TRIPs rules". It has identified three areas, namely, patent term extension, data exclusivity, and protection of plants. These would have significant impact not only on the access to medicines for the people of Mexico, but also the US citizens as many manufacturing plants servicing the US market are located in Mexico and will be governed by the provisions of the EU-Mexico treaty. The Agreement also envisages empowering the customs authorities for targeting alleged IPR infringements.

The other major development relates to NAFTA. At the time of writing this article, the Mexican Secretary of Trade with his negotiating team is in Washington DC. The outgoing President Pena Nieto is keen to strike a deal with the US on NAFTA. It is noteworthy that the USTR is negotiating the NAFTA bilaterally with Mexico, leaving Canada on the sidelines. Any further concession by Mexico would leave Canada in a tight spot.

Summing Up:

It thus appears that going forward, patients may have to wait longer for access to affordable generics. The new trade agreements will delay access to generics. In addition, they would result in higher health expenditure of both the developed and the developing countries. This would be a misfortune for the pharmaceutical industry as a whole. An industry that saves lives of people will unwittingly provide further fodder to the civil society, health activists and the governments to tarnish its image.

References

1 This estimate is based on savings from generics in the U.S. reported by Association for Accessible Medicines (AAM).
2 American Patients First, The Trump Administration Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs May 2018
3 Released on 24 July 2018.
4 Released by the Office of the United States Trade Representative in April 2018
5 For greater certainty, that ex officio action does not require a formal complaint from a third party or right holder

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As Regulatory Philosphies Diverge, the Technology and Innovation Gap Converges Over the Next Decade

Five-year trend summary

- Innovation convergence and science-based approaches will allow for divergent yet integrated regulatory pathways
- China is issuing new guidelines at a feverish pace and will be harmonised with ICH very quickly. The result is that over the next two to three years poorer quality manufacturers will drop out of the market and China's manufacturers will look to compete in international markets as well as domestic
- Over the next five years big data will catalyse drug discovery with R&D leading to quicker advancement of more targeted therapies
- The future will be constructed on science-based regulatory frameworks – for example, with process validation done for individual patients, not batches. CAR-T and NGS have opened up the a regulatory pathways for even 3-D bioprinting of organs to follow

Introduction

It is difficult to remember a time when we have seen such a rapid escalation of groundbreaking technology and science in our industry. The impact of these advancements would have been far less had they been restricted to academia and research. However, the leap to industry was made deftly, within a decade, which in our industry is light speed, fueled partially by a harmonized global shift toward a more scientific-based, rather than a documentation-intensive, compliance and regulatory philosophy.

The International Committee on Harmonization (ICH) has been a huge catalyst for change within our industry at a technical and drug development level, harnessing and coalescing best practices from Europe, Japan, and the U.S. to establish a suite of guidance documents that are universally recognized for their balanced scientific rigor by global regulatory authorities. Combine this with the propagation of the Pharmaceutical Inspection Co-operation Scheme (PIC/S), whose charter is the establishment of harmonized Good Manufacturing Practices (GMPs), and it's easy to see why there has been so much movement in the field of quality to elevate the minimum standards and ensure safe and efficacious drugs on a global basis. Hand in hand with this initiative

is the long-term potential of access to the major markets including the U.S. and Europe if each qualifying nation chose to invest in meeting these higher regulatory standards.

Beyond access to these markets, regulatory authorities also saw an opportunity to conduct international inspections in a more efficient way. Under the Food and Drug Administration Safety and Innovation Act, enacted in 2012, the FDA has the authority to enter into agreements to recognize drug inspections conducted by foreign regulatory authorities if the FDA determines those authorities can consistently conduct inspections that met U.S. requirements. The FDA and the EU have collaborated since May 2014 to evaluate the way each inspects drug manufacturers and to assess the risk and benefits of mutual recognition of drug inspections. To date, 15 countries have been qualified under this program and the U.S. looks to complete its capability assessment of all EU inspectorates by July 2019.

The second largest market in the world, China, is issuing new guidances at a feverish pace, delivering new updates on almost a monthly basis as they strive to establish standards mirroring ICH. The escalation to a higher standard has had a positive effect in the local and global marketplace in that less reputable manufacturers in China are finding it more difficult to get a foothold. However, the rapid evolution of the compliance and regulatory framework challenges ethical drug manufacturers and, in some cases, even regulators, to keep pace with the new regulations. However, the commitment to a higher standard is laudable and will result in a market that is better poised to compete in the world market in addition to the Chinese market.

Data is King

The debate about clinical trial data transparency has raged for decades with advocates crying for greater transparency to avoid bias in published data. In 2015, the World Health Organization (WHO) published a statement that updates and expands their 2005 position on clinical trials registration and reaffirms the ethical imperative to report the results of all clinical trials. Historically, approximately only 9 percent of the data generated as part of the drug development process is submitted as part of a regulatory filing. The EU was the first major market to attempt to legislate clinical data transparency, sparked by a 2013 report from the European Parliament (EP) stating that one of the major problems with the regulation and performance of clinical trials in Europe is the lack of transparency of results. The report concluded that this lack of transparency has reduced public trust in trials and their findings. The EU is looking to issue its updated clinical trial regulation by October 2018 and will harmonize the conduct of clinical trials in the EU while establishing new transparency requirements for the disclosure of clinical trial information, which will require a portal for the publication of clinical trial data within 60 days of a marketing authorization decision.

The U.S. had ignored the issue of data transparency until this year when the FDA launched a clinical data transparency pilot program aimed at making Clinical Study Reports (CSR) public upon approval. The pilot program begins with the recent approval of nine new drugs. So what was once a key point of divergence in philosophy has converged to address the rising need for data objectivity through transparency.

Unfortunately, the U.S. and Europe have diverged when it comes to the issue of data privacy. The EU has enacted the strictest data privacy regulation in the world with its Good Data Protection Regulation (GDPR), which went into effect in May 2018. This sweeping legislation was immediately enforceable by all EU member states and carries penalties starting at 20 million Euros for violations. The regulation advocates the creation of a Data Protection Officer (DPO) to monitor, enforce, and report on compliance with the tenets of the regulation including such rights as "the right to be forgotten" and the "right to consent" that must be absolutely enforced across the entire information chain, including third party entities.

The U.S. has not moved so aggressively. Previously the U.S. and the EU had regulated information privacy via the International Safe Harbor Privacy Principles developed between 1998-2000 but the European Court of Justice declared this regulation invalid in October 2015. The U.S. put in place the EU–U.S. Privacy Shield as a replacement but this again was found to be very weak as it

pertained to the deletion and collection of data. Complicating matters is the current presidential administration position that U.S. privacy considerations will be extended only to U.S. citizens and residents. Clarity is not likely to come any time soon as it relates to privacy in the U.S. The Supreme Court has ruled in favor of data privacy several times regarding the government's ability to obtain data, but as technology continues to evolve look for these principles to be further tested.

Despite these disparate positions we can look for the intelligent gathering and application of data to transform the healthcare landscape

Artificial Intelligence

Few developments have received as much hype as artificial intelligence (AI). AI is often used to describe anything a computer can do as well as a human often as a byproduct of what is called "machine learning." However, the truth is that in medicine many of the current applications of AI rely upon human developed algorithms to do the analysis. Machine learning by contrast utilizes neural networks that are intended to mimic the human brain and its activity. Machine learning can uncover new and innovative approaches to problem solving and do not rely on programmer algorithms. One of the most innovative ways AI is being used to today is to understand colloquial human speech. These applications are being used to provide medical diagnoses and recommend treatment for remote regions of the world where a physician is not available. Combining this capability with machine learning could provide physicians with insight about likely future health events before they occur and recommend potential courses of treatment.

Big Data

Big Data Analytics is the process of examining large and varied data sets to uncover hidden patterns, unknown correlations, market trends, customer preferences and other useful information that can help organizations make better-informed business decisions. Clinical data derived during the drug development process is one of the richest repositories for hidden drug opportunities. Big Data is slowly gaining traction within the life sciences. Big data allows large amounts of data to be analyzed to provide descriptive, predictive diagnostic or prescriptive analytics. Coupled with open source portals such as www.PatientsLikeMe.com where patients can share their health data, the hope is that researchers and patients alike can influence the treatment of their disease and improve their overall outcomes. Intelligent devices, embedded within drug delivery technology, smart pills, lifestyle solutions and diagnostic technology will fuel a renaissance in disease management insight. The science and tools behind Big Data are well defined and the potential for catalyzing discovery and R&D is limitless at this point.

21st Century Cures Act

One of the most significant U.S. legislations impacting the FDA's approach to drug and medical device approval has been the 21st Century Cures Act (Cures Act). The Cures Act was signed into law on December 13, 2016, and is designed to help accelerate medical product development and bring innovations and advances to patients who need them faster and more efficiently. The law builds on the FDA's ongoing work to incorporate the perspectives of patients into the development of drugs, biological products, and devices in the FDA's decision-making process. The Cures Act enhances our ability to modernize clinical trial designs and clinical outcome assessments, which in turn,

will hopefully translate into speedier development and review of novel medical products. It also established new expedited product development programs, including:

- The Regenerative Medicine Advanced Therapy, or RMAT, that offers a new expedited option for certain eligible biologics products
- The Breakthrough Devices program, designed to speed the review of certain innovative medical devices

The Cures Act... is designed to help accelerate medical product development and bring innovations and advances to patients who need them faster and more efficiently.

Most notable was the establishment of a regulatory evaluation and approval path, based upon real world evidence for medical devices[1]. The FDA issued a guidance describing the predicate requirements for pursuing this path and to date the FDA has approved several systems under this regulatory guidance.

The RMAT designation has expedited the approval of many therapies utilizing human tissue, regulating them under Section 351 of the Public Health Service Act, which is considerably less stringent than section 361 for pharmaceutical drug therapies. Many of these products are approved for their mode of action, such as anti-inflammatory or anti-scarring, as opposed to treating a specific disease state. This has broadly introduced such healthcare solutions as a standard of care in for many ailments. The FDA has followed up this legislation with a new guidance regarding Human Tissue that is minimally manipulated, requiring the use of the Biologic License Application (BLA) regulatory pathway to stay on the market. These disease therapies are not going away: they will make the transition to a biologic drug therapy as they present the potential for building on the rapidly growing regenerative medicine marketplace.

EU Medical Device Regulations

The EU has moved in the other direction however, from the U.S. The new EU Medical Device regulations (MDR) have made significant changes that will take full effect by 2020. The MDR will change the way medical device manufacturers bring their devices to the European market, and how they maintain compliance throughout the product's life cycle. The regulation actually modifies the classification of some devices that have been CE marked and approved. The new regulation requires manufacturers to address the additional requirements prior to the 2020 deadline or face having the products withdrawn from the market! Under the MDR, there is a much greater emphasis on more thorough reviews by Notified Bodies to confirm manufacturers are fully compliant and devices are fully supported by adequate data and technical documentation. The MDR's requirements for acceptable clinical evidence are stricter as well so it is very likely you will need new data and updated, robust clinical evaluations for most legacy devices.

Science-Based Regulatory Framework

While there are divergences between the U.S. and EU's regulatory philosophy, they both have their foundation in a desire for risk-based control derived from scientific insight. Next Generation Gene Sequencing (NGS), which was originally approved under a 510K waiver has evolved to where it can meet the requirements of a Pre-Market Authorization as a Companion Diagnostic, allowing physicians the ability to pinpoint the genetic modifications that drive the disease state, and apply a drug therapy specifically designed to target that anomaly. To do so required the FDA to deal with a number of paradigm-shifting issues. Huge data sets are generated as part of the NGS process that is known to be only 97% accurate. Data integrity of 400,000 data point per run had to be developed and explained to the FDA. The assay used control regents with 100-200 oligonucleotide sequences blended together

requiring the agency to shift its expectations of process validation. The same can be said for the latest Chimeric Antigen Response-T Cell (CAR-T) therapies. These CAR-T therapies are personalized to an individual and again required shifting the FDA's expectation regarding process validation as only one batch is made per patient and each batch is unique to that patient.

In the future we will have additive manufacturing being routinely used for medical devices and 3-D bioprinting systems that will be able to build replacement organs that are fully biocompatible with any prospective patient. These technologies are in development today. CRISPR-Cas9 has allowed us to customize DNA sequences and even allowed us to embed technology that replicates them. A team of scientists in 2017 embedded a video in bacteria DNA[2]. The scientific tools available today provide the opportunity for unparalleled insight and understanding that will translate into lower regulatory risk.

Next Generation Gene Sequencing allows physicians the ability to pinpoint the genetic modifications that drive the disease state, and apply a drug therapy specifically designed to target that anomaly.

Conclusion

The foundation for the next generation of drug therapies, devices and diagnostics will rely heavily on data and analytics to drive insight and understanding. The regulatory philosophies of the U.S, and Europe are not completely aligned in their approach to fostering innovation while ensuring patient safety. We have, however, seen groundbreaking drug therapies and diagnostics approved in the last five years that position regulatory bodies to embrace these new innovations. Whether risk is managed via enhanced control and oversight, such as with the EUs GDPR legislation, or is a by-product of intelligently gathered real-world data, as provided under the US's 21st Century Cures Act, the regulatory evaluation in each framework required to evaluate these new technologies will be grounded in today's scientific tools and analytic techniques.

References

1 FDA Guidance for Industry: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf

2 Who needs film when you can store a movie in bacteria DNA? LA Times, http://www.latimes.com/science/sciencenow/la-sci-sn-dna-movie-20170712-story.html

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Great Expectations: Pharma vs Excipient Data Integrity

"Take nothing on its looks; take everything on evidence. There's no better rule."
–Charles Dickens, Great Expectations

Introduction

Data integrity refers to the completeness, (logical) consistency and accuracy of data over its lifecycle, and is applicable to both paper and electronic records. Data must be accurately captured, and that accuracy must be maintained during data storage, replication, transfer, and processing. These activities have the potential to degrade or compromise the data. Error checking methods and validation procedures ensure the data remains intact and unchanged. Data security prevents unauthorized alteration of data. The term data integrity may refer to a state (the dataset is accurate) or a process (measures to ensure completeness, consistency and accuracy).

Data integrity is key to demonstrating compliance with Pharmaceutical GxPs, such as manufacturing, documentation and laboratory practices. Failure to ensure data integrity is a breach of cGMP. In 2016, 80% of the FDA Drug Product and API warning letters included a reference to the lack of data integrity, mainly due to incomplete data. (Unger 2017)

In this article the term "maker" refers to the excipient manufacturer or supplier and the term "user" refers to the finished drug product manufacturer or customer that uses the excipient.

Regulatory Requirements

Several regulatory agencies have issued guidance documents in recent years on data integrity.

- FDA (2016) Data Integrity and Compliance with CGMP Guidance for Industry
- EMA (2016) Data Integrity
- PIC/S (2016) Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments (Draft 2)
- WHO (2016) TRS 996, Annex 05, Guidance on good data and record management practices
- TGA (2017) Data Management and Data Integrity [follows PIC/S 2016]
- MHRA (2018) GxP Data Integrity Definitions and Guidance for Industry

While no regulatory guide explicitly references excipients, the draft PIC/S guidance refers to raw materials which may be understood to include excipients. The guidance in section 10.1 "General supply chain considerations" states;

Data integrity plays a key part in ensuring the security and integrity of supply chains

10.1.1 Data integrity plays a key part in ensuring the security and integrity of supply chains. Data governance measures by a contract giver may be significantly weakened by unreliable or falsified data or materials provided by supply chain partners. This principle applies to all outsourced activities, including suppliers of raw materials or contract manufacture / analytical services. (PIC/S 2016)

It should also be noted that the WHO guide references contract acceptors/suppliers from the perspective of the pharmaceutical manufacturer, which can be interpreted to include excipient suppliers.

"The principles of these guidelines apply to contract givers and contract acceptors. Contract givers are ultimately responsible for the robustness of all decisions made on the basis of GXP data, including those made on the basis of data provided to them by contract acceptors. Contract givers should therefore perform risk-based, due diligence to assure themselves that contract acceptors have appropriate programmes in place to ensure the veracity, completeness and reliability of the data provided" (4.4)

All six guidance documents follow the definition embodied by the 1990s FDA acronym "ALCOA"

- **Attributable**
  Data must be attributable to the person generating the data. Who performed an action and when? This can be recorded by initialing and dating a paper record, or by audit trail in electronic records.
- **Legible**
  All data recorded must be legible and permanent, even if corrected or updated.
- **Contemporaneous**
  Recorded at the time of task or measurement. Date and time stamps should match order of execution and data should never be back dated.
- **Original**
  Original data, recorded for the first time in database, approved form, or a dedicated notebook. Recording results on paper for transcription later can introduce errors. If hand written data or thermal printouts need to be stored electronically, verified "true copies" may be needed.
- **Accurate**
  Free from errors, reliable, truthful and reflective of the observation. No editing without documentation/ annotation of amendments.

Implicit in the above-listed requirements for ALCOA are that the records should be complete, consistent, enduring and available. To emphasize these requirements the following terms are sometimes added and referred to as ALCOA+ (WHO)

- **Complete**
  Includes any test, repetition or reanalysis performed. Data (records)
- **Consistent**
  Logical structure. E.g. date and time stamps reflect sequence of events.

