CPhI insights

New modalities, new methods and new thinking to solve old problems

Industry Expert Panel Submissions

CPhI Annual Industry Report 2019

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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.

Contents

CPhI's Pharma Industry Rankings: Evaluation of current Pharma

This year's CPhI Pharma Industry Rankings report once again returns, bringing a key analysis of the strength of the major pharmaceutical markets and the industry as a whole.

The survey has been completed by 350 top pharma experts giving the best picture possible of global performance in 2019. Country's pharmaceutical markets are assessed on a range of key indicators, such as market 'growth potential', 'API manufacturing', 'Innovation', 'Competitiveness', and 'Finished Product' – all which are taken into consideration for their final overall scores.

The report comes just in time for CPhI Worldwide 2019 taking place November (5-7) in Frankfurt, Germany. CPhI Worldwide 2019 is expecting over 45,000 visitors from more than 160 countries, making it the largest pharma exhibition ever. The event promises unbeatable insights on pharma's latest trends, with forecasts on potential future implications, as well as unrivaled networking opportunities.

The overall index: what do the collated findings mean for the global industry in 2020?

When collated across all markets, and all survey categories, the industry as a whole has experienced a 2.48% increase, which indicates the market has increased its overall confidence.

Perhaps more significantly, overall growth is perceived to be rising by an impressive 5.4% annually, which bodes extremely well for CPhI Worldwide attendees in the year ahead.

Pharma market growth potential

This year's report sees China (7.66) surge to the top of the rankings for growth potential overtaking both India (7.43) and USA (6.92). China also displayed the biggest growth in percentage terms, increasing 12.5% from last year. This likely reflects the real effort to increase standards throughout the supply chain, which have been recognised by executives, generating an increasingly prominent international business reputation.

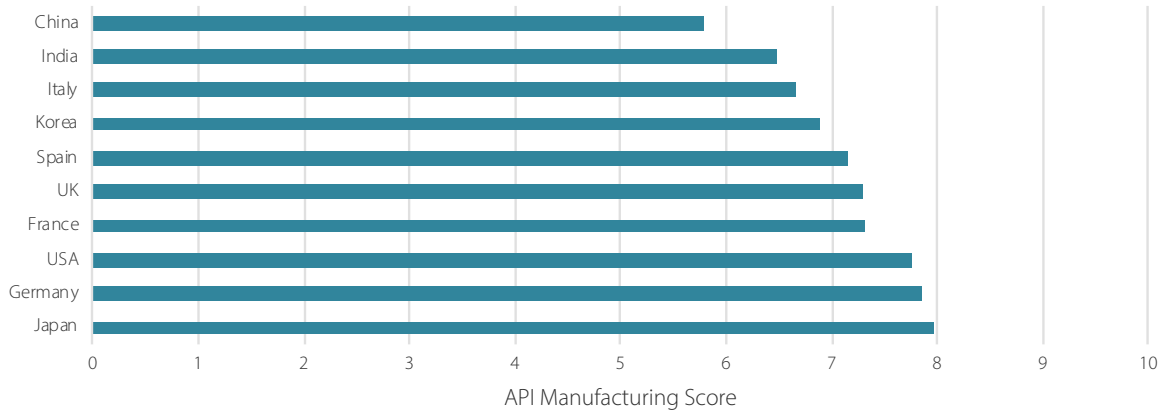
Germany (6.92) – the host of this year's CPhI Worldwide – retains its place as Europe's leading market for growth potential. It has, significantly, also overtaken the USA, boasting an impressive 11.4% increase in 2018, and becoming the leading Western economy for growth. Such exceptional growth coincides with the UK's declining fortunes in growth potential terms, as industry experts envisage (whether based on reality or perception) Germany being the leading beneficiary of the UK's exit from the European union.

Growth Potential of Pharma Industry 2019

API manufacturing

API manufacturing quality is always a key indicator for the performance of pharmaceutical markets – with many of pharma's developed markets still perceived as ahead of the large volume producers. With a respectable growth of 2.5%, Japan (7.97) has pushed ahead of Germany (7.85) to the number one spot for API manufacturing quality. But, it is Spain (7.16) and Korea (6.89) that are the big movers, with scores increasing by 6.4% and 5.5% respectively overtaking Italy (6.7). Korea's performance sees the country improve its perceived quality of manufactured APIs, which could be a positive response from the market of recent government efforts to repatriate manufacturing and the desire for generic companies to source locally manufactured APIs. In Europe, Germany (7.85) retains its position as the preeminent API Manufacturer (7.78) ahead of France (7.31) and the United Kingdom (7.30).