- **Enduring**
  Sustainable records systematically documented in laboratory notebooks or validated systems.
- **Available**
  Accessible for review, audit or inspection over the lifetime of the record.

There is no difference in expectations regardless of which acronym is used since data governance measures should ensure that data is complete, consistent, enduring and available throughout the data lifecycle. (MHRA 2018)

Excipients vs API and Drug Product

Excipients are much more diverse than APIs; excipients having compositional and molecular weight polydispersity, and excipients often extracted rather than synthesized, from operations such as harvesting and mining. An important distinction of excipients is that they are typically manufactured by continuous processes and in much greater volumes than would be encountered in the Pharmaceutical industry, which is still developing its own understanding of continuous Pharma manufacturing. Generally, most excipients were not designed for pharmaceutical use and seldom developed for specific formulations, but excipients have long histories of patient safety via various routes of drug administration or from legacy applications as food additives.

The various data integrity guidance differs slightly in approach and specific details but are intimately bound to the wider regulatory framework of GMP and good documentation practices, which are based on APIs and drug products. Pharmaceutical usage may only be a small part of a specific excipient market, so most excipients are not manufactured under API or drug product ("Pharma") cGMPs. Excipient GMPs may be used such as "The IPEC PQG Joint Good Manufacturing Practices Guide for Pharmaceutical Excipients" or NSF/IPEC/ANSI 363-2016 "Good Manufacturing Practices (GMP) for Pharmaceutical Excipients". Food ingredients used as excipients should be manufactured under Food GMPs. Some suppliers may sell to the pharmaceutical market and leave it to the users to establish pharmacopoeial compliance which means limited compliance with GMP. The further one gets from pharmaceutical cGMP the less likely it is that detailed data integrity expectations will be met. ALCOA principles are good business practice in any commercial sector, but judgement will be required in the application of specific Pharma data integrity requirements to excipients.

With excipient GMP on a sliding scale, users should anticipate varying degrees of applicability of specific Pharma data integrity requirements. Therefore, users need to define which specific data integrity requirements are expected from their excipient manufacturers. This is anticipated by the MHRA guidance which states that the implementation of measures to ensure data integrity should be commensurate with safety of the ingredient used...

"The scope of the measures taken should be commensurate with the risks to data integrity, the type of decision that the data is relevant for (e.g. whether decisions relate to product quality or safety) and the importance of the data in making such decisions. The guidance provides factors that senior management should take into account when assessing risks such as the complexity and consistency of data processes, subjectivity of outcomes, and vulnerability of data to involuntary or deliberate amendment or deletion."

Based on the known marketed applications of their materials, excipient manufacturers should define which records are necessary to support their GMPs and the measures taken to ensure data integrity. If a customer uses an excipient for a novel application without the knowledge of the excipient supplier, the customer creates both safety and regulatory risks. Examples would include the use in injections of grades not intended for injectables, or use of excipient as an active ("atypical active") in the drug formulation. Since excipients are often manufactured in great volumes for markets other than pharmaceutical, very few excipient manufacturers would be willing or able to comply with ICH Q7 requirements for APIs, and the corresponding data integrity burden.

Communication is key but the WHO guidance states that quality agreements include:

"the need for risk-based monitoring of data generated and managed by the contract acceptor on behalf of the contract giver."

"The increasing outsourcing of GXP work to contracted organizations, e.g. contract research organizations, suppliers and other service providers emphasizes the need to establish and robustly maintain defined roles and responsibilities to assure complete and accurate data and records throughout these relationships. The responsibilities of the contract giver and acceptor should comprehensively address the processes of both parties that should be followed to ensure data integrity. These details should be included in the contract described in the WHO GXPs relevant to the outsourced work performed or the services provided."

It should not be assumed that excipient manufacturers lack adequate control of the integrity of their data when they do not literally follow the regulatory guidelines. Excipients may come from continuous high-volume hazardous processes. Investment in, and design and safe operation of such plants under multiple regulatory jurisdictions is not possible without reliable supporting data. Only a subset of this data, which may be distributed across multiple sites and databases, supports excipient GMP compliance. The Pharmaceutical proportion of that excipient usage may also be small. The details of data integrity principles found in the guidance documents will not necessarily be applied across all manufacturing data collected.

A common expectation is for excipient manufacturers to provide validation reports for their excipients, analogous to those generated by Pharmaceutical companies during API and Drug Product development. FDA requirements are very specific in this respect: -

"In computer science, validation refers to ensuring that software meets its specifications. However, this may not meet the definition of process validation as found in guidance for industry Process Validation: General Principles and Practices: "The collection and evaluation of data … which establishes scientific evidence that a process is capable of consistently delivering quality products. See also ICH guidance for industry Q7A Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, which defines validation as providing assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. For purposes of this guidance, validation is being used in a manner consistent with the above guidance documents." (FDA 2016)

"Validation" may be interpreted by technologists in an engineering-based "does it work?" viewpoint, whereas pharmaceutical quality and compliance professionals see "validation" as also encompassing data integrity, personnel qualifications, training, risk assessments and other cGMP requirements. Excipient manufacturers may not have formal validation reports but generally have years of process statistics to demonstrate their process capability and control to consistently produce quality product.

Other than the legally mandated requirement for users to confirm the identity of each consignment of raw material, there is no reason for users to routinely repeat compendial compliance testing on each received batch of raw material (21 CFR 211.84). As part of the strategy for assessing data integrity in the supply chain, the draft PIC/S guidance suggests that results of raw material testing by the pharmaceutical manufacturer be compared against those of the excipient manufacturer (10.3.4).

"Compare the results of analytical testing vs suppliers reported CoA. Examine discrepancies in accuracy, precision or purity results. This may be performed on a routine basis, periodically, or unannounced, depending on material and supplier risks".

If done routinely this would imply lack of knowledge or lack of trust in the supplier data integrity, in which case, should a supplier with more reliable results be sought? Outsourced clinical or analytical testing would not similarly be routinely duplicated by the user. Marginal compliance with raw material specification on a frequent basis is cited as an incentive for data falsification but it could also be due to lack of sufficient process capability, or inhomogeneity.

The draft notes that the supply chain relies upon the use of documentation and data passed from one organisation to another, and that it is often not practical for the contract giver to review all raw data relating to reported results. Emphasis should be placed upon robust supplier and contractor qualification, using the principles of quality risk management (10.2).

PIC/S also suggests the contract giver (user) may offer Supplier use of their own hardware and software system (deployed over a Wide Area Network) to use in batch manufacture and testing, so that the user may monitor the quality and integrity of the data generated by Supplier in real time. For excipient manufacturers, it would be more realistic to offer users access to the manufacturers data for multivariate oversight.

"The expected data integrity control strategies should be included in quality agreements and in written contract and technical arrangements, as appropriate and applicable, between the contract giver and the contract acceptor. These should include provisions for the contract giver to have access to all data held by the contracted organization that are relevant to the contract giver's product or service as well as all relevant quality systems records. This should include ensuring access by the contract giver to electronic records, including audit trails held in the contracted organization's computerized systems as well as any printed reports and other relevant paper or electronic records." WHO 7.5

Big Data in QbD

Traditionally, pharmaceutical companies performed full compliance testing on each received batch of excipient which meant that less emphasis was placed on supplier Certificate of Analysis (CoA) data integrity. Where users rely on data from qualified suppliers without confirmatory testing (21 CFR 211.84), supplier CoA data integrity is critical. Pharmaceutically aligned suppliers utilize controlled platforms such as LIMS and SAP like those used in the Pharmaceutical industry.

From an QbD perspective, reliance on purchased CoAs fails the ALCOA criterion of completeness. The number of batches purchased may not be sufficient to statistically represent supplier performance. Access to all CoA data over a period of time gives a more representative picture of supplier process variability for that timeframe. In turn, the CoA data is only complete if there are no out-of-specification (OOS) excipient batches. Full batch data including OOS is necessary for assessment of supplier process capability. It should be noted that for some excipients produced to serve multiple industries there may be "second quality" markets for material outside the Pharma specification. Recycling of material would also need to be taken into account in determining process capability.

Many excipients are produced by high-volume continuous production. Of necessity CoA values will be either average or composite results. If an excipient attribute is critical to finished product quality the user may wish to have access to in-process data for better risk assessment of that excipient variability and intra-batch homogeneity on the drug product performance.

QbD drives utilization of more data from excipient manufacturers by pharmaceutical companies, beyond the traditional CoA. It is unlikely that pre-existing systems dating back years if not decades were designed with the data integrity requirements of the end-pharmaceutical user in mind. If the data is used for information only and does not control finished product safety or quality data integrity is less of an issue. At the other extreme, real time release (RTR) of continuously produced pharmaceuticals utilizing supplier data would require maximum data integrity. If using Process Analytical Technologies (PAT) to control RTR, does signal quality of the excipients become a specification parameter?

A second driver to greater utilization of supplier data is the need to demonstrate user oversight of supplier quality. Users are strictly liable for the quality and GMP of their suppliers, including data integrity.

Multivariate quality control is superior to the traditional univariate statistical process controls (SPC) and multivariate monitoring of supplier data by users is an effective means of demonstrating oversight.

Sharing of data by excipient manufacturer with users may require confidentiality agreements to maintain the manufacturers' proprietary know-how. There may also be restrictions on use of the data in patent applications and regulatory submissions.

Why is data integrity different for excipients?

Industrial control systems are often more focused on safety. Changes to address Pharma requirements may have unintended consequences. It is not easy to harden/improve compliance without revalidating safety critical systems. Excipient manufacturers typically use networked control systems to afford remote monitoring and control, in contrast to the small-scale batch operations, typical of Pharma.

Many legacy control systems used by excipient manufacturers make data attribution difficult because their control systems are open. If a specific operator is not identified for every action it may be possible to ameliorate by shift rosters, physical access security, training, or a control/data entry log. The degree of GMP at various stages of production may influence the extent of data integrity. For example, purification or isolation stages may render preceding steps less critical (also common for APIs).

Many industries, including those manufacturing excipients, use redundancy, with multiple sensors and in process tests to reduce dependence on a single data stream. In contrast, pharmaceutical operations are often dependent on a single sensor, which places more emphasis on validation and calibration. Multiple sensors allow voting and reduce dependence on calibration. Data integrity is at a system level higher than that of the individual sensor.

High frequency testing, using "quick and dirty" (nonspecific) methods or sensors, outweighs a limited number of test results from more precise but onerous methods. A better population estimate is obtained, and sampling error is reduced by higher frequency testing, which compensates for lower data integrity at the level of individual measurement. High frequency automated data capture reduces potential for operator error in sampling or testing. The consistency of surrogate signals can be used for online monitoring with more specific methods to investigate changes.

Increasing utilization by users of supplier data may also pose data retention challenges for the supplier. What data should be retained, for how long, and should it include metadata to enable interrogation of dynamic records? Audit trails and security access controls would be needed for such data. The data retention period could be linked to retention samples, but the excipient manufacturer needs to define this.

User considerations for reliance on third party data sets.

If data integrity is uncertain (paper or electronic) the questions to assess the risk are:

- Will patients/consumers be injured?
- Will product quality be jeopardized?
- Will compliance with any cGXP be uncertain?
- Will there be increased risk of product liability?
- Will there be costs of the poor data quality?
- Where on the continuum (information-only to control signal) will the data be employed?

This analysis will allow development by the user of a prioritized data integrity plan in order to:

- Make product safety decisions.
- Make product quality decisions.
- Prove compliance with:
  - Regulation or statute
  - Guidance document
  - Quality Agreement
  - Other Commitments

Data integrity must be balanced against utility when using a variety of large externally sourced datasets for novel analyses. It is difficult to retrospectively implement controls for validating the data at point of creation or capture, and correcting errors may cause inconsistencies.

Rather than trying to control the data creation to preempt errors, the focus changes to identifying inconsistencies and standardizing the data.

It is important to note that the user may not be able to impose specific data integrity requirements on the maker. If pharmaceutical consumption is minor and the requirements too onerous, without commensurate return on investment, there is a risk of the maker withdrawing from the Pharma market if no longer economically viable to serve. In the large plants producing excipients there is a bias towards simplification and commodity volumes versus complexity and specials. Pharmaceutical requirements that can be met with incremental investment, and which does not increase operating costs to serve majority markets, are more likely to be accepted.

Quality culture is perhaps more important than integrity of specific data. Pharmaceutically aligned excipient manufacturers should have the personnel, expertise, training and a culture for employees to raise issues and follow good data governance. It will then be much easier to deal with any mismatch in data integrity expectations between user and maker.

"All actors in the supply chain play an important part in overall data integrity and assurance of product quality."

"Data governance systems should be implemented from the manufacture of starting materials right through to the delivery of medicinal products to persons authorised or entitled to supply medicinal products to the public." WHO 7.1

References

EMA (2016) Data integrity

http://rx-360.org/wp-content/uploads/2016-EMA-QA.pdf

FDA (2016) Data Integrity and Compliance with CGMP Guidance for Industry

https://www.fda.gov/downloads/drugs/guidances/ucm495891.pdf

MHRA (2018) GxP Data Integrity Definitions and Guidance for Industry www.gov.uk/government/uploads/system/uploads/attachment_data/file/412735/Data_integrity_definitions_and_guidance_v2.pdf

NSF/IPEC/ANSI 363-2016 "Good Manufacturing Practices (GMP) for Pharmaceutical Excipients https://standards.nsf.org/apps/group_public/download.php/36444/NSF%20363-2016%20-%20watermarked.pdf

PIC/S (2016) Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments (Draft 2)

https://picscheme.org/layout/document.php?id=715

TGA (2017) Data Management and Data Integrity

https://www.tga.gov.au/data-management-and-data-integrity-dmdi

The IPEC PQG Joint Good Manufacturing Practices Guide for Pharmaceutical Excipients https://ipec.org/sites/default/files/files/20170323%20IPEC-PQG%20GMP%20Guide_Final.pdf

Unger, Barbara. An Analysis of FDA FY2016 Drug GMP Warning Letters, Pharmaceutical online, Jan 16, 2017 https://www.pharmaceuticalonline.com/doc/an-analysis-of-fda-fy-drug-gmp-warning-letters-0001 WHO (2016) TRS 996, Annex 05, Guidance on good data and record management practices http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

CPhI Pharma Insights

Part 3.

Opportunities and threats from continuous processing and opioid quotas

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Continuous Manufacturing: What is/ is not Happening and Why

Five-year trend summary

- Huge opportunity for China to be the fastest adopter to Continuous Manufacturing in the next 5-years.
- Predicts that generic manufacturers and CMOs will all need continuous manufacturing facilities to complete within 10-years
- Warns biosimilars may well bring prices down in the short-term, but warns in the longer-term will remove incentives to perform innovative research.
- Big pharma will reinvest profits and bring down cost meaning its products, once off patent, can compete with generics. Big pharm that declines to invest will be left behind, especially as development timelines could be sped up by 6-months in one year with CM (no scale-up).
- A convergence of more advanced equipment, competitive pressures, a wider pool of trained scientists and the backing of regulators will see exponential growth of continuous manufacturing over the next 5 years
  - initially these may not be optimally economically efficient, but in 5 years these will bring in tremendous economic and business process advantages, including faster and more efficient drug development

Introduction

A number of years ago, while I was a high school science teacher (a mere four years, but worthwhile), I was addressing some young people at a science fair. I did not go with a set agenda but wanted to field questions about science. One youngster asked about robots and when they will be coming (remember, this was 20+ years ago). I outlined what a robot did, in simplest terms: it 1) performs a simple operation, over and over, 2) without constant intervention, and 3) needs occasional calibration. When I asked what would qualify, only one young lady stated, "a clock." Indeed, she nailed it.

She saw that, no matter how complicated a machine becomes, each part only performs a simple task. A gear rotates; a spring slowly uncoils; the hands (independently) move at a constant rate, and so on. In Physics, when describing any complex motion, it may be broken down to any point in the motion, where its X, Y, and Z vectors can be measured. The entire waveform, no matter how complex, is merely a summation of these simple points. In a similar analogy, the process of assembling a pharmaceutical dosage form is a series of very simple machinations: weighing, pouring, mixing, wetting, drying, sieving,

tableting, and coating may all be broken down into very, very simple motions.

Thus, whether the tablet is made over several weeks/months or in minutes, the actual physical steps are the very same. The difference in the time scale is solely from the "finish-one-step," stop, store, test, "move-to-new-location," repeat steps until the product is complete. The difference in time scales is simply the intervention of operators and physical movement of the in-process materials from step-to-step. Adding continuous monitors and connecting the steps in a single location is named "continuous manufacturing (CM)." Well-known in almost every other manufacturing industry, it is a recent "Johnny-come-lately" to the Pharma and Biopharma industries. The companies who have begun using CM have enjoyed (overall) success, making product faster and with virtually no rejects. The movement from development to full-scale production, skipping the scale-up step (as much as six months) brings the product to market faster.

The question is no longer, "Will Continuous Manufacturing work?", but "When will everyone be doing it?"

The question is no longer, "Will Continuous Manufacturing work?", but "When will everyone be doing it?" There are still many objections (from "the usual suspects") including (but limited to),

1. We've never done this or we have no one with experience on staff.
2. We have so much money invested in traditional equipment, so why spend more?
3. We can't get it past Quality Assurance (QA) – a cry against ANYTHING different,
4. We have no place to set it up, and the most common excuse,
5. We've always done it this way (and, its twin: "we've never done it that way")

If you squint your eyes and look through a pair of reversed binoculars, you can see these arguments applied to the "large" commercial tablet presses in the 1940s; assembly lines for cars in 1905; interchangeable parts for airliners in 1920, and almost any innovation over the last 150 years. In truth, these people tend to defer to "common knowledge" such as "a train can never go above 40 MPH (67 KPH) because people couldn't breathe at that speed" rather than try to prove whether something will or won't work.

Indeed, as my father told me, "If you don't want to do something, you will find an excuse; if you want to do something, you will find a way." We also have industry "experts" who declare that Pharma and Biopharma can't do PAT/QbD/CM because, no matter how quickly steps are enhanced, it is merely a batch-driven technology, so CM cannot be applied. They see CM as week-long moving product processes.

In the 1970s, the Japanese surfactant manufacturers used CM in its simplest form: a long line of railroad tank cars, containing fatty alcohols or fatty acids; a second string of cars, on an adjoining track there was a string of cars with chlorosulfonic acid, a third (smaller) line of cars contained caustic (NaOH solution), and, lastly, a line of empty tank cars. The fatty acid/alcohol is mixed/reacted in a larger tube, transferred to a second reactor to be quenched with the caustic, then continuously pumped into the empty railcars.

The "pharmaceuticals can't be done this way" crowd seem to miss the crux of the matter: detergent brings manufacturers pennies per gallon as a profit, while (top selling) drugs can glean dollars to thousands of dollars per tablet. There has been far less financial impetus to streamline the process, when compared with consumer products. There have always been dozens of laundry detergents on the market. They do not have the same kind of patent protection as a new drug entity (NDE), where the sole provider of that drug can charge whatever they wish with no concern of economizing the production process, so they need to generate the best product possible as

quickly as possible. In the new economy, the new "fight or flight" reaction may be expressed in economic terms: "modernize or close your doors."

In short, no one does anything unless they feel a need. As long as the U.S. Congress, for example, has a political agenda to allow companies to charge whatever they can for their products, even for products off-patent. E.g., following the announcement last week that Pfizer would increase the price of dozens of drugs, President Trump took to Twitter to lambaste the company, saying that it should be "ashamed." Initially, Pfizer defended its decision and said the new prices weren't likely to impact consumers. But now, Pfizer's CEO has said it will delay the scheduled price increases until January first and give the president "an opportunity to work on his blueprint to strengthen the healthcare system and provide more access to patients." Part of the changing landscape is that Pfizer (like many established Pharma giants), is facing an aging population and many older products going off-patent, and so, is reshaping its structure into three businesses.

These include Innovative Medicines (biological science and a new hospital medicines business), Established Medicines (to include sales for older drugs like Lipitor and others that have lost patent protection) and Consumer Healthcare (for over-the-counter medicines). This seems to be an industry-wide trend and places production costs under a new microscope. With multi-country competition (especially those with far lower labor costs), many nations imposing pricing restrictions, and the cost of R&D not becoming lower, simply raising prices to consumers is rapidly becoming a liability, no longer the "go-to" choice.

The companies are also outsourcing much of their work as they shrink to "virtual" companies, concentrating on R&D. They are using contract manufacturers for packaging (old-hat), distribution (also, been around for a while), and now, for manufacturing off-patent products (to compete with generic houses), and even some research (adding to the previous relationships with research universities). As the supply-chain (everything from raw materials through delivery to pharmacies and hospitals) stretches over thousands of miles and dozens of countries, the crux of the problem can be distilled to one word: Quality.

Now, when our industry began as a commercial enterprise (around WWII), it moved from the back rooms of pharmacies (chemists to Europeans) to factories. The rules, as is the case for any innovation, lagged behind (e.g., road rules, following the popularity of automobiles). When a neighborhood pharmacist made a lot of 50-100 pills (no longer made, replaced by tablets) or capsules, "quality" merely meant using proper materials and accurate weights. The earliest production facilities could only produce product in the thousands, so the USP suggestions for analysis were deemed sufficient. In reality, compendial tests are almost all for identity (is it lactose?), purity (heavy metals, moisture), and final assay (originally monographs cited titrations, now chromatography). The analysis situation 60-70 years ago was clearly different from today in several ways:

1. The original compendial tests assumed that
   a. All APIs were synthesized in-house or purchased from domestic sources, both under FDA (or EMEA) surveillance.
   b. Excipients were obtained domestically from sources that were under FDA or (EMEA) supervision.
   c. Suppliers were meticulous and "tests" were merely to assure the correct grade of material.

2. The supply chain was far different then, but has changed in several ways:
   a. A typical Pharma company will purchase most, if not all APIs from third-party suppliers, often in different countries.
   b. Excipients are also purchased, if not directly from other countries, then from distributers who, in turn, purchase from multiple countries.
   c. Many larger Pharma houses (and generics) produce products in other countries where they source their own APIs and excipients; seldom can any Agency find all the sources without some difficulty.

So, you may well ask, "how can we assure product quality AND consistency from country to country?" Well, the first attempt was to initiate the USFDA PAT (process analytical technologies) draft Guidance in 2002 (final 2004). Its purposes were:

1. To assure the grades and purity of API(s) and excipients: ID, polymorphic forms, particle sizes, residual solvents, crystallinity, etc.
2. To check each step:
3. To use the monitoring data from each step to (eventually)

control that step, assuring each point of the process was in control.
4. Assure both quality and consistency throughout each process and from batch to batch.

With PAT in place, manufacturers had control and a HARD COPY of data proving they were in control, THROUGHOUT the process. The fine-tuning Guidance concerned Quality by Design (QbD), where known and/or unexpected variation in raw materials and intermediate products were anticipated and the effect on the final product was known, allowing operators to (the collective gasp you will hear is from "old-school" QA people) make changes to the process to assure compliance with known acceptable product parameters.

OK, now we have the tools necessary to assure that a product being made in France is (essentially) the same as in the US or Poland or Malaysia, with a "paper-trail" to show how the process proceeded. As new, rapid, reliable monitoring tools became available, pure economics dictated where materials were purchased or fabricated. Now that spectrometric methods can assure similarity or equivalence of materials, we simply need to assure that the final products are equivalent.

We work on the assumption that, with guidelines from ICH, FDA, and EMA for the calibration, validation, and application of spectrometers in pharmaceuticals, performing an analysis in Thailand will give the same results as would be seen in Switzerland. What has not been standardized is finished product analytical methodology and in-process controls. Let us assume for a moment (I am blindly optimistic here) that all jurisdictions suddenly homogenize finished product specifications. NOE, we can work on making the same product at every location.

How, you may well ask? Continuous manufacturing (CM), I respond. When you are monitoring every material (from weigh-additions to final dosage weight) at every step and using those data to control every step, there is a pretty good chance that the product from country/location "A" will be almost identical to that from country/location "B."

For those (small minority of people) who are not familiar with CM, it consists of a multi-story facility where the raw materials (API and excipients) are in dispensing hoppers. These are dispensed by weight into some blending apparatus, often a screw-type blender. This blender has (at least) one monitoring point, normally for a NIR fiber probe. And further blending (as with a lubricant), drying, etc. is also monitored by NIR, Raman, etc. The tablets are monitored, as is any coating process.

The beauty of this technology is multi-faceted:

1. Scale-up is unnecessary, since development scale-batches are the same as production-scale batches (which are just run longer).
2. Clean-up is simplified.
3. Development (DoE) is faster and cheaper, since smaller lots are made and as many as 30-40 batches can be generated (and simultaneously analyzed) in a few days vs. weeks for "traditional" sized lots.
4. And, most importantly, lot #1 will be the same as lot #1,000,001.

So, to paraphrase my financial guru (Jack Carroll), "you don't have to use PAT, QbD, or CM; neither do you have to remain in business."

This article has been abridged from the 2018 CPhI Annual Report, the full report can be found at: **https://www.cphi.com/europe/pharma-insights-reports-cphi-worldwide**

There is a symbiotic relationship between analytical instruments (including operating software) and the processes they measure. Remember how the personal computer began as an expensive (Apple IIe was US$ 2500 in 1985: dual floppy disks, 64K memory, etc.) oddity and improved as demand increased (a typical laptop has between 250 GByte and 1.0 TByte storage and many magnitudes or speed enhancement can cost well below US$ 1200) the computing power both improved and cost came down. As far as data storage, a "thumb-drive (small USB removable-storage solid-state device) with 1.0-32 MByte of storage once cost US$ 25-50 and was an oddity. Now, these are given away in lieu of paper information by vendors at trade shows.

NIRS instruments, for example, in the mid-1980s were sensitive bench-top units that took a minute or two to analyze a single sample. The computers were slow and many had NO memory, depending on removable

magnetic disks. As NIR was seen as a potential production tool, the instruments became movable (even able to be placed on carts and wheeled to where the analysis was to be performed), but still were relatively slow and had minimum data storage capacity computers running them. As the value of NIR, for example, in raw material classification became popular, smaller, faster, and (sometimes) less expensive units were developed.

When the USFDA proposed using PAT in pharmaceutical manufacturing, instrument companies sped up development of fiber optic-based units, wireless (WiFi) units, all built stronger and smaller, with an eye on process control. As continuous manufacturing (CM) was introduced into Pharma, the sheer amount of data produced demanded better (and faster) computers and software. So, as with all commercial products, the demand and the appearance of the product walked hand-in-hand: demand spurring development of newer equipment which increased demand, and so forth.

What I see for the next five years is exponential growth of CM, buoyed by financial pressures, competitive pressures, and better equipment. As the "knowledge-pool" of trained scientists grows, more companies will be able to join "the CM club." This is a case where a "feeding frenzy" of hardware, software, and technical expertise will be a win-win-win for Pharma companies, physicians (more choices of better-made drugs), and patients (lower prices and better made products).


PANEL MEMBERs
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Controlled Substances in 2018: Challenges and Opportunities for the Contract Manufacturing Industry

Introduction

Two moves this summer by the US Drug Enforcement Administration (DEA) are set to prompt changes to US production volumes of many of the most strictly controlled substances, including opioids and cannabis-derived pharmaceuticals. Although this will mean cuts to manufacturing quotas for some notoriously misused compounds, such as oxycodone, CMOs with the appropriate controlled substance capabilities will face several opportunities elsewhere. The DEA's plans to more than double marijuana production limits and to reschedule a newly approved cannabis-derived epilepsy treatment demonstrate increased interest in the development of cannabis-based pharmaceuticals and an accompanying opportunity for controlled substance CMOs: an impressive position considering the field's almost global illegality 20 years ago. Meanwhile, significant cuts to opioid volumes will be felt in the services industry, but efforts against opioid abuse are likely to bring some manufacturing contracts in the form of alternative analgesics and medicines to treat addiction.

Trump Administration Takes Aim at Opioid Addiction – But How Will This Affect Controlled Substance CMOs?

In March 2018, the National Institute of Drug Abuse (NIDA) reported that more than 115 people in the US die each day from overdosing on opioids. This national crisis has a total economic burden of $78.5B per year from prescription opioid misuse alone. In 2017, fentanyl was responsible for more than 29,000 deaths in the US, making up the majority of the approximately 49,000 US opioid overdose deaths last year. At least seven US manufacturing sites are involved in the API or finished dose production of fentanyl, according to the PharmSource Products Database, a GlobalData product.

In a quasi-competitive world where products are needed to sustain and extend life above norms may or may not apply. Needed new products are created and sold at the highest possible price unless there is governmental price intervention. Justification for high prices is recovery of the R&D efforts. Manufacturing technology innovation is generally not a criterion to sustain such businesses especially when the products have a limited patent life. Innovation might be incorporated to meet regulations. After patents expire company or companies may or may not create or use the most economic processes because the product demand to extend life will be there. This generally prevails in the pharmaceutical world.

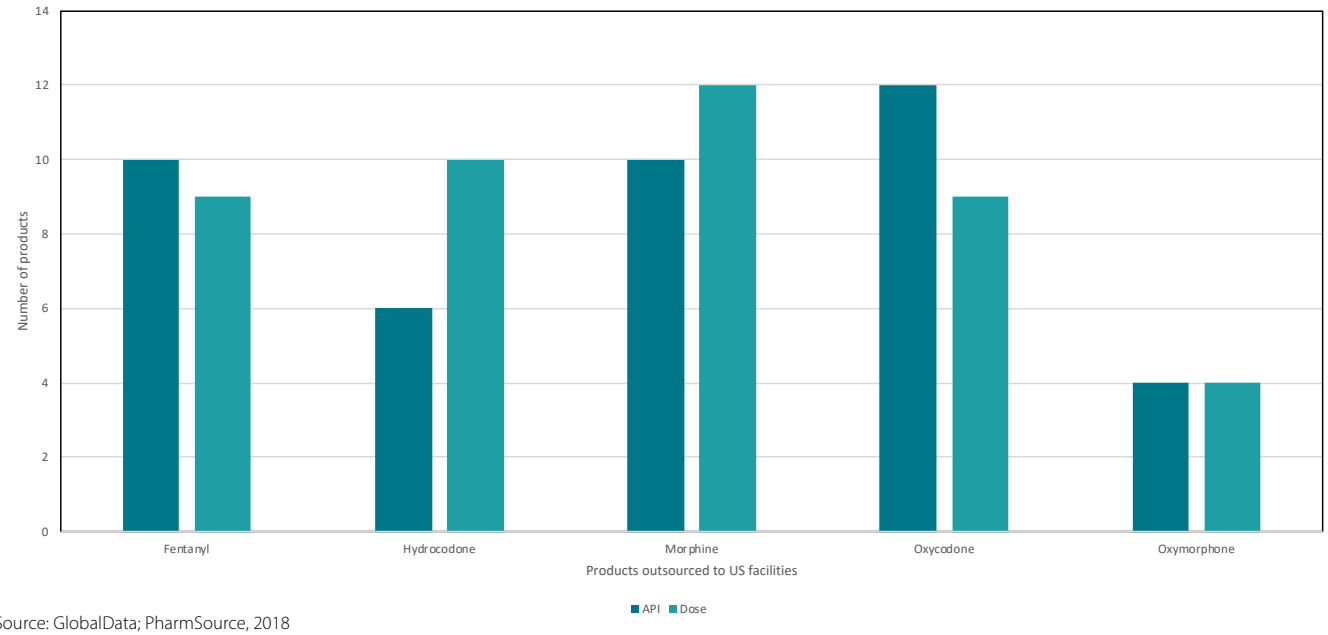
At times, I feel that the pharmaceutical industry biggest shortcoming has been in manufacturing technology innovation. It does the minimum for technology innovation or does it under duress because the regulators want them to. Some may disagree with it.

Manufacturing technology innovation in pharmaceuticals is constrained by three factors. In edition to economics they are government regulations and drug dose needed to cure diseases. Why the drug dose? Drug dose (micrograms to milligrams) and patient population heavily influence the needed manufacturing technologies. These nuances are discussed later. All said and done pharmaceutical industry has done a yeoman job in curing diseases.

Government regulations are critical and an essential part of the pharmaceutical landscape for product quality. They assure that the processes are repeatable and the product quality is maintained. Record keeping of manufacturing and test methods are essential. It is expected that once followed diligently, processes will produce repeatable quality products. My conjecture is that companies have to have an excellent understanding and command of the process that they can reproduce any process upset and correct them without much effort. Such knowledge will shorten processing times and result in optimum processes producing quality products all the time. If done so quality diligence will be ingrained in their overall business.

Regulatory bodies at times are and can be labeled as overbearing and demanding. In the last decade or so the USFDA has been nudging manufacturing companies to innovate manufacturing technologies. They can cajole but cannot force new or better manufacturing technologies or methods. Each company has to have financial justification for their investment in manufacturing technology and methods innovation. Since there are many products each could require their own financial justification.

Figure 1: The Most Abused Opioids and Their Outsourcing in US-Based Facilities

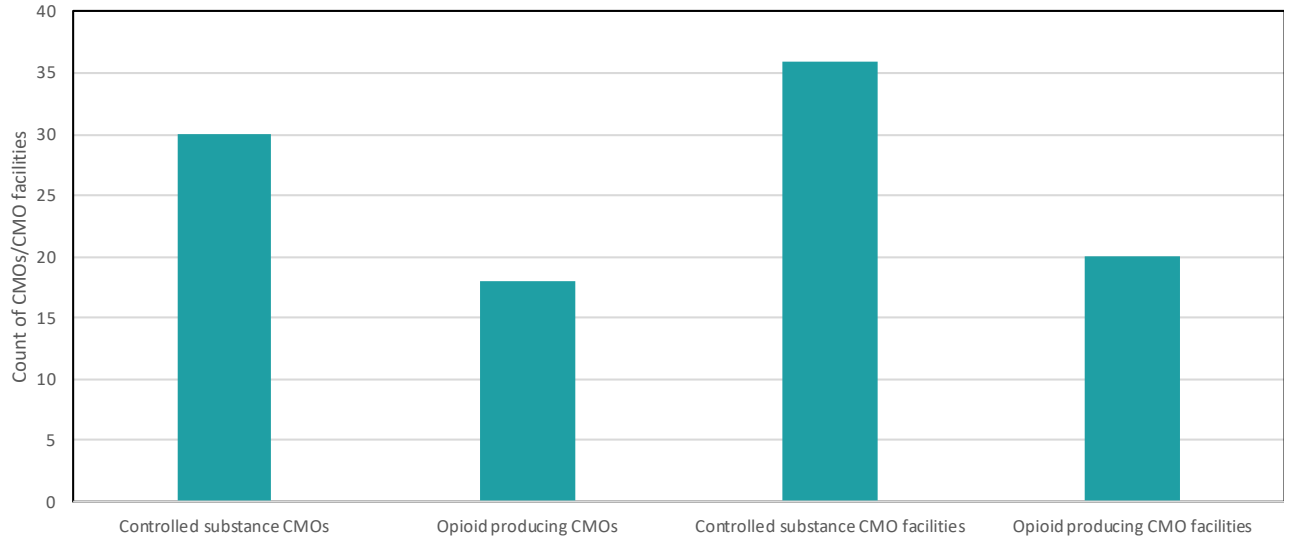


Source: GlobalData; PharmSource, 2018

Out of the 30 CMOs involved in commercial drug manufacture using controlled substances, 18 (60%) produce opioids. While contractors involved in controlled substance production constitute a minority of US CMO facilities, it is clear that they will be hit particularly hard by the reduced volumes of opioid manufacturing. The ever-growing number of opioid lawsuits—such as the US state lawsuits against Purdue Pharma—is likely to deter pharma companies from producing and outsourcing these products in the future.