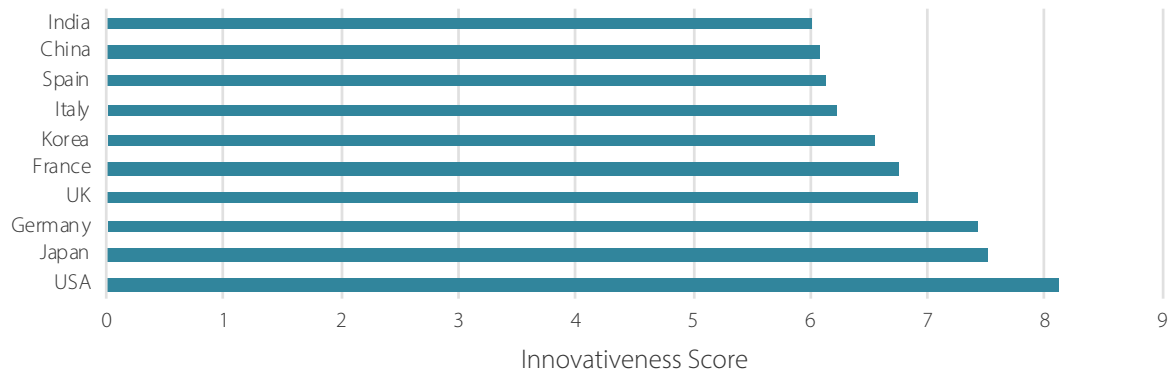
API Manufacturing 2019



Innovation

The USA (8.12) retains its top position in this year's report. It also boasts the largest growth increase (2.5%) out of all assessed markets, while Japan (7.51) and Germany (7.43) remain in second and third position respectively. 2019 has seen Korea take huge strides forward in innovation, scoring a reputable 6.54 and overtaking Spain (6.13) and India (6.01). Korea's reputation continues reaping the rewards of recent regulatory reforms and a growing biotech market, with an increasing number of companies highlighting Korea as the up and coming region for innovation (experiencing an 8% rise over the last two years). India, surprisingly, has fallen to the bottom of the table with the worst growth rate (-6.3%) of all the countries. However, according to a recent report , the Indian Pharmaceutical Alliance (IPA) is urging the government to set up a fund to provide a 'much-needed boost to innovation in the pharma and biopharma space'. If enacted, this may see an improved reputation for innovation in the next few years.

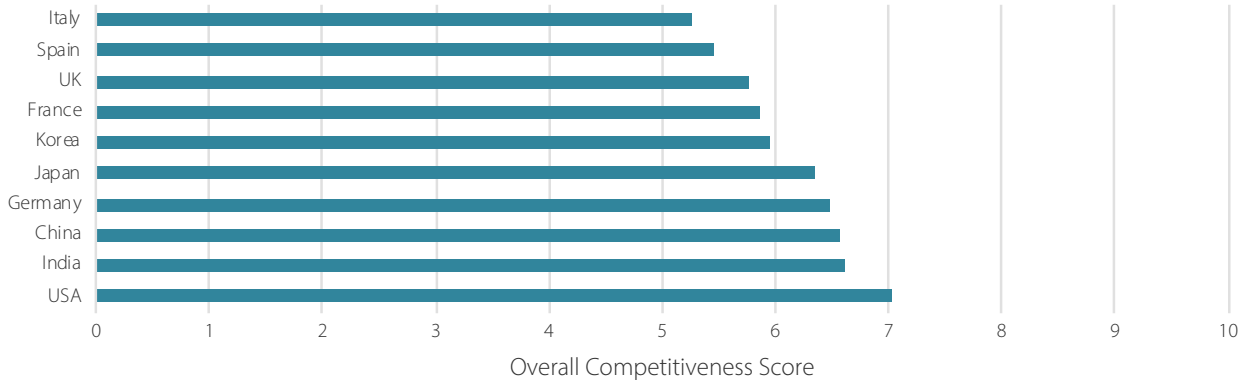
Innovativness of The Pharma Industry 2019



Competitiveness

As with innovation, the USA (7.04) takes the top spot for Competitiveness. Surprisingly, given its strong showing in other categories, Germany (6.47) has slipped from second to fourth, with a decrease of 1.3%. Moving up to third is China (6.56) with the largest increase in growth (3.9%) for competitiveness. This may stem from executives belief that the Chinese government is actively increasing standards throughout its pharma sector and becoming increasingly competitive across more sectors than ingredients. At the opposite end of the table, Italy falls to last position, with a score of 5.25. The UK also slides down the rankings scoring 5.77, down 2.8% on last year's score of 5.94. Competitiveness was assessed through respondents evaluation of each country's tax environment, quality of employees, infrastructure, research potential, labor costs, accessibility, and access to funds.