Figure 2 shows the proportion of DEA Schedule I and II controlled substance CMOs and facilities that produce opioids in the US.

Figure 2: DEA Schedule 1I and 2II Controlled Substance CMOs and Their Facilities in the US



Source: GlobalData; PharmSource, 2018

However, opportunities for CMOs and drug companies relating to non-opioid painkiller manufacture are likely to become more lucrative in the future as alternatives to addictive opioids are sought. Recently, numerous bills such as the Opioid Crisis Response Act of 2018 have been introduced in the US to support the development and FDA approval of non-opioid analgesics. Marketed alternatives to opioid pain relief are already available, but physicians will require increased awareness and education regarding their use to move away from habitually prescribing opioids.

Moreover, the manufacturing of new drugs to treat opioid addiction is commonly outsourced. The finished dose form of Indivior Group's recently approved Sublocade, an extended-release once-monthly subcutaneous injection of buprenorphine used to treat moderate to severe opioid use disorder, is manufactured by Albany Molecular Research Inc. (AMRI); the finished dose of Johnson & Johnson/Alkermes' Vivitrol (naltrexone), a once-monthly medication to prevent relapse, is produced in-house and by both American Regent/Luitpold Pharmaceuticals (Shirley, New York) and Baxter BioPharma Solutions, according to the PharmSource Products Database, a GlobalData Product. This outsourcing will continue to provide opportunities to the CMO industry as the US government attempts to slow the opioid addiction crisis, and as the development pipeline matures.

GW Epilepsy Approval Prompts Cannabidiol Rescheduling

Meanwhile, there are strong signs from the DEA that developments in the cannabinoid-based medicines field will lead to more FDA approvals and services opportunities.

The DEA's quota shake-up will increase maximum marijuana volumes by 250% from 444kg to 1,140kg. At the same time, the FDA's approval of GW Pharmaceuticals' Epidiolex (cannabidiol/CBD) for epilepsy this summer has prompted an overhaul of controlled substance scheduling at the DEA that is likely to decriminalize some marijuana-based medicines.

The FDA approved Epidiolex for two severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older. This is the first FDA-approved drug to contain a purified drug substance derived from cannabis.

Physicians will have the option to prescribe Epidiolex for other uses and it could bring new interest and pharmaceutical research into cannabis-based products. According to a GlobalData report (PharmaPoint: Epilepsy – Global Drug Forecast and Market Analysis to 2026), Epidiolex is forecast to reach $1.2B in sales in 2026, largely due to its expected high annual cost of therapy, further reinforcing the large commercial potential of cannabinoid-based therapies.

However, at the time of going to press, US patients cannot yet take the drug; the DEA must first make a scheduling determination. Under the Controlled Substances Act (CSA), CBD is currently a Schedule I substance because it is a chemical component of the cannabis plant, a status that means the product is deemed to have no medicinal value and is illegal.

The DEA has signaled that the categorization of CBD-based medicines will change to allow patients access to Epidiolix. "We don't have a choice on that," DEA public affairs officer Barbara Carreno said in June. "It absolutely has to become Schedule II or III."

The DEA has previous form with loosening restrictions to allow controlled drugs to enter the market: it has previously downgraded FDA-approved medicines with synthetic cannabis-based APIs—such as Insys Therapeutics' Syndros (dronabinol)—to Schedule II or III. This strongly suggests Epidiolix, the first FDA-approved plant-derived cannabinoid drug, will be successfully rescheduled, and will herald the first of many approvals, Schedule changes, and manufacturing contracts.

Table 1: DEA Proposed Adjustments to Aggregate Production Quotas

Basic Class	Established 2018 Quotas (g*)	Proposed Revised Quotas (g*)	% Change
Temporarily Scheduled Substances			
1-(4-Cyanobutyl)-N-(2-phenylpropan-2-yl)-1H-indazole-3-carboximide	N/A	25	5
1-(5-Fluoropentyl)-N-(2-phenylpropan-2-yl)-1H-pyrrolo[2,3-b]pyridine-3carboximide	N/A	25	5
Cyclopropyl Fentanyl	N/A	20	5
Fentanyl related substances	N/A	25	5
Isobutyryl Fentanyl	N/A	25	5
Methyl-2-(1-(cyclohexylmethyl)-1H-indole-3-carboxamido)-3-methylbutanoate	N/A	25	5
N-(1-Amino-3-methyl-1-oxobutan-2-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide	N/A	25	5
Naphthalen-1-yl 1-(5-fluorpentyl)-1H-indole-3-carboxylate	N/A	25	5

Ocfentanil	N/A	25		5
Para-flourobutyryl fentanyl	N/A	25		5
Tetrahydrofuranyl fentanyl	N/A	5		5
Valeryl fentanyl	N/A	25		5
Schedule I				
1-[1-(2-Thienyl)cyclohexyl]pyrrolidine	0	20		5
1-(1-Phenylcyclohexyl)pyrrolidine	10	15	150%	5
1-(2-Phenylethyl)-4-phenyl-4-acetoxypiperidine	0	10		5
1-Methyl-4-phenyl-4-propionoxypiperidine	2	10	500%	5
Diapromide	0	20		5
Diethylthiambutene	0	20		5
Dimethyltryptamine	35	50	143%	5
Marihuana	443,680	1,140,216	257%	5
N-Ethyl-3-piperidyl benzilate	0	10		5
Schedule II				
1-Phenylcyclohexylamine	4	15	375%	5
1-Piperidinocyclohexanecarbonitrile	4	25	625%	5
Amphetamine (for conversion)	11,280,000	12,700,000	113%	5
Anileridine	0	20		5
Codeine (for conversion)	15,040,000	12,900,000	-14%	6
Hydrocodone (for sale)	50,348,280	44,710,000		5
Levomethorphan	30	2,200	7333%	5
Levorphanol	12,126	38,000	313%	5
Lisdexamfetamine	17,869,000	19,000,000	106%	5
Meperidine	2,717,540	1,913,148	-30%	6
Meperidine Intermediate-A	5	30	600%	5
Meperidine Intermediate-C	5	30	600%	5
[846,000 grams of levo-desoxyephedrine for use in a non-controlled, non-prescription product; 564,000 grams for methamphetamine mostly for conversion to a Schedule III product; and 36,754 grams for methamphetamine (for sale)]				5
Morphine (for sale)	33,958,440	31,456,000	-7%	6
Nabilone	31,000	62,000	200%	5
Noroxymorphone (for conversion)	14,044,540	16,440,000	117%	5
Oxycodone (for sale)	95,692,000	85,578,000	-11%	6
Oxymorphone (for sale)	3,395,280	3,137,240	-8%	6
Remifentanil	2,820	3,000	106%	5
Secobarbital	161,682	172,100	106%	5
Thebaine	94,000,000	86,200,000	-8%	6
List I Chemicals				
Pseudoephedrine (for conversion)	40	1,000	2500%	5

*Expressed in grams of anhydrous acid or base

Source: DEA; PharmSource, a GlobalData Product, 2018

CPhI Pharma Insights

Part 4.

The rise of the integrated CDMO and 'ADCs the intersection of small and large'

PANEL MEMBER
Vivek Sharma, CEO Piramal Pharma Solutions.

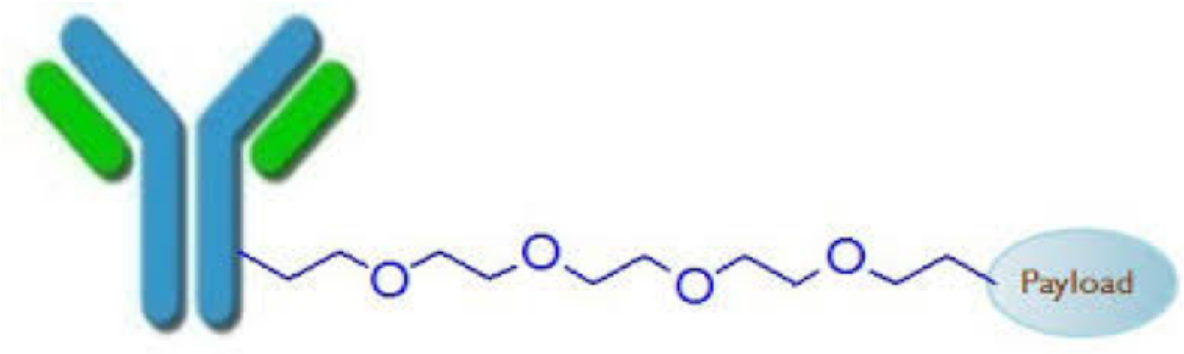
ADCs growth driven by lack of inhouse facilities, oncology and integrated CDMOs

Summary of trends forecast: the next 1-3 years

- Novel payloads that target tumour-initiating cells on third generation ADCs in phase iii will come to market in the next couple of years
- ADCs market forecast estimated to expand at nearly 20% CAGR until 2030 with 17 new drugs in late stage development, and double digit approvals of ADCs over next 3-years.
- Outsourcing of ADC manufacturing will continue to rise past 70% of overall manufacturing, with increased co-development – driven by increased biotechs and smaller companies in the pipeline needing specialist development expertise and facilities.
- Longer term (circa 5-years) the expansion of ADCs into therapeutic areas other than oncology will be the next evolution – bioconjugation in infectious disease is one potential area

Abstract

The past decade has seen significant advances in new cancer treatments through the development of highly selective small molecules that target a specific abnormality responsible for the disease. Traditional cytotoxic agents were another approach to treat cancer; however, unlike target-specific approaches, they suffered from adverse effects stemming from nonspecific killing of both healthy and cancer cells. A strategy that combines the powerful cell-killing ability of potent cytotoxic agents with target specificity would represent a potentially new paradigm in cancer treatment. Antibody Drug Conjugate (ADC) is such an approach, wherein the antibody component provides specificity for a tumour target antigen and the drug confers the cytotoxicity.



An ideal ADC has:

A highly selective Monoclonal antibody (mAb) for a tumour-associated antigen to identify cancer cell

A linker that is stable in circulation, but releases the cytotoxic agent in target cells

A potent cytotoxic agent that induces target cell death after being internalized in the tumour cell and released

Evolution of Antibody Drug Conjugates (ADC)

The foundation of ADCs' was laid back 100 years ago by Paul Ehrlich, by postulating 'magic bullets' for selectively delivering a cytotoxic drug to a tumour via a targeting agent. Nearly 50 years later, Ehrlich's concept of targeted therapy was first epitomized when clinically approved drugs with well-established mechanisms of action, such as antimetabolites (Methotrexate and 5-fluorouracil), DNA cross linkers (mitomycin) and anti-microtubule agents (vinblastine) were used by linking to an antibody targeting leukemia cells. At this point of time, polyclonal antibodies were used which had higher potential for cross reactivity due to ability of recognizing multiple epitopes on target antigen. In 1975, mouse monoclonal antibodies (mAbs) were developed using hybridoma technology by Kohler and Milstein wherein the antibodies were highly specific towards a single epitope on an antigen. This greatly advanced the field of ADCs and eventually led to development of first-generation of ADCs. For example, ADC-doxorubicin conjugate 1 (BR96-DOX) was designed using a bifunctional linker, wherein the cytotoxic drug was appended via a hydrazone moiety , and the BR96 antibody was conjugated using maleimide moiety via cysteine residues. Although curative efficacy was observed in human tumour xenograft models, the relatively low potency of doxorubicin necessitated high Drug to Antibody ratio (DARs, 8 per antibody) and high doses of the ADC to achieve preclinical activity. In clinical trials, significant toxicity was observed due to nonspecific cleavage of the relatively labile hydrazone linker and expression of the antigen target in normal tissue.

Further advancements including higher drug potency and careful selection of targets, ultimately led to the first ADC Mylotarg1-, i.e. Gemtuzumab ozogamicin to gain accelerated US Food and Drug Administration (FDA) approval in 2000 for Acute Myeloid Leukemia (AML). Despite initial encouraging clinical results, Mylotarg1 was withdrawn from the market a decade later owing to a lack of improvement in overall survival and higher rate of fatal toxicity compared to chemotherapy. Lessons learned from these failures were:

- Instability of the linker that attached the drug to the mAb
- Insufficient potency of ADC
- Immunogenicity issues observed with murine mAbs
- High antigen expression on normal cells leading to toxicity

Second-generation ADCs

The limitations and failures of first-generation ADCs were eliminated in second-generation ADCs. The premature release of drugs because of the unstable hydrazone linker in Mylotarg® had been avoided in second-generation FDA approved ADCs, by using different linkers such as:

1. Cleavable linkers: -E.g. Valine-citrulline (cathepsin cleavable) linker in Adcetris® for Hodgkin lymphoma
2. Non-Cleavable linkers: - E.g. Thioester linker in Kadcyla ® for Breast Cancer

The cytotoxic payloads used in second-generation ADCs were also more potent than in first-generation ADCs. For example, tubulin-targeting agents, such as MonoMethyl Auristatin (MMAE) used in Adcetris® is approximately 100–1000-fold stronger than DNA-intercalating doxorubicin of BR96 Dox.

Despite the improvement in cytotoxic payloads and the introduction of stable linkers, second-generation ADCs had significant limitations in terms of their heterogeneous DAR, resulting from stochastic coupling strategies between the antibody and drug. Typically, chemical conjugation between the drug and antibody occurs via the lysine or cysteine residue of the mAb, which generates DAR (range 0–8) with an average value of 3–4. Therefore, heterogeneous ADCs can contain a mixture of un-conjugated, partially conjugated, and over-conjugated antibodies leading to competition between unconjugated antibodies and drug-conjugated species for antigen binding that diminishes the activity of the ADC. By contrast, over-conjugation (DAR>4) results in antibody aggregation, a decrease in stability leading to incremental increases in nonspecific toxicity, and a reduction in the half-life of ADCs in the circulation. Overall, heterogeneous ADCs have a limited therapeutic index and tumor penetration abilities, resulting in induction of drug resistant in the tumour microenvironment. Apart from this, sometimes the ADC is poorly internalized; in such cases the cytotoxic drug does not reach the target as it is attached to antibody via a Non-cleavable linker.

Flaws from 2nd generation could be summarised as:

- Heterogeneous nature leading to limited conjugated ADC amounts with nonspecific toxicity and efficacy
- Eventually only DNA alkylating agents and tubulin polymerization inhibitors with subnanomolar activities proved to be useful for targeted delivery through ADC technology, due to limited delivered amount of ADC available in the tumour. Such drug could be used in monotherapy due to high cytotoxicity which creates resistance and narrow the therapeutic window
- Conjugation site on mAb which affects potency, stability and PK properties of the ADC
- Limitations due to nature of the linker and delivery mechanism: Only cleavable linkers have a broader efficacy as they can be active even when they are poorly internalized

Third-generation ADCs

The evolution continues and aforementioned concerns regarding the heterogeneous DARs of second-generation ADCs are been addressed in third-generation ADCs. Site-specific conjugation has been introduced to produce homogenous ADCs with well-characterized DARs and desired cytotoxicity. The site-specific conjugation of the drug to antibody provides a single isomer ADC with a uniform DAR value. Such ADCs can be made using bioengineered antibodies containing site-specific amino acids, such as cysteine, glycan, or peptide tags. For example, precise site-specific conjugation of MMAE to human IgG was developed by replacing the Ala114 amino acid of the CH1 domain of the IgG with cysteine to create a selectively engineered antibody, called THIOMAB. This ADCs had a DAR of 2 with an improved safety profile and maintenance of efficacy, compared with traditionally

conjugated ADCs with higher DARs. Alternative approaches to site-specific drug conjugation include:

(i) A thio-bridge approach : Interchain disulfides (four per mAb) are reduced and re-bridged with the drug generating a near homogenous ADC with DAR 4 and increased stability

(ii) Bio-orthogonal chemistry : Introduction of unnatural amino acids, such as p-acetylphenylalanine, or non-canonical amino acids

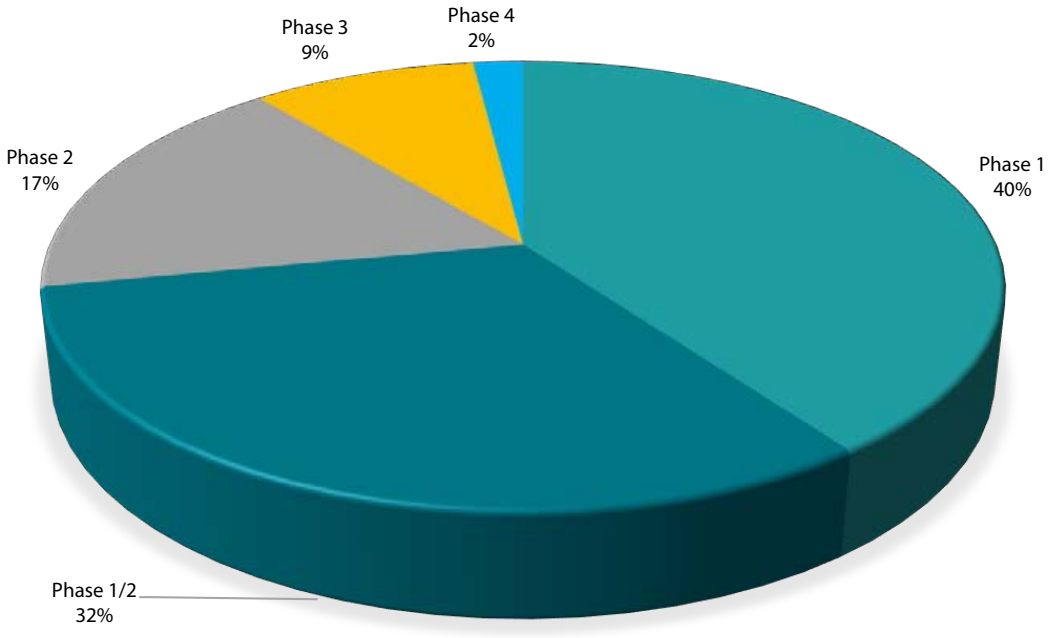
At the same time, efforts are continuing to expand on payloads with novel modes of action with a focus on agents having activity against non-proliferating cancer cells in order to widen the target area to include tumour-initiating cells (TICs) and to overcome resistance. Furthest in development are:

1. Pyrrolobenzodiazepines (PBDs):- Currently 4 molecules are in clinical phase with Rovalpituzumab tesirine moving through Phase 3
2. Topoisomerase inhibitors (Irinotecan metabolite) e.g.:- Sacituzumab govitecan has progressed significantly in Phase 3 with an average DAR of 7.6 and a relatively hydrolysable linker.
3. Cell cycle-independent activity comprise the duocarmycins E.g.;- trastuzumab-duocarmycin conjugates in Phase 3
4. Pseudomonas Exotoxins : E.g.: Oportuzumab monatox in Phase 3

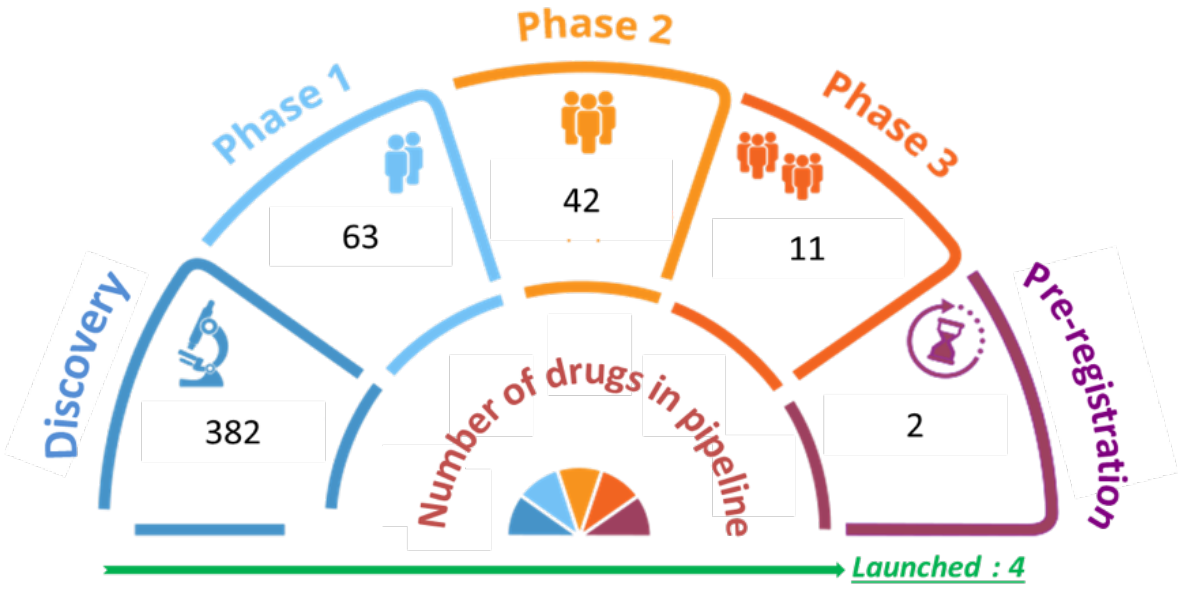
Market Outlook

Preclinical evaluation of the recent wave of third-generation site-specifically and homogenously conjugated ADCs has offered reasons for optimism in the ADC field. This understanding has speeded up the FDA approval rate of ADCs and has led to drastic increase in the number of clinical trials, especially in solid tumours. Currently 600+ clinical trials are been conducted worldwide on ADCs'.

ADC Clinical Trials



Nearly 202 ADCs have been entering into clinical trials out of which 116 are actively progressing. There are about 23 new ADCs in last 12 months increasing at a rate of 30%.



Around 70% of these drugs are in the preclinical / discovery stages. Of the clinical stage candidates, more than 12% are being developed for breast cancer, while around 10% are being developed for the treatment of Non-Hodgkin's Lymphoma. Candidates targeting AML and multiple myeloma together occupy 14% (7% each) of the clinical pipeline. More than half of the ADCs in the current clinical pipeline are being developed using the technologies provided by Seattle Genetics ; however, several small sized companies have emerged in last few years, offering novel technology platforms.

Some of the approaches that have been adopted for the development of third generation ADC conjugation platforms include:

- Limiting retro-Michael drug de-conjugation (Kyowa Hakko Kirin, MedImmune, Pfizer, ProLynx, Seattle Genetics, Syndivia),
- Cysteine re-bridging (Abzena, Igneica Biotherapeutics, University College London / ThioLogics),
- Enzyme-assisted ligation (Catalent / Redwood, Innate Pharma, LegoChem Biosciences, NBE Therapeutics, Pfizer, Sanofi, Tubulis Technologies, ProBioGen),
- Glycan re-modelling (Philogen, Seattle Genetics, Sanofi, Synaffix, University of Georgia, US National Cancer Institute), and
- Ligation at Fab nucleotide-binding site (Meditope Biosciences, University of California)

With close to 17 drugs, that are either approved or are in late stages of clinical development, the ADCs therapeutics market is anticipated to grow at a CAGR to 19.4% between 2017 and 2030 with an estimated value of $8 Billion in next 5 years.

The global market for antibody drug conjugates is expected to be driven by the advancement in medical technology, rising incidence of cancer, and an increasing demand for biologic therapies. In the quest for more targeted therapies and potentially more clinically efficacious drug, bio/Pharma companies are increasing their research and product development in biologics. Many players are investing huge capital in this space that justify the market potential of ADCs' namely Wuxi; invested $20 Million to start new facility located in China. Abzena has been investing nearly ~$17 Million in past 2 years to upgrade and expand its California site that is dedicated to bioconjugation. Seattle Genetics has invested $17.8 Million in antibody production to support its ADC pipeline and so on..

Unlike conventional chemotherapies that also damage normal tissue, ADCs target only cancer cells and

hence majority of the antibody drug conjugates under development are for oncological indications propelled by the availability of monoclonal antibodies targeting different types of cancer. Some market players are also looking outside the oncology domain to develop antibody drug conjugate, though, such drugs are limited in number are in preclinical stage of development. ADCs' that would fuel the market growth which are in late phase pipeline are Sacituzumab Govitecan by Immunomedics, Moxetumomab Pasudotox by Astra Zeneca, Rovalpituzumab Tesirine and Depatuxizumab Mafodotin by Abbvie, polatuzumab vedotin by Genentech

Hurdles/ Challenges in ADC Manufacturing/ Importance of CMOs' in ADC Space

The ADC field is in a good space yet has been humbled by clinical failures due to great technical and manufacturing challenges. Technical challenges include development issues like:

1. Optimizing additional process steps in developing conventional mABs' from ADC perspective
2. Controls in conjugation chemistry to avoid aggregation of ADCs
3. Antibody binding activity after conjugation
4. Biological activity of cytotoxic drug after conjugation
5. Limited choices of highly effective linkers and few classes of highly potent cytotoxic agents
6. Production of components requiring both cell culture and synthetic chemistry capabilities
7. Limited and complex purification platforms

ADCs manufacturing requires a cGMP facility designed with the proper engineering controls to provide product and personnel protection from the highly potent compounds. This includes isolators being operated at containment Category 4 designated as Safebridge® for to cope with very low occupational exposure range (OEL). For ADC fill-finish, a fill line with lyophilization capability enclosed in a separate isolator is an additional requirement. Containment at this level is also required to maintain an aseptic biological manufacturing environment to avoid contamination which must be verified through surrogate testing, which can be challenging with the most potent toxins currently under development. An ADC manufacturing/fill finish facility is a substantial investment, which is why most ADCs are manufactured at CMOs. Most smaller companies, and even some larger companies, do not have enough of a pipeline to justify the level of facility investment needed for ADCs and/or cannot keep the facility fully utilized. In addition, the supply chain for manufacturing ADCs is complex, including linker/toxin manufacture, antibody manufacture, conjugation/ QC / stability testing, and fill finish. The more of these the CMO can offer as an integrated service, the better for the client which is backed up by multiple advantages:

1. CMOs offer technical expertise in conjugation and linker developments with robust platforms
2. Utilizing an integrated CMO reduces an ADC's time to market as they can perform all steps like conjugation , scale up , commercial manufacturing and the fill finish of ADC saving a considerable amount of time in scheduling and testing
3. Opportunity to eliminate penalties associated with rescheduling due to delays in a prior part of the supply chain
4. Reduced sponsor effort associated with management of inventory and logistics by the CDMO
5. Also, integrated CMOs' offer flexibility for any changes made during the process which are well co-ordinated by adept program managers at the site
6. Lower risk associated with transfers if the different units are co-located

As a result, most of the pharmaceutical companies have opted to outsource the manufacturing of their ADCs with approximately 70% of all ADC manufacturing activities conducted by CMOs'. Major players in ADCs' like Genentech, Sanofi, Takeda, Pfizer either rely on CMOs by outsourcing or follow a co-development model with them. ImmunoGen, recently shifted its ADC Manufacturing work to an outsourcing model mentioning its benefit to have increased access to the expertise which a CMO brings in, in turn saving about $20 Million!

While many of these challenges exist with other biologics, the complexity of ADCs can make the drug development process and tech transfer process even more difficult. However, through fruitful partnerships and the right expertise, these problems can be overcome and ADCs can continue to have an increased impact as targeted cancer therapies. Piramal Pharma Solutions is one of the global leaders in providing integrated ADC manufacturing solutions from development through clinical and commercial GMP batch manufacturing and ADC fill/finish. Our facility in Grangemouth, UK is dedicated to process development, scale up and manufacturing of bioconjugates which is forward integrated with our Lexington, US facility for Fill/Finish activities. Our Facility located in Riverview, US provides API for cytotoxic payloads and linkers. We are the pioneers in the field of GMP manufacturing of ADCs' and we have partnered with leading ADC technology companies for over past 10 years. Our experience counts in terms of:

- 850 ADC batches manufactured
- 440 GMP batches manufactured
- 118 Development programs completed
- 180 Different ADCs from over 110 antibodies
- 55 Different toxin/toxin-linker systems
- 20 ADCs and other antibody/protein conjugate projects
- 6 integrated programs for ADC across Piramal sites

A better ADC for future…

Expansion of ADCs' into therapeutic areas than than oncology can be the next thing in evolution. Opportunities for improved therapeutics made through bioconjugation exist in infectious disease, where an Antibody–Antibiotic Conjugate (AAC) was shown to be more effective than the free antibiotic payload for treating infections caused by drug-resistant bacteria. ADCs' can also help to improve treatment of chronic conditions e.g., autoimmune and cardiovascular diseases through reducing side effects by selective payload delivery. Wisely chosen target antigen, novel linker technology and original mode of drug action continue to be investigated to fully optimize ADC-based targeted therapy and holistic approach to the development of ADCs remains paramount!

PANEL MEMBER
Minzhang Chen, Ph.D. CEO of STA Pharmaceutical, a WuXi AppTec company (WuXi STA)

'Pharma's golden age' needs geographically integrated CDMOs to sustain pipeline growth – **Innovators to use CDMOs for parallel approvals in US and China**

A background to growth and integration for CDMOs

This year we are very much approaching a crescendo moment for the contract services industry, as the global supply chain integrates and there is a continual diversification of targets in the pipeline. Overall, the past year and a half have been a spectacularly good period for the global drug development industry, in 2017 there were a record 46 FDA approvals and a further 40 have followed this year so far – with a remarkable six approvals in July, five more in August and six more in September[1] alone. This is amongst the best ever 3-months we have had, so the rate of change appears to still be accelerating. It's not too bold a statement to say we are experiencing a golden period for the drug development pipeline. In fact, if you look a little deeper than the headline approvals, you will see there are more compounds under development than at any period in pharma's history – with more than 15,000 investigational products at various stages in the development cycle[2].
But for the purposes of this piece and the impact on the contract services industry, I will focus solely on the new chemical entities space. What is gradually changing is the diversification of both compounds and developers. The traditional biotech hubs of Boston, San Diego and San Francisco remain strong, as does the pipeline in Europe, but added to this, has been the rapid growth of Asian biotechs in Singapore, Korea and in particular China.

Big pharma is also streamlining its resources to concentrate on areas of discovering and marketing new compounds, with an ever increasing proportion of the development work being outsourced to contract services providers. The role of the contract service provider is also changing simultaneously, with smaller pharma clients and biotechs requiring much greater support in the development stages - particularly when sponsors have limited prior knowledge of CMC (chemistry, manufacturing and control). Added to this, is big pharma's desire to streamline its global supply chain and to more tightly control manufacturing processes. A final consideration is that as an industry we are searching for new ways to shorten development cycles, thereby reducing cost, whilst also accommodating drug

targets that maybe particularly difficult to formulate. The knock-on effects of these trends is that over the **next 5-years it's clear that CDMOs will be required to have the full scope of development** capabilities to meet client needs. So that means both drug product and substance capabilities in development and commercial stages. If you look at the wider market, WuXi STA has integrated both drug product and substance, as has Patheon, but these trends are also clearly apparent in several large acquisitions; notably, Lonza acquiring Capsugel last year, and Cambrex's purchase of Halo pharma in July. So certainly, we will see the larger players investing in or acquiring full service capabilities. For the mid-sized CDMO there could be challenges ahead unless they are offering particularly specialist services, and ultimately we expect the sector to become more streamlined with a smaller number of larger strategic partners.

How are we defining integrated?

Put in its simplest terms, an integrated CDMO needs to help customers expedite the development process, but then also be capable of meeting the customers commercialization needs with a smooth tech transfer and no disruption of supply. So when you look at the products in the development pipeline that means being able to handle even the most complex and difficult classes. In the previous 10-years, there was perhaps more of trend for CDMOs to specialize in one particular area, rather than being a 'jack of all trades', but in the future CDMOs will need to be 'capable of all parts of development and commercialization' to survive and prosper.

But what we now believe will also become a focus of contract services efforts is how they can bring different parts of the supply chain closer together – as this could bring down development times further by several months. Traditionally, the CDMO model has been to acquire ex-pharma sites often in disparate locations around the world, but in order to expediate development timelines we see a trend to have CDMOs with R&D, API development and manufacturing, as well as **drug product development and manufacturing all in close geographic proximity**. We have led the way in building integrated sites to this end, but as the contract services industry continues to grow, we anticipate sites being built nearby each other by global CDMOs. The advantages are clear in reducing development timelines and helping customers to get vital milestone payments faster. Bringing all CMC services not just into one group of companies, but closer together is the next evolution of contract services. As an added benefit, this will also help reduce the need for complicated supply chains.

Another area we see a shift is for CDMOs to now lead the way in all aspects of manufacturing process research and development. In the past these were often researched and set by the pharma customers, but increasingly we now see **CDMOs providing these optimization services and often with future commercialization in mind**. This is especially true in cases where they can implement new chemical and formulation pathways without impacting development timelines. So it is now not uncommon for a biotech to come to a contract services partner with a preliminary synthetic route or dosage form already in mind, and then have the CDMO recommend an improved scalable alternative approach or dosage form that offers greater ADME properties or release profile.