Overall Competitiveness 2019



Finished product manufacturing

Germany (8.17), the U.S. (8.11) and Japan (7.97) are again ranked, as tier one nations, above all other major pharma economies in terms of the quality of finished formulations. Interestingly, CPhI Worldwide 2020 host country, Italy has grown by almost 14% over the last two years, emphasizing the strength of market conditions in Italy in the finished product manufacturing sector. A separate report by Farmaindustria provides some context to this, with the findings showing that, in the last year, Italy has equalled Germany in total production, as well as production per unit[1].

All markets except the UK showed positive growth. As mentioned previously, Brexit is looming large over the UK's pharma industry with Germany perceived as the chief beneficiary.

Korea registered the biggest percentage growth rate in this category. Reporting, a healthy 3.72% increase, which sees it rise above Spain (6.79) – a nation that recorded a marked decrease (-3.10%). Spain's performance may be a consequence of German and Italian improvements in finished product perception. India (5.86) and China (5.28) – who both see notable decreases in score from last year – remain at the bottom of the rankings.

Quality of Finished Products 2019

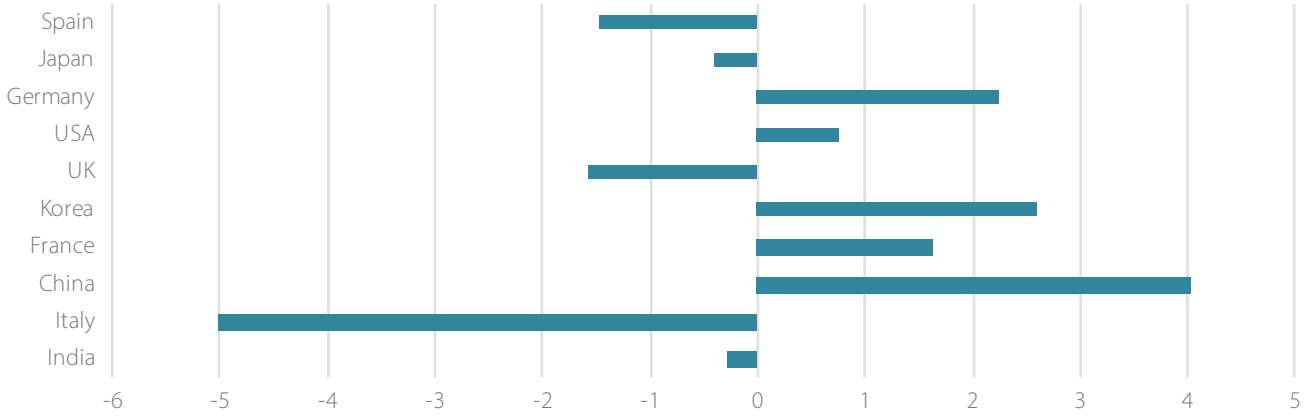
Change in Country overall score

To calculate the overall score, the results from five main (solid dose) categories are collateralized and each is given equal weighting in the determination. Yet again, USA (7.56), Germany (7.37), and Japan (7.16) make up the top three with Germany showing significant growth (2.24%) from the previous year. The result reflects each market's current performance, in particular, in API manufacturing, Innovativeness, Competitiveness, and Quality of finished products.

France (6.66) has climbed above the UK (6.56), taking second place in European Pharma markets behind Germany. This is mostly due to the UK suffering from the largest growth decrease (1.6%) of all the markets reported on, with significant decreases seen in competitiveness (-3%), growth potential (-4%), and innovation (-2%). Korea (6.50), surprisingly was the market with the second largest overall rise, who have seen a fantastic overall growth increase of 2.6% from 2018. Korea appears to be one of the industry's rising stars, as the nation displayed true progression across the five key indicators. Such progression was also reflected in this year's CPhI Korea event, which saw record numbers of attendees and domestic exhibitors. At the other end of the scale, Spain suffered a percentage point reduction in overall score (1.48%). This can be attributed to decreases in scores for innovation, competitiveness, and finished product.