The final trend, which we are witness to first hand, is of course the changing role of China. Not only is the biotech industry here opening up very quickly and developing innovative formulations for the domestic market, but more Western pharma companies are motivated to introduce their products to China market sooner than in the past. Hence they have started to consider China strategy very early in development cycle, unlike before when they waited until the product was first approved in US or Europe. In addition, progressively, we are also seeing the reverse with Asian biotechs widening their interest to produce drugs for global approval – with many license holders looking to expand to Western markets simultaneously as they seek NMPA's (formerly known as CFDA) approval while concurrently applying for US FDA or EMA approval.

Taken a step further, many Asian biotechs started to out-license products very early in development to Western pharma companies and this is a rapidly emerging trend that creates growing opportunities for any CDMOs with both NMPA and FDA approvals.

So if we are to look five years ahead, the overall CDMO market could indeed look very different. Certainly, there will be consolidation amongst the larger organizations – with most of the top providers offering integrated services across drug substance and drug product. The major contract providers will also be able to simultaneously develop products for launch in multiple markets and across various formulations. This is will be helped by the harmonization of standards we are now seeing from the EU to the USA and China. But perhaps most interestingly, it is likely that by integrating services geographically clinical development timelines will fall and, with better technologies, it is hoped that attrition rates may also improve.

Additionally, because a large amount of biotechs are now emerging in Asia, we will see either new CDMOs emerging or large players expanding here. Bringing the industry closer to several emerging high growth markets, as well as this new base of innovative customers.

Big pharma's requirements are also evolving and they will not only be looking for integrated providers, but also contract services organizations that can match internal standards – so that will mean everything from QbD and supply chain control to minimizing any environmental impact of drug manufacturing. With more modern manufacturing technologies expected at CDMOs, coupled with a desire to reduce overall costs, this could well be a major development for the industry.

Our conclusion is that the complete CMC package will be routinely outsourced, development timelines reduced, and most excitingly, CDMOs will help drive these changes as active partners not suppliers. So the next few years will clearly be amongst the best ever for contract services, as there are more opportunities in the development pipeline than ever before. But a word of caution, to match this growth, CDMOs will need to be able to offer broader and higher quality services and keep pace with changes – using the same approach of five years ago, will not sustain the market's needs for the next five. For example, CDMOs will also need to keep pace with capacity, but it will need to be 'future-proof' capacity in the right place, with the right technologies. For the latter, CDMOs have often received pharma support. However, we anticipate the fastest growth rates will be experienced by CDMOs that invest ahead of the curve – as they will have readymade facilities to meet the new wave of compounds.

References

1. https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm592464.htm

2. https://pharmaintelligence.informa.com/products-and-services/data-and-analysis/pharmaprojects

CPhI Pharma Insights

Part 5.

The bioLIVE biologicals predications and trends – processing advancements, capacity changes and cross industry learnings


PANEL MEMBERs
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Supply and Demand Trends: Mammalian Biomanufacturing Industry Overview

Trends overview 2018-2022

- Demand for biological by volume projected to reach over 4,300 kL, a 5-year growth rate of nearly 14% per year (2,300kL in 2017)
  - If Alzheimer's drugs and PDL/PDL-1 checkpoint in cancer are approved demand could be much higher and lead to capacity shortages.
- Capacity of global production will increase to 5,600kL by 2022 from 3,700kL in 2017
  - The distribution of capacity is shifting slightly more towards CMOs (21%) and hybrid companies (14%) by 2022 away from in-house facilities (65%).
  - By 2022 Europe (38%) will have slightly overtaken the USA (38%), with capacity in Asia (24%) also growing
- 55% of products in late phase (ii/iii) development can be met by a single 2000 or 5000L bioreactor
- Overall capacity should experience some loosening in short-term constraints, but may tighten after 2022. With the majority of capacity still in-house, it may be difficult for biotechs with products in development to access capacity at the right time and under the right conditions

Abstract: Biologic-based drugs are an increasingly important part of the portfolio growth strategies for pharmaceutical and biopharmaceutical companies. As the number of commercial products and pipeline candidates grows, a crucial issue facing the industry is the current and future state of biomanufacturing capacity, the availability of that capacity, and the technologies impacting upstream and downstream bioprocessing. BPTC provides a high-level overview of the current status of the supply and demand of mammalian-based biopharmaceuticals, forecasting where the industry is heading and how manufacturers are keeping pace.

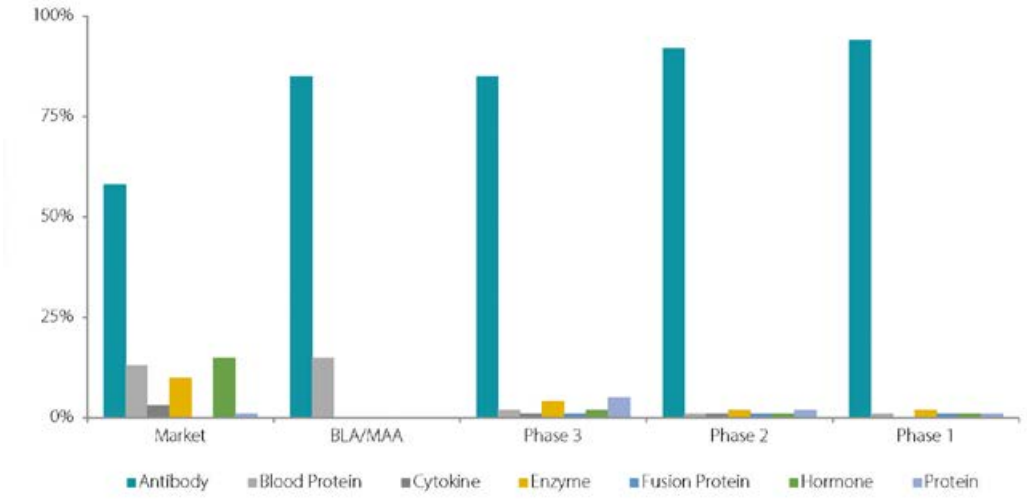
Introduction

Since the approval of the first recombinant therapeutic antibody, OKT3, in 1986, biopharmaceutical products have become a larger percentage of overall pharmaceutical company revenue, with sales of the top six selling antibody products, Humira, Enbrel, Rituxan, Remicade, Herceptin and Avastin, totaling just over $54B in 2017. The compound annual revenue growth rate for antibody products, which include naked monoclonal antibodies, Fc-fusion proteins,

antibody fragments, bispecific antibodies, antibody conjugates, and other antibody-related products, from 2003 to 2014 was 21%; however, this growth has slowed to the low teens in the recent years due to the maturation of many products and emerging alternative technologies. Also, it is more difficult to sustain such growth rates the larger the market becomes.

To provide context about this growing segment of the market, BPTC's proprietary bioTRAK® database of biopharmaceutical products and manufacturing capacity estimates that there are nearly 1,300 biopharmaceutical products in some stage of clinical development in the United States or Europe, and the majority of these products, over 80%, are produced in mammalian cell culture systems. To further refine the biopharmaceutical manufacturing market, we evaluate the distribution of mammalian products by product type and phase of development. **Figure 1** shows the distribution of product types, including antibody products, defined previously, blood proteins, cytokines, enzymes, fusion proteins, hormones and other recombinant proteins, by phase of development. Antibody products are the dominant commercially marketed product type (58%) and are the largest product type for all phases of development, with the early stage pipeline consisting of nearly all antibody products (>90%). It is important to note that many of the early commercial biopharmaceutical products, such as growth hormones, insulins and interferons, are produced in microbial systems.

Figure 1: Distribution of Mammalian Products by Product Type and Phase of Development



Whether commercially approved or in development, each of these products need access to mammalian production capacity. For current commercially approved biopharmaceutical products the future demand is estimated from each product's reported annual sales data, along with estimates of each product's future growth rates. A product's growth in sales is calculated from actual sales data for the current and previous years. Our future product growth estimations also take into consideration a product's age, as sales growth typically slows as a product matures, while newly approved products often do not reach full market penetration for several years.

Using the sales growth data along with the number of patients treated in the current year, based on price per mg and sales, an estimated treatment population for future years can be calculated for each year during the forecast period. This projected treatment population, combined with the yearly per patient dosing, calculates the kilogram quantities of each product that will be required in future years. These estimated product demand quantities along with cell line expression level and overall purification yield estimates for each product are used to calculate the estimated amount of manufacturing capacity (L/year) required for each product in future years.

These estimates are based on industry norms at the time the product was being developed and the maturity of the company developing the process. For example, the commercial process for a product launched more than ten years ago will likely have a lower expression level assigned in our forecast algorithm than a product currently in clinical development. For products in development, future commercial demand is estimated based on the market penetration of currently approved products or proxy products with similar indications. Additionally, for products in development, we employ a phase-based commercialization probability when calculating future demand.

Figure 2 shows the projected kilogram quantities of product needed to meet annual commercial and clinical demand for all products types produced using mammalian production systems. In 2017, approximately 19 metric tons of product were needed. As more products enter the pipeline and products in development receive commercial approval each year, the overall kilogram requirements needed to meet product demand increase from just over 19 metric tons in 2017 to nearly 43 metric tons in 2022.

Figure 2: Estimated Quantity of Bulk Kilograms Needed to Meet Product Demand

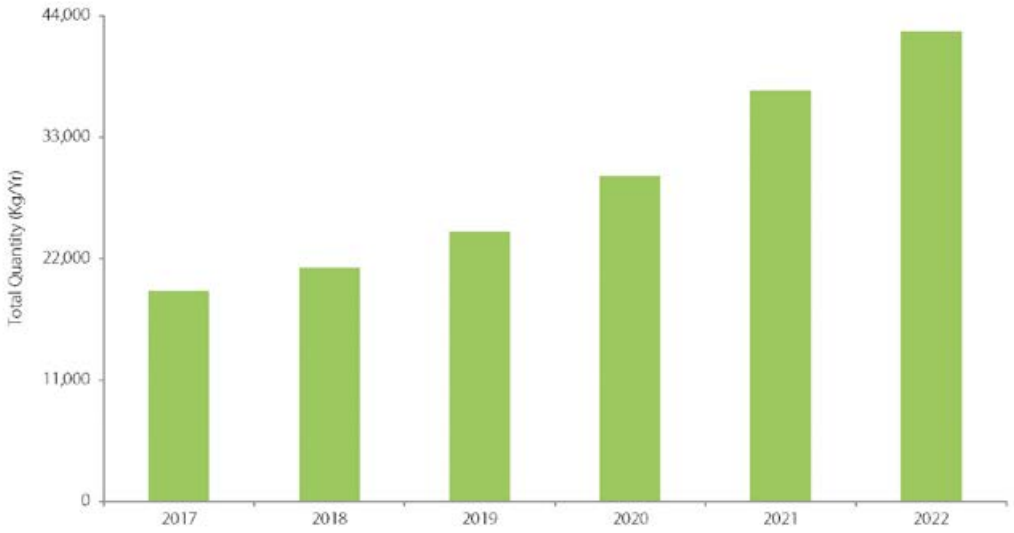
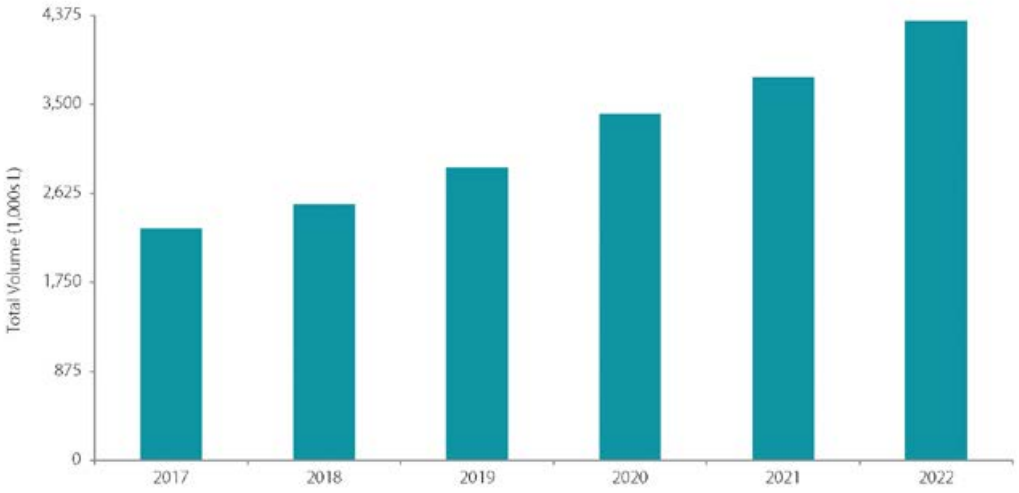


Figure 3 shows the volumetric capacity required to support the clinical development and eventual commercial sales of all current pipeline product candidates in the year shown. Each bar represents the total estimated volume required to meet the annual commercial and clinical demand for all product types using mammalian production systems in a given year. In 2017, the annual volumetric requirements were just over 2,300 kL, while in 2022, the volumetric requirement is projected to be just over 4,300 kL, a 5-year growth rate of nearly 14%.

Figure 3: Estimated Volumetric Capacity Needed to Meet Product Demand

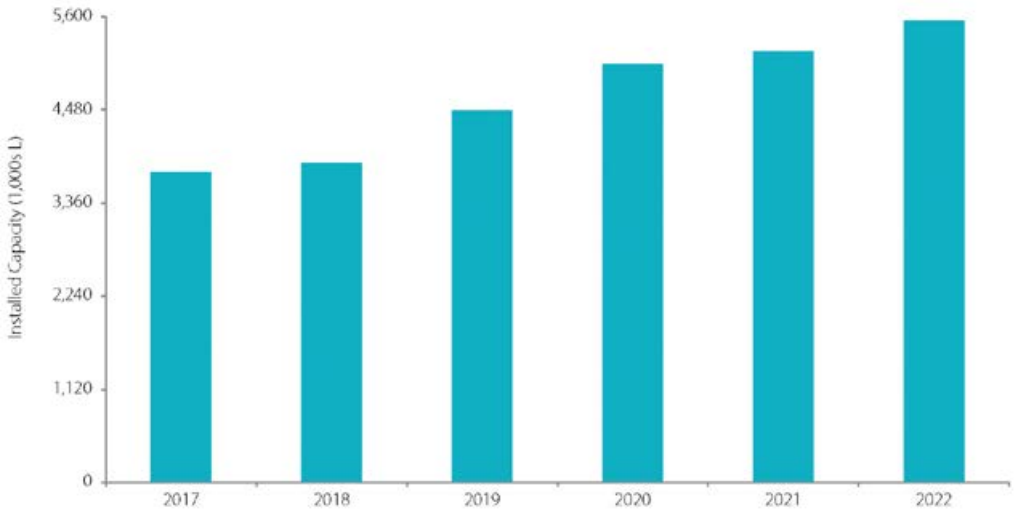


As with any forecasting model, our assumptions are based on the mostly probable scenarios. However, if biopharmaceuticals being developed for certain large patient population indications such as Alzheimer's disease or those targeting the PDL/PDL-1 checkpoint in cancer are approved and covered by Pharmacy Benefit Managers, a significant increase in demand for manufacturing capacity could occur potentially leading to a serious capacity shortage. Conversely, there are other manufacturing trends which could result in a lesser demand for some biopharmaceuticals, such as the increased focus on orphan indications, a shift from full length naked antibodies to alternative antibody formats and more potent products, e.g., antibody drug conjugates (ADCs) or bispecific antibodies, which would require lower doses, that in turn, would reduce the demand for manufacturing capacity. Given the projected increase in volumetric demand over the next 5 years, the industry is cognizant about the inherent volatility of production capacity forecasts. There is always a degree of uncertainty in balancing the demand and supply equation due to production problems, market demand over time, regulatory and reimbursement issues, and competitive factors.

To understand how the industry is positioned to meet these product demands, we estimated the 2017 mammalian cell culture supply to be approximately 3,700 kL and predict it to grow to approximately 5,600 kL by 2022, a 5-year growth rate of 8% (**Figure 4**). However, not all capacity is equally available throughout the industry. In 2017, Product companies, i.e., companies focused on product development, control approximately 70% of the installed mammalian cell culture capacity, while Hybrid companies, i.e., companies that are developing products,

but also sell or make available any excess manufacturing capacity, and CMOs control significantly less capacity, 13% and 17%, respectively. The distribution of capacity changes slightly in 2022, with Product companies controlling 65% of the installed capacity, while CMO and Hybrid companies increase their control to 21% and 14% of the capacity, respectively.