Of the countries survey, China has again made the largest overall improvement, with a 4% rise this year and a 13.6% increase over the last two, moving up one place. However, in Europe, what is interesting is the trend of Germany and France seeing overall improvements – possibly at the expense of the United Kingdom, Italy and Spain, which all saw overall score reductions.

Change in Overall Scores (%) 2019

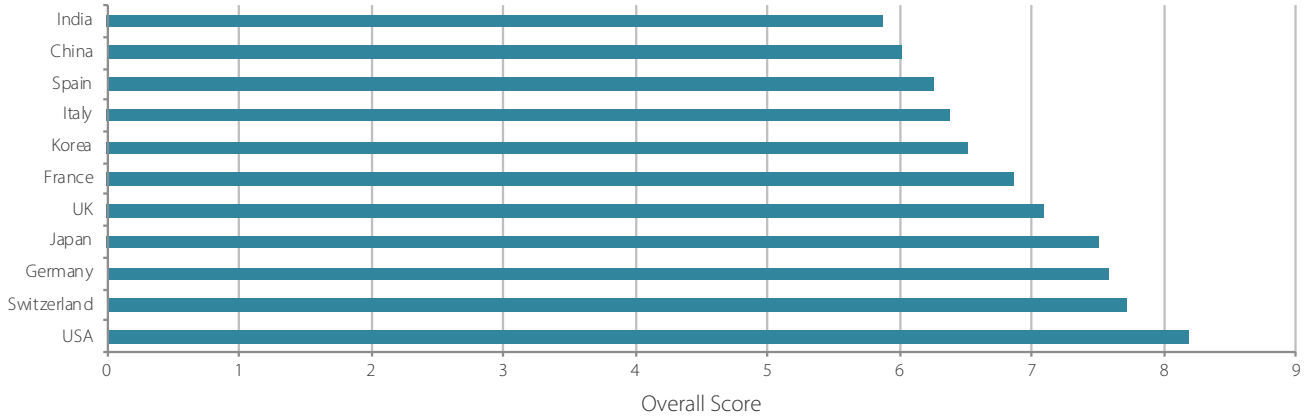


Innovativeness in drug delivery

The United States maintains its position as the world's pre-eminent drug delivery economy, with a score of 8.2. In the last year, it opened up a substantial lead over Germany and Japan – 2018's second and third placed economies – as both saw a year-on-year score decrease of around 5%. The positions of the United Kingdom and France have remained largely unchanged. However, the most significant result is Switzerland. The biggest year-on-year increase of around 6% has seen Switzerland move ahead of Germany and Japan to claim second place with a score of 7.7. As a result, we now see a four-strong, tier one market. The United Kingdom and France make up tier two, and Italy, Spain, and Korea a third tier amongst the most innovative nations.

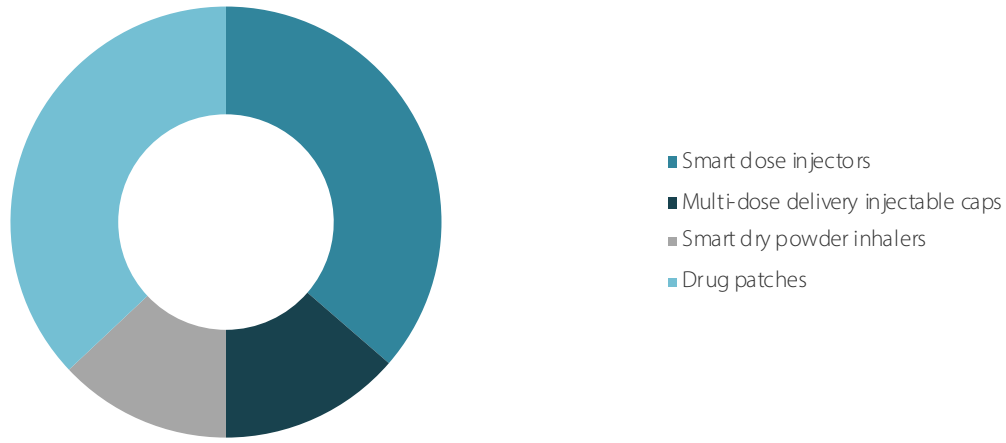
India and China remain at the bottom, but the real insight is in how they have again made substantial gains. Respective scores are up by a remarkable 25% and an even more astounding 43%. Maintaining these rates of improvement could see both countries achieving parity with tier 3 markets in the next year. This would represent a key milestone for the global industry and signal that these two vast nations are now entering a mature stage. Executives are increasingly regarding India and China as equals of many western markets. This could well signal completive challenges ahead as the emerging nations compete on quality as well as cost.