Figure 4: Mammalian Manufacturing Capacity



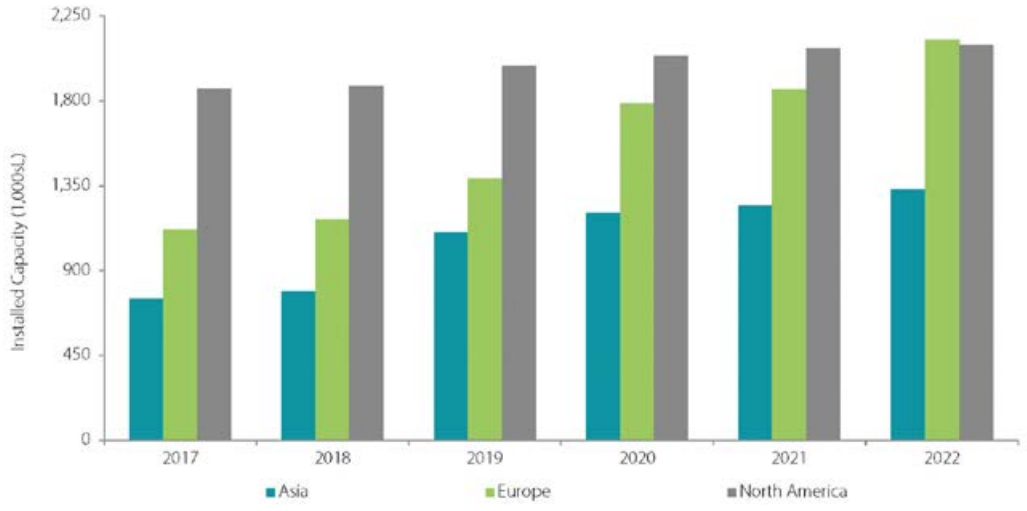
While Product companies control the majority of cell culture capacity, the distribution of this capacity is highly concentrated within ten companies, as shown in **Table 1**. Capacity for companies not ranked in the top ten are included in the "All Others" category. The "All Others" category included 127 companies in 2017, and 134 companies in 2021. Currently, 66% of the capacity is controlled by ten companies; in 2021, this changes to 62%. Based on substantial capacity investments, Novartis, Bristol-Myers Squibb and WuXi Biologics will displace Merck KGaA, Celltrion and Lilly from the top ten.

Table 1: Control of Manufacturing Capacity

2018 Rank	2022 Rank	Company	Company Type	2018 Volume (1,000sL)	2022 Volume (1,000sL)
1	1	F. Hoffmann-La Roche	Product	873	909
2	3	Lonza	CMO	253	371
3	6	Amgen	Product	225	246
4	2	Boehringer Ingelheim	Hybrid	218	401
5	5	Biogen	Product	186	306
6	-	Merck KGaA	Hybrid	183	-
7	4	Samsung Biologics	CMO	182	362
8	10	Pfizer	Product	149	183
9	-	Celltrion	Product	140	-
10	-	Eli Lilly	Product	137	-
-	7	Novartis	Hybrid	-	233
-	8	Bristol-Myers Squibb	Product	-	225
	9	WuXi Biologics	CMO	-	185
		All Others		1,296 (34%)	2,131 (38%)

These manufacturing facilities are located globally, as shown in **Figure 5**. In 2017, North America holds the greatest percentage of capacity (50%), followed by Europe (30%) and Asia (20%). There has been significant growth of capacity in Europe and Asia, with growth rates over 10% for both geographies, and by 2022, Europe (38%) has essentially equivalent installed capacity as North America (38%, differing by less than 30 L) while Asia has increased its capacity share slightly to 24%. The capacity growth in these areas, particularly in Korea and Singapore as well as Ireland, are due to government incentives and tax advantages, among other factors.

Figure 5: Geographic Distribution of Capacity



As described earlier, different products require different capacity. For example, the 2017 kilogram demand for each of the top six selling antibody products was >0.75 metric tons for a total approximately 8.8 metric tons. The demand for the remaining 73 marketed antibody products combined was approximately 9.4 metric tons.

For products still in development, in a best-case commercial scenario, where market success and maximum market penetration are assumed, projected demand for approximately 60% of these development products is expected to be less than 100 kg per product per year. Only 10% of the products, such as those for Alzheimer's Disease, Parkinson's Disease, Diabetes, and possibly some coronary heart disease or atherosclerosis products, are projected to require over 750 kg per year.

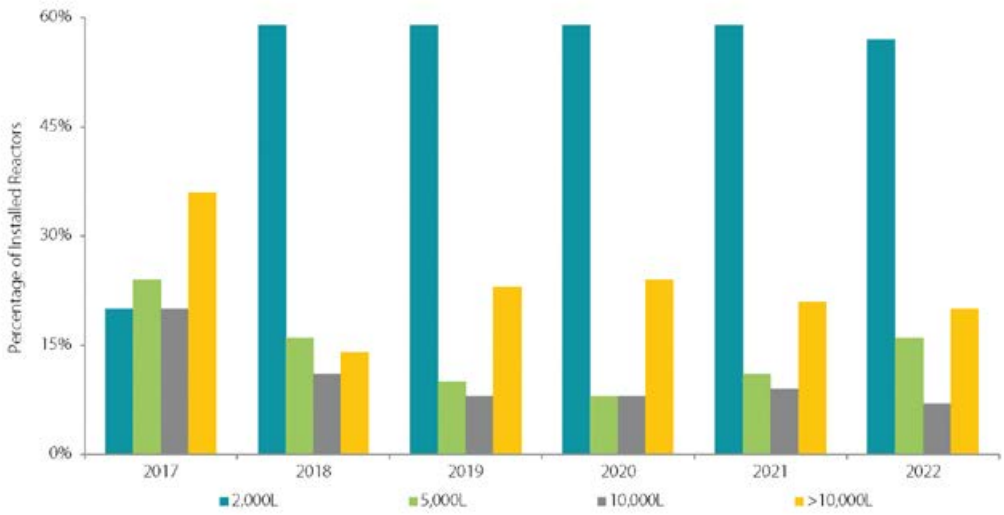
A closer review of future commercial manufacturing demands for products in Phase 2 and Phase 3 clinical development reveals that 55% of the products can likely be met with a single 2,000 or 5,000L bioreactor assuming 18 batches per year per bioreactor (**Table 2**). However, this does not mean that large scale capacity is no longer needed. Our model predicts that the remaining 45% of products will need bioreactor capacity of 10,000L and greater to meet the predicted demand. Increasing the number of bioreactors increases the manufacturing capacity and not surprisingly causes a shift in the percentage of products whose development can likely be met with a trio of 2,000L bioreactors to nearly 60% of the products in development.

Table 2: Control of Manufacturing Capacity

No. Bioreactors	2,000L Bioreactor	5,000L Bioreactor	10,000L Bioreactor	>10,000L Bioreactor
1	45%	10%	11%	34%
2	51%	15%	10%	24%
3	59%	13%	10%	18%

If we analyze the cumulative number and scale of bioreactors coming on line between 2017 and 2022 at the 2,000, 5,000, 10,000 and >10,000L scale (Figure 6), it is evident that the vast majority, nearly 60%, of the bioreactors projected to come on line are 2,000L. Nearly a third of the bioreactors are at a scale of 10,000 or greater. Interesting these values are somewhat similar to the proportion of products which will require manufacturing at a given scale.

Figure 6: Percentage and Scale of Future Bioreactors



Overall, the biopharmaceutical industry will continue to have strong growth for the foreseeable future, and antibody products will be the dominant driver of this growth. Installed capacity is currently able to meet the manufacturing demand for these products, but control and location of capacity can affect accessibility. The majority of capacity is product based, rather than CMO based, which could make it difficult for companies without capacity to access it at the right time and under the right conditions. North America has the greatest percentage of installed capacity, but Asia and Europe have seen a surge in new capacity installation.

While capacity will increase over the next five years, demand for capacity will increase at a slightly faster rate allowing for some short-term loosening of capacity constraints, but after 2022, capacity tightening may occur. In recent years, we have noted that the industry was experiencing some capacity constraints at the clinical scales due to very high clinical demand and the industry has responded in kind with a wave of facility expansions not seen in the recent past. The type and scale of capacity being installed will also be important as the demand for nearly half of products in mid-to-late stage development can be met with 5,000L of capacity or less; while the remaining half of products will need larger capacity to meet future demand. With new bioreactor installations mimicking the demand profile, we are keenly watching how the industry is responding to these demands for capacity as it is critically important to ensure current and future products are available to the patients.

PANEL MEMBER
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Top Bioprocessing Trends for the Next Five Years

5-year trend summary

- *Increased cell line productivity,* particularly for recombinant proteins – such as fusion proteins and enzymes – to increase productivity towards 2-5g/L range. This means potentially smaller bioreactors in the future, lower capital and operating costs.
- *Development timelines to fall* – with high-throughput techniques helping to optimise culture conditions.
- *High-efficiency perfusion techniques* to enable extremely high densities (~ 108cells/mL) in small volumes.
- *Rise in continuous bioprocessing* will see the return of perfusion bioreactors aided by inline new filtration technologies – ultrafiltration, diafiltration and concentration equipment.
- *Rapid growth of CAR-T and gene therapies* now that bioprocessing techniques have proved reliable in bringing product s through clinical and commercial production.

This article will highlight some of the top trends in bioprocessing now as this exciting field continues to flourish.

Introduction

Bioprocessing refers to the development and manufacturing processes to produce biopharmaceuticals, which are typically therapeutic proteins that are macromolecules 100-1000 larger than chemical drug molecules. Such proteins are produced in living cells through recombinant engineering, and then purified from the cells or their culture media using sophisticated protein-purification techniques in a multi-step downstream process. All of these areas have seen remarkable progress in the past thirty years since the first biopharmaceuticals were approved for human use. This article will highlight some of the top trends in bioprocessing now as this exciting field continues to flourish.

Rapid Development of High Productivity Upstream Processes

The productivity of a cell line is a product of its specific productivity, which refers to how much of the desired protein product the cell is producing, multiplied by the density to which the cells grow. Both of these areas have shown enormous growth that will continue due to the powerful economic drivers behind them. Simply put, higher productivity cultures mean smaller bioreactors and lower capital and operating costs. For production of well-defined proteins such as monoclonal antibodies, expected productivities in standard fed-batch cultures are now in the 2-5 g/L range. While that will probably increase slightly in the next five years, what is more likely is that such titers will be seen for other recombinant proteins such as fusion proteins and enzymes. These have lagged behind antibodies due to their higher variability and complexity, as well as the greater popularity and widespread application of antibody therapeutics. Furthermore, thanks to the continuing advances in understanding of recombinant engineering of production cells, the time to select cells with high specific productivities will continue to shorten.

Once several high-titer cell lines are selected for a protein therapeutic, the time to develop high productivity cultures will continue to shorten thanks to greater application of high-throughput techniques for the optimization of culture conditions. Micro-bioreactor arrays such as the ambr® (Sartorius), CellBRx (OmniBRx Biotechnologies) and BioLector (Mp2 Labs) allow rapid screening of a large number of media, feeds, and operating conditions such as temperature to determine those producing the highest titers. The top selections can then be further developed in micro and bench-scale bioreactors to simulate more closely the scale used in manufacturing.

Furthermore, cell densities in culture can be aggressively boosted using high-efficiency perfusion techniques to allow extremely high densities (~ 108 cells/mL) in small volumes. This type of process intensification will find increasing application in the next five years as the challenges from such intense processes are addressed.

Advances in Purification Resins and Membranes

Downstream technologies for the purification of proteins has been driven to higher capacities and speed due to the intense pressure from higher productivity upstream processes[1]. This is most clearly seen in the widely used affinity supports containing Protein A as the specific binding ligand. While early versions of this affinity resin had capacities of 10-20 mg/mL resin, newer versions now reach 80-100 mg/mL[2] .

Furthermore, the architecture of the chromatographic resins has been improved to provide a more rigid support allowing for faster flow rates. Finally, as membrane technology improves, it has been possible to reach very high flow rates and still achieve high capacities, such as seen with Natrix and similar new generation supports. This trend toward increasing capacities and flow properties of chromatographic supports will continue for the foreseeable future.

The valuable selectivity of Protein A for IgG antibodies and Fc-fusion proteins has proven itself in that affinity resins with this ligand have become the backbone of downstream processing for these biopharmaceuticals. However, as bioprocessors face new molecules lacking the binding site for Protein A, they are reaching out to alternative affinity supports such as custom supports generated via recombinant technologies from specialized antibodies (nanobodies, BAC Ligands) or via selection of binding peptides utilizing vast libraries of peptide structures. Alternatively, increasing the selective power of standard chromatographic modalities by combining two of them one support to generate a "multi-mode" or "mixed-mode" support can provide highly selective supports and combine two chromatographic steps into one. Both the custom-affinity and multi-mode supports will see increasing application as the variety and complexity of protein therapeutics increases.

Continuous Bioprocessing

This is a trend that has finally come to the biomanufacturing as competitive pressures force more efficient bioprocessing to reduce time and costs[3,4] While most bioprocessing is still performed in batch mode, both upstream and downstream, most companies are evaluating ways to decrease the batch nature of their processes to streamline them. On the upstream side this has meant a return to consideration of perfusion bioreactors to continuously produce product. While a perfusion mode can be more complex operationally, advances in process controls and single-use technologies have addressed many of the difficulties. Furthermore, for more sensitive proteins, perfusion can help address degradation in the bioreactor by continuously removing the protein product for downstream processing[5].

On the downstream side, one can take steps towards continuous processing by combining two previously separate orthogonal purification steps into one step by vertically integrating the buffers and flow rates. But reaching a full continuous process from typically at least 4-5 separate steps has needed to advent of simulated moving bed (SMB) or sequential multi-column chromatography (SMCC) technology such as now being offered at process scale by companies such as Pall and Novasep. Utilizing an array of precisely controlled valves, detectors and arrays of 3-6 columns per step, one can flow directly through such an instrument to harvest purified protein continuously.

New filtration technologies such as inline ultrafiltration, diafiltration and concentration equipment allow these steps to now be added into continuous processes[6].To this has been added techniques for clarification of bioreactor cultures such as acoustic wave technology[7] and continuous centrifugation[8] that can streamline and reduce the filter burden of clarification. This is particularly valuable as cell-culture densities have increased to as much as 50-100 million cells/mL with concentrated upstream processes.

While a perfusion mode can be more complex operationally, advances in process controls and single-use technologies have addressed many of the difficulties

Improvements in Manufacturing of Biosimilars

The manufacturing challenges of biosimilars has been well documented[9,10] and is attributed to the need to produce a highly similar version of a complex macromolecular protein drug that really represents a collection of closely related variants of the intended structure. The use of different cell lines, culture media and conditions, and downstream processing can affect the proportion of these variants and hence the similarity of the biosimilar to the reference drug. Nevertheless, thanks to advanced analytical techniques, improved understanding of molecular biology and recombinant technology, and biochemistry of post-translational modifications and protein degradation, great progress has been made in manufacture and licensure of biosimilars. This trend will continue as more companies are investing in biosimilar manufacturing and more reference drugs are amenable to biosimilar competition due to patent expiries,

Bioprocessing for Cellular and Gene Therapy

Advances in new therapeutics such as Chimeric Antigen Receptor T-Cells (CAR-T) and Gene Therapies have brought to the fore the bioprocessing of a very different type of biologic product than the standard protein therapeutic. Rather than growing cells that produce a desired recombinant protein, in which case the production cells are removed, for cellular therapy the cultured cells become the product to treat the patient. This brings extraordinary

new challenges, including the need to keep the cells alive for the patient and the absolute requirement that any particular cell culture be matched to the patient to avoid immunological rejection. Gene therapy generally relies on a vector such as a virus to introduce and propagate the desired genetic material in the relevant cells of the patient. Such vectors must be carefully selected and controlled, and grown and stored under conditions that maintain viability. In spite of such challenges, bioprocessors have risen to the occasion to allow production of clinical trial and more recently commercial material for approval for patient treatment of these exciting new therapies. The trend toward such biotherapies will continue as they are perfected and applied to more diseases.

Conclusion

Bioprocessing continues to be a growth field in biotechnology thanks to the great success of biotherapeutics at addressing previously unmet medical needs and their continuing application to new disease challenges. The key trends detailed above of improvements in upstream, downstream and continuous bioprocessing, as well as greater numbers of biosimilars and new applications for cellular and gene therapies, will continue to push the field of bioprocessing forward.

Bioprocessing continues to be a growth field in biotechnology thanks to the great success of biotherapeutics at addressing previously unmet medical needs

References

1 Clinke M.-F., Mölleryd C., Zhang Y., Lindskog E., Walsh K., Chotteau V. Very high Density CHO Cells in Perfusion by ATF or TFF in Wave Bioreactor. Biotechnol Prog 2013 29(3): 754-767.

2 Mehta K.K., Soderquist R., Shah, P., Marchand N., Bolton G.R. Comparing Performance of New Protein A Resins for Monoclonal Antibody Purification. Amer Pharm Rev 2018 21(1): 61-64.

3 Jungbauer A, Hammerschmidt N., Integrated continuous manufacturing of biopharmaceuticals. In Continuous Manufacturing of Pharmaceuticals, P. Kleinebudde, J. Khinast, J. Rantanen, eds. Wiley & Sons, New York. 2017

4 Zijlstra G, Gupta P. Moving toward continuous processing. Gen Eng News 2017 Sep 15; 37(16).

5 Jorjorian P, Kenyon D. How to set up a perfusion process for higher productivity and quality. Bioproc Intl. 2017. Apr 17.

6 Sutton S. The evolution of continuous processing. Medicine Maker 2017.

7 Gjoka X, Gantier R, Schofield. Platform for integrated continuous bioprocessing. Biopharm Intl 2017; 30(7) 26-32.

8 Richardson A, Walker J. Continuous solids-discharging centrifugation: A solution to the challenges of clarifying high-cell-density mammalian-cell cultures. Bioproc. Intl. 2018 Mar.

9 Wechsler J. Biosimilars raise manufacturing and regulatory challenges. Pharm Tech 2018; 42(7) 14-15.

10 Martin J, Ultee M. Manufacturing biosimilars: know the challenges and best practices. Pharm Manuf 2017 Jul 12.

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The Intersection of Small Pharma and BioPharma

Introduction

Over the past few decades, as the biopharma industry has emerged and matured, there has been an increasing merging of interests between the biopharma and pharma industries. One critical area is in hiring excellent staff. The density of biopharma opportunities in Boston and San Francisco create a challenge to recruiting managers as they find supply does not always keep up with demand. In contrast, other geographies where growth of Pharma companies historically created consistently large demand for new staff, companies now have many talented scientists who, after restructuring, eagerly seek opportunities to add value to new enterprises. These individuals are already well versed in cGMP compliance, while not all may be able to bridge the gap between small molecules and biologics. Some have skills that are directly applicable while others have worked in adjacent spaces that at least are relevant.

Data has been published for BioPlan Associates, 15th Annual Survey on Biopharmaceutical Manufacturing Capacity and Production (see: www.bioplanassociates.com/15th). This provided insights into functional skill areas that could be portable between Pharma and Biopharma manufacturing. The findings from recent Annual Reports continue to suggest a shortage existed in bioprocessing expertise translating to bottlenecks in the biomanufacturing space. BioPlan Associates independently compiled the data referenced in this section. Questions focused on which functional skill areas are perceived to be portable from Pharma to Biopharma in comparison to actual hiring practices. The two questions below specifically asked Biopharma professionals to select from a list of about 30 skill categories that apply to the following:

"In which of the following areas could large molecule biomanufacturing benefit from small molecule Pharma manufacturing experience [in hiring manufacturing, operations, GMP]"

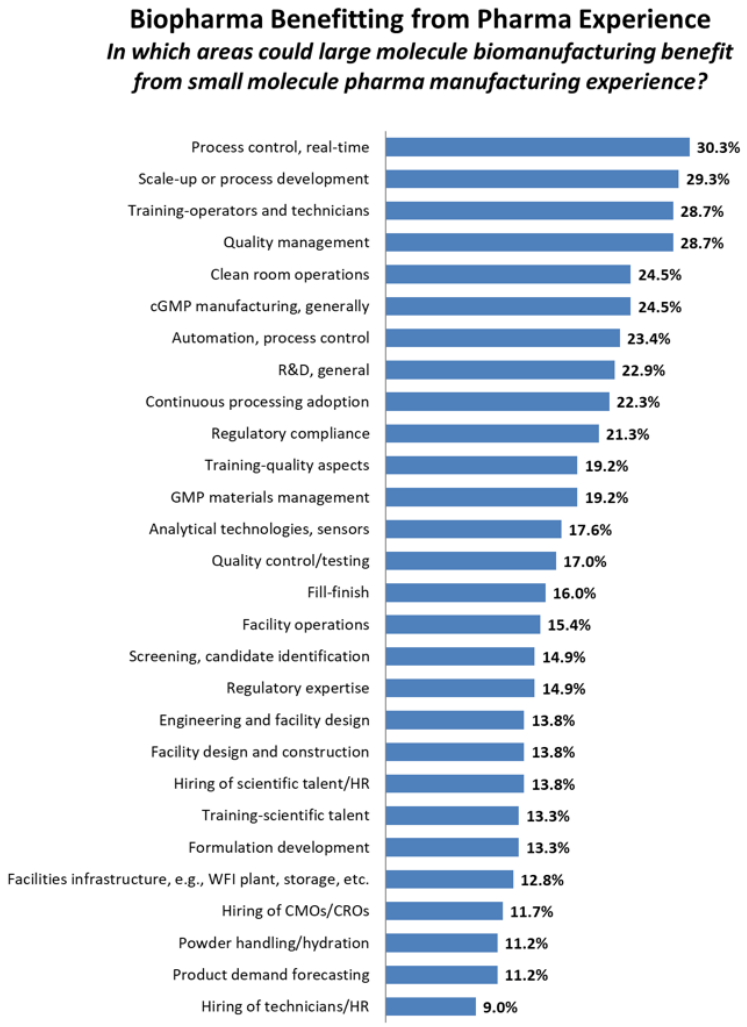
"Large molecule (Biopharma) vs. small molecule (Pharma): For which areas has your large molecule biopharmaceutical facility hired consultants, staff, contractors, engineers, etc. particularly for their small molecule pharmaceutical industry expertise?"

More than 220 professionals participated in the survey. This data will also be used as part of a new event called bioLIVE that will launch at CPhI Worldwide later this year. The intent of this effort is to help bring small and large molecule industries closer together.

The first question seeks to obtain feedback on perceived portability of the listed functional skill areas, while the second provides insight to demonstrated behavior.

Evaluating the responses to the first questions (refer to Figure 2.1): The most frequently selected skill areas include Process Control (real-time); Scale-up or Process Development; Training operators and technicians; and Quality Management. Nearly 30% of those responding felt these four skill areas could port between industries. It is not unexpected to see quality and process control to be considered highly portable. However, given the specific and distinct nature of the associated processes, the selection of Scale-up or Process Development is interesting.

Fig. 2-1: Biopharma Benefitting from Pharma Experience



Nearly a quarter of the respondents considered R&D (General); Clean Room Operations; cGMP Manufacturing (General); and Automation, Process Control to be the next most portable skills.

About one in five indicated that the following skill areas were portable:
1. Continuous processing adoption
2. Regulatory Compliance
3. Training (quality aspects)
4. GMP Materials Management

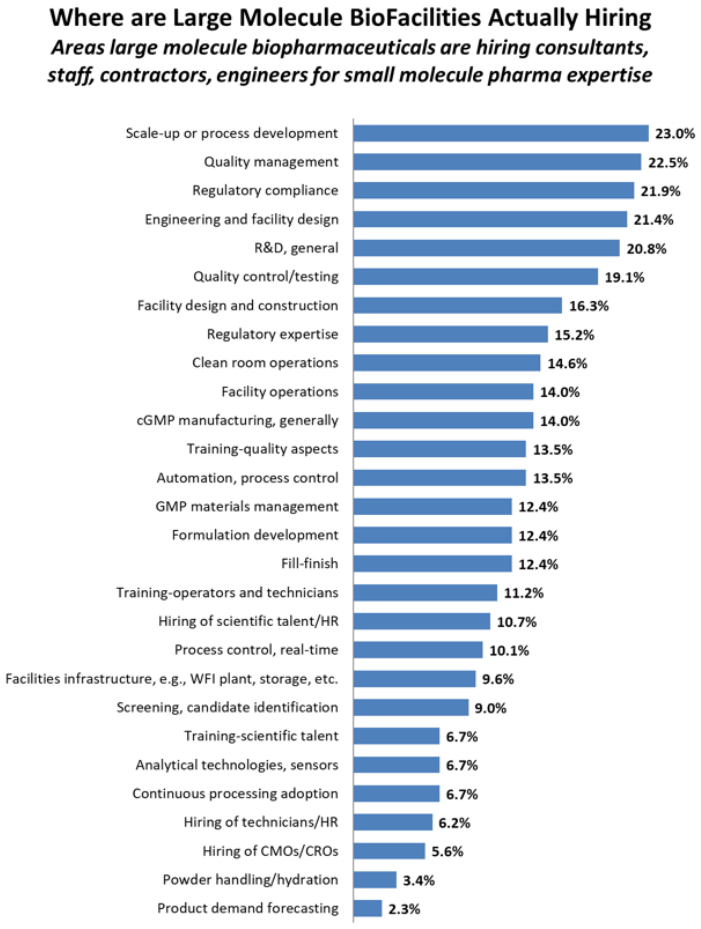
Between 15-18% of respondents selected the following as portable:
1. Analytical technologies (sensors)
2. Quality Control Testing
3. Fill Finish
4. Facility Operations
5. Screening candidate identification
6. Regulatory expertise

The reported areas perceived as least portable (9 to 12%) were:
1. Hiring of CMOs /ROs
2. Powder Handling/Hydration
3. Product demand forecasting
4. Hiring of technicians/HR

In contrast, some significant shifts were noted in actual hiring responses (refer to Figure 2-2). Nearly 23% of respondents most frequently hired for: Scale-up or Process Development; and Quality Management. About 20% hired for: Regulatory Compliance; Engineering Facility Design; R&D General; and Quality Control Testing.

Regulatory Expertise and Facility Design and Construction hires were reported by nearly 16% of respondents.

Fig. 2-2: Where Large Molecule BioFacilities Are Hiring From



Contrasting the perceived vs. actual numbers provides additional insight. Table 2-1 lists the top ten skill categories selected by respondents.

Table 2-1: Top Ten Skill Categories Perceived to be Portable

Category	Perceived Need %	Actual Hired %	Delta %
Process Control (real-time)	30	10	(20)
Scale-up or Process Development	29	23	(6)
Quality Management	29	22	(7)
Training-operators and technicians	29	11	(18)
Clean Room Operations	24	15	(9)
cGMP Manufacturing (General)	24	14	(10)
R&D (General)	23	21	(2)
Automation, Process Control	23	13	(10)
Continuous Process Adoption	22	7	(15)
Regulatory Compliance	21	22	1

Looking at the top three categories perceived to be portable, the actual hires reported for Quality Management; and Scale-up or Process Development were within 6-7% of reported perceived portability. Quality Rx experience is generally regarded as being very portable. Professionals who truly understand and have participated in robust quality management systems (QMS) have acquired a set of guiding principles that transcend specific technologies or applications. Most QA professionals already have technical degrees and have already found it necessary to come up to speed in areas new to them and bridge across more than a few technical fields as they rotate through various parts of organizations.

Ironically, the most frequently selected category, Process Control roles, shows the largest deviation for actual hires. In this case, the ratio of those reporting actually hiring for Process Control positions vs those who perceived this skill as portable (33%) is less than half the ratio reported hiring a position in Scale-up or Process Development (79%); and Quality Management (76%).

Of the top ten categories in Table I, only the hiring rate for Regulatory Compliance showed an increase vs. the perceived percentage. The other categories (refer to Figures 2-1 and 2-2) with a reported hiring rate greater than their perceived rate of portability were: Quality Control Testing; and Facility design and construction; (both within 3%). Engineering and Facility Design were almost 8% higher, while Regulatory Expertise was at just under 1%, which compares almost equivalently with Regulatory Compliance perception vs. actual hiring.

The rest of the reported categories ranged from between 0.25 to 11% lower than the reported perceived percentage. Clearly, caution should be exercised when drawing too many conclusions from this limited data. Opportunities to hire against specific positions are not constant.

Without further data, it is difficult to determine whether other underlying factors are at work. What can be said is that ***up to a third of respondents clearly indicated openness for importing talent from Pharma into Biopharma manufacturing to help close hiring gaps.*** The concept of some skill sets being portable between industries is not new. The natural tendency is to hire people with similar backgrounds to ourselves. However, in many instances, and for a variety of reasons, an exact fit may not be available. Companies that operate in rapidly growing markets such as biomanufacturing today often face situations where "ideal" candidates are in short supply. This is where successful leaders differentiate themselves by identifying and hiring against core skill sets balanced against candidates with demonstrated learning agility.

The challenge is to be able to move away from the idea that, "since I have been successful in a particular area, only people like me will be successful," vs. identifying core skills that enable success. Employers must be willing to hire those who can quickly ramp-up and apply their existing skills in a new environment.

In my experience, I have seen many examples of people successfully porting skills from one industry to another. During the late 1990s and early 2000s, the pharmaceutical industry was rapidly growing with many start-ups along with expansive growth among traditional players. Demand for talent was high, and it was often difficult to find strong candidates who also had industry experience. In one specific instance, a manager seeking a strong senior scientist in Analytical Development found an individual who demonstrated excellent scientific, problem–solving, and leadership skills. The challenge was that this individual's experience was in the petrochemical industry. While his analytical skills were strong, he had no drug development, nor cGMP experience. There was a lot of push-back from other department leaders: "he doesn't know cGMP," vocalizing their concern that he would not succeed. We all know that cGMPs are important and require serious study and discipline. However, the key point is that everyone in our regulated industry has to learn them sometime. By interviewing for the right analytical scientific problem-solving skills; evaluating the individual's learning agility combined with open conversations about cGMPs and related expectations, this candidate from the petrochemical industry was eventually chosen. With focused training (and the right mindset) an appropriate level of competence was quickly achieved. He came up-to-speed quickly on cGMPs and became a valuable team member. He continues to work in the pharmaceutical industry today in a leadership role. Ironically, the primary concern raised by others in this example focused on the gap in cGMP experience. Fortunately, in considering the transition from Pharma to Biopharma, not only is this not a concern, it may well be an advantage.

They say that the only constant is change. If so, learning agility needs to be high on the list of core competencies in recruiting. Employers must be able to differentiate between skills that cannot be learned on the job vs. those that can. This is applicable whether a person is transitioning between market sectors or trying to keep up with the rapid changes that occur within a given sector. The changes occurring within the Biopharma sector will require new approaches to meet today's needs as well as to drive innovation to improve productivity, increase quality, and decrease costs.

I recently spoke with colleagues about the exponential growth in Biopharmaceuticals that the associated hiring challenges has created. Many companies have experienced a hiring crunch, especially near large biotech hubs and this has increased the cost of hiring. As staff are trained and move past entry level positions, they become increasingly attractive to potential poachers.

"We have directly imported many employees from Big Pharma with small molecule chemical skills who have successfully bridged into development and manufacturing for ADCs where their small molecule experience is actually key to successful bioconjugates,"

An example where directly applicable skills applies to companies who have strong antibody drug conjugate (ADC) capabilities. "We have directly imported many employees from Big Pharma with small molecule chemical skills who have successfully bridged into development and manufacturing for ADCs where their small molecule experience is actually key to successful bioconjugates," said Sven Lee, Chief Business Officer for Abzena. Positions with relevant skills include Process Development, conjugation, QA and formulation development.

Related to this topic, BioPlan Associates have commented on the maturation process experienced in the biomanufacturing sector.

"In the past, biologics manufacturing had to be done at most any cost, simply to get a product to the clinic. In comparison to small molecule drug production, which has had many decades (if not centuries) to improve its production efficiency, biologics are relative newcomers to modern production technology, automation, monitoring and optimization."

Biomanufacturing has been transitioning from an industry in its infancy to one with tailored, sophisticated optimization data and techniques. As processes for biologics manufacturing continue to mature, there are lessons to be learned from their Pharma peers to help drive enhanced productivity and quality while simultaneously lowering costs, creating a need to bring process efficiency to the small Biopharma companies. The processes and skills that have been honed at larger companies to drive operational excellence (whether those manufacturing executives are coming from Big Bio or Big Pharma) are key to the smaller companies' growth and profitability prospects. As small companies reach a tipping point in their life cycle, they must move beyond the "just get it done by any means" mode to a "growth by design" mode in order to be prepared for commercialization and beyond. These processes and skills need to be injected into the organization early enough to ensure everything from strategy planning through expansion projects are designed with commercial efficiency in mind. It takes too long and can be costly to a business' existence to try and build this experience organically through trial and error.

Over the last decade or so, many of the larger biomanufacturing players have implemented more sophisticated production management systems to provide real monitoring/optimization. Nevertheless, in comparison to small molecule counterparts, there is still much room for improvement.

Biomanufacturing has been transitioning from an industry in its infancy to one with tailored, sophisticated optimization data and techniques.

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CPhI drives growth and innovation at every step of the global pharmaceutical supply chain from drug discovery to finished dosage. Through exhibitions, conferences and online communities, CPhI brings together more than 100,000 pharmaceutical professionals each year to network, identify business opportunities and expand the global market. CPhI hosts events in Europe, China, India, Japan, Southeast Asia, Russia, Istanbul and Korea co-located with ICSE for contract services, P-MEC for machinery, equipment & technology, InnoPack for pharmaceutical packaging and BioPh for biopharma. CPhI provides an online buyer & supplier directory at CPhI-Online.com.

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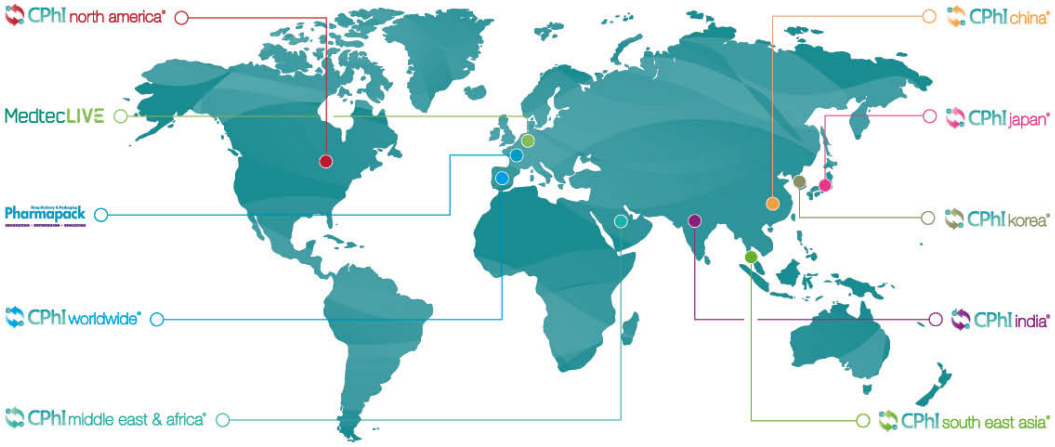

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