Innovativeness of each country's drug delivery company industry



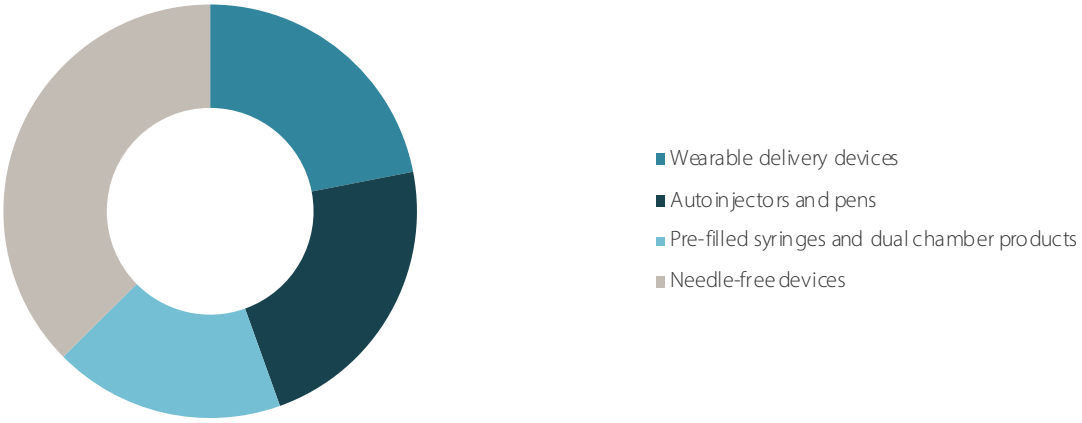
The most promising recent drug delivery devices

37% of our experts believe that drug patches are the most promising drug delivery device, which is closely followed by smart dose injectors, taking 36% of the votes. Multi-dose delivery injectable caps and smart dry powder inhalers receive 14% and 13% of the votes, respectively.



The most anticipated drug delivery device to double in growth in 2020

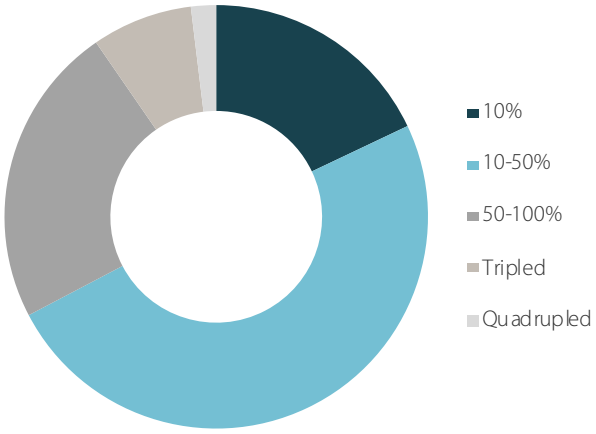
Out of the provided options, needle-free devices are predicted to most likely witness a doubling in growth within the next year by 37% of our executives, with autoinjectors (23%), 'wearable devices' (22%), and 'pre-filled syringes and dual chamber products' (18%) trailing behind. These scores demonstrate the patient-centric emphasis in the market – that is, a want for the most painless and easy-to-use devices, with minimally invasive routes of administration.



Anticipated investment in Eco-packaging over the next 5 years

The pharmaceutical industry – particularly, the packaging sector – is no stranger to striving towards sustainability and eco-friendliness by aiming to reduce produced waste, use of plastics, and its overall footprint. With a wave of new regulatory reforms and innovations, we are starting to see positive changes take shape. And, with these changes, more investment into eco-packaging.

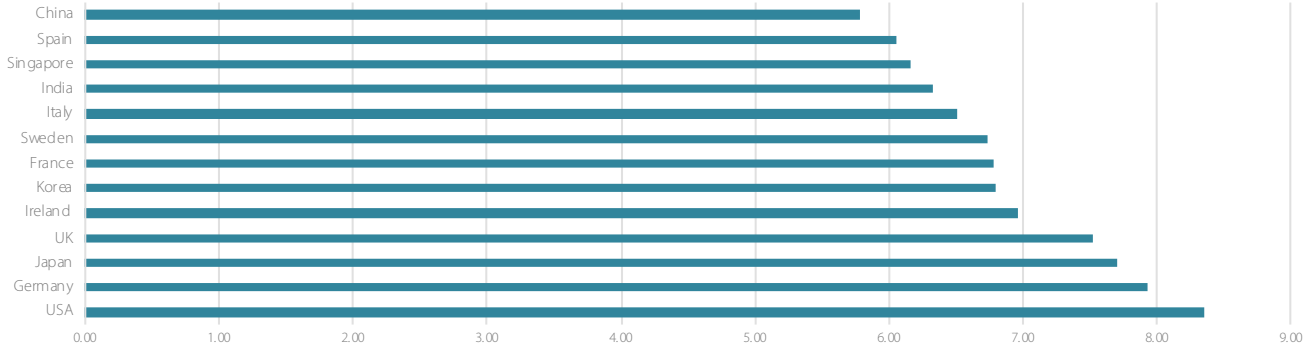
From a total of 156 respondents, 49% of executives believe that investment in eco-packaging will increase by 10-50% by 2024. A substantial 23% feel that investment will increase by 50-100% in this timeframe, with nearly 10% believing that it could even triple, or better yet, quadruple.



Knowledge of Biologics Professionals

The U.S. (8.35), Germany (7.93) and Japan (7.69) remain the industry leaders for knowledge of their biologics professionals, with a second tier featuring the UK (7.52) and Ireland (6.96). Interestingly, Korea (6.80) has overtaken France (6.78) for knowledge of their biologics professionals and this is perhaps reflected by the significant growth of manufacturers such as Samsung Biologics and Celltrion over the last few years. The industry's other key movers are India (6.46), overtaking both Singapore (6.15) and China (5.78), which is now perceived as Asia's second most knowledgeable biologics market. This may be reflective of the surge of Indian biosimilars manufacturers – but the results might be tempted by a large number of Indian executives contributing to the report's findings.

Knowledge of Biologics Professionals

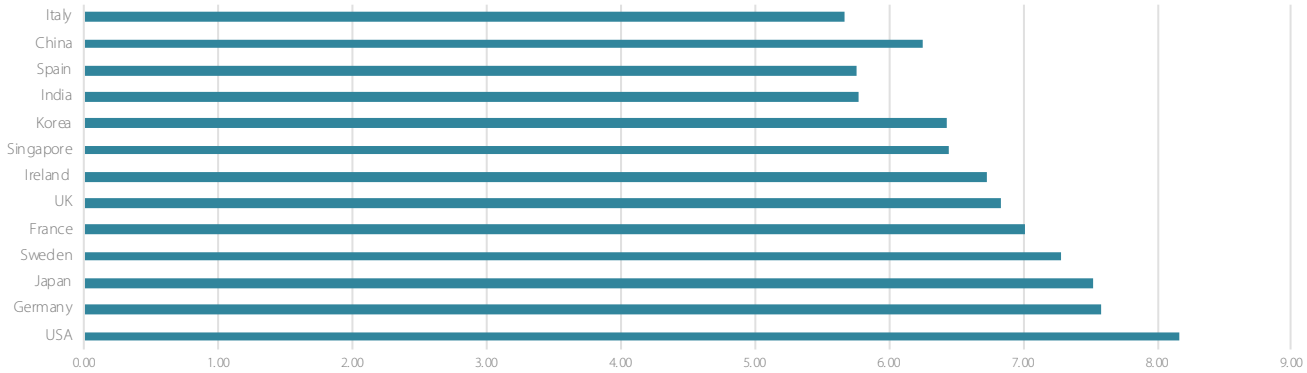


Innovativeness of Biologics industry and Quality of Biological Processing

It seems as an apt time to host BioProduction in Germany for the first time as, while the U.S (8.16) still leads the way in biologics innovation, CPhI host country Germany (7.59) has overtaken Japan (7.52) as the world's second most innovative biologics industry. This healthy 3% increase in innovativeness coincides with the 3% drop in the United Kingdom's score (6.83), indicating that biologics business has also been impacted by Brexit. The remaining second tier includes Sweden (7.28), France (7.01) and Ireland (6.73). Unsurprisingly, China (6.25) has again soared up the rankings, overtaking Italy (5.67), Spain (5.75) and India (5.77) – exhibiting an impressive 7.5% increase in innovativeness – and is likely to overtake prominent bio regions in Korea, Ireland and Singapore in the near future. This can be attributed to the massive interest in biologics in China driven by recent investments, the rise in domestic innovators, biologics expertise and global CMOs.

The U.S. (8.01) once again consolidated itself as a leader in biologicals processing, ranking ahead of Germany (7.86) and Japan (7.61), with European countries largely making up the second tier.

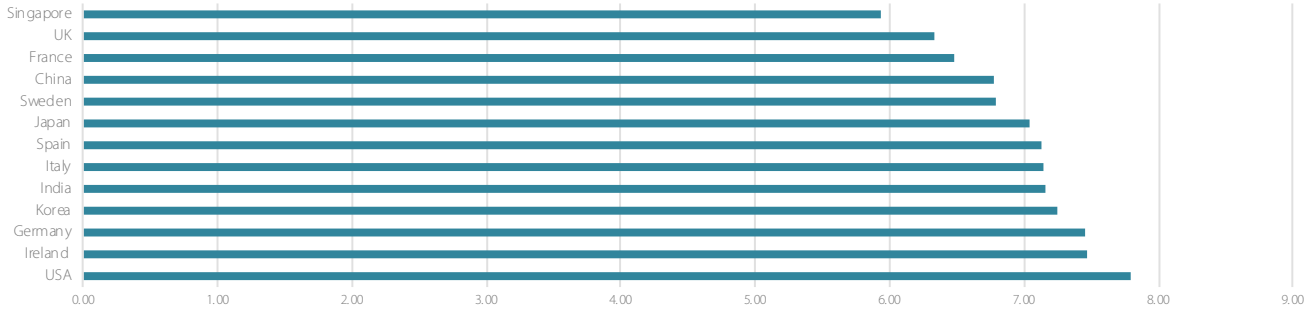
Innovativeness in Biologicals



Growth Potential of Biologics Manufacturing Industry

The U.S. (7.80) saw the highest score for growth potential of its biologics manufacturing industry. Ireland (7.48) consolidated its position as a first-tier market with the second largest growth, finishing ahead of Germany (7.45) and Korea (7.24). The confidence within the region is demonstrated by industry giants such as Pfizer, GSK, Allergan and MSD having prominent operations and investments in the country. The country has also significantly grown the number of biologics sites from 2 in 2003 to around 20 this year[2]. Singapore (5.94) and the UK (6.33) were once again ranked the lowest by respondents in terms of their growth potential.

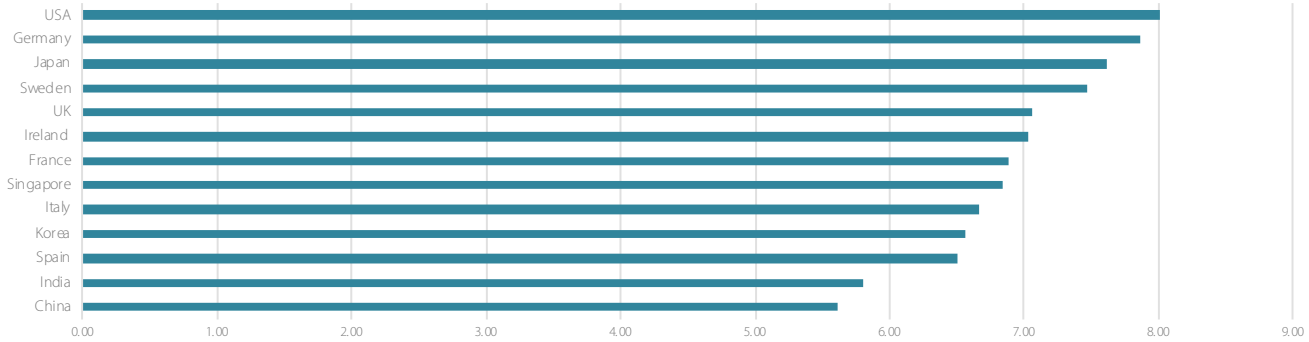
Growth Potential for Biologics Manufacturing Industry



Bioprocessing quality perception

Perceived quality of bioprocessing seems to closely relate to the results for innovativeness of bio markets. Once again, the USA (8.01) lead tier-one, followed by Germany (7.86) and Japan (7.61). Sweden (7.48) leads the 'best of the rest', with the UK (7.05), Ireland (7.04), France (6.89) and Singapore (6.84) a little behind. Despite its impressive results in the innovativeness category, China has not mirrored those improvements in perceived quality of bioprocessing, which has remained flat year-on-year – suggesting that whilst the market is acknowledged to be growing strongly some executives still have reservations about bioprocessing techniques.

Quality of Biologics Processing



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[1] https://www.pharmaworldmagazine.com/italy-has-overtaken-germany-pharmaceutical-production/

[2] https://www.idaireland.com/doing-business-here/industry-sectors/bio-pharmaceuticals

CPhI insights

Part 1.

Innovation, AI and Regulation

informa markets

PANEL MEMBER
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Building Quality into Pharma Manufacturing, from Molecule to Medicine: Pharma 4.0

Introduction

A race is being run to create the pharmaceutical manufacturing of the future and with Pharma 4.0, powerful market trends are shaping the running field. Fueled by a growing global marketplace, tempered by the ever-present need for pharmaceutical manufacturers to remain competitive, and heated by escalating complexity as regulators push for continuous product monitoring, we are living in a period where many elements are about to change. Economic progress in the BRIC nations, Brazil, Russia, India, and China, has expanded market opportunity and added greater complexity to developing and marketing safe and efficacious drugs across the global supply chain.

Healthcare expenditure per capita is set to rise from its 2017 level of $1,137 to $1,427 by 2021. To many, this trend is unsustainable, and if industry does not set its sights on cost containment while managing business performance, there will be a severe reckoning in the marketplace.

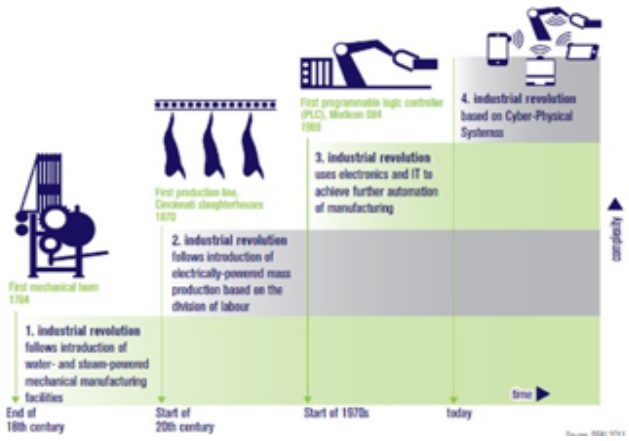
Drug Development Challenges

Meanwhile, pharmaceutical companies are locked in a perpetual race against time to innovate and bring these new drug therapies to market as quickly and cost-effectively as possible. Innovator companies find their patent protection eroding, and, while a patent can provide a company intellectual property protection for twenty years or more, more than half of that time will be spent turning the ideas embedded in an individual patent to a marketable product, leaving only a few years to recover the often billions spent in development. Combine this with a development engine in which only 13 percent of the drugs developed ever reach the market, and the need to improve the current model could not be more self-evident.

Industry 4.0: Evolution

The term "Industry 4.0" was coined by the German federal government in 2011 in a national strategy to promote computerized manufacturing. The 4.0 designation was a play on software version control, and represents the fourth evolution of the industrial revolution. The previous three industrial revolutions are shown in figure 1 and described as follows:

Figure 1 Evolution of Industry 1.0 to 4.0



- Industry 1.0 refers to the first industrial revolution. It was marked by a transition from hand production methods to machines, using steam power and waterpower.
- Industry 2.0 is the second industrial revolution, better known as the technological revolution. It was made possible with the extensive railroad networks and the telegraph that allowed for faster transfer of people and ideas. It was also marked by ever more present electricity that allowed for factory electrification and the modern production line. It was a period of great economic growth, with an increase in productivity.
- Industry 3.0 occurred in the late 20th century, after the end of the two world wars, as a result of a slowdown with the industrialization and technological advancement. It is also called the digital revolution, characterized by extensive use of computer and communication technologies in the production process.

Industry 4.0 is based upon the emergence of four technologies that are disrupting the manufacturing sector: the astonishing rise in data volumes, computational power and connectivity, especially new low-power wide-area networks; the emergence of analytics and business-intelligence capabilities; new forms of human-machine interaction such as touch interfaces and augmented-reality systems; and improvements in transferring digital instructions to the physical world, such as advanced robotics and 3-D printing.

Pharma 4.0

The goal of Pharma 4.0 is to create the intelligence needed for engineers and operators to make smarter decisions that increase operational efficiencies, improve yield and engineering productivity and, lastly, substantially drive business performance. Pharma 4.0 applies Industry 4.0 concepts to the pharmaceutical setting. Within modular structured smart factories, cyber-physical systems monitor physical processes, create a virtual copy of the physical world, and help make decentralized decisions. With the connected devices of the Internet of Things (IoT), cyber physical systems communicate and interoperate with each other—and with humans—for real-time control and data collection that contributes utilizable information shared among participants of the overall pharma manufacturing value chain.

The concepts behind achieving this enhanced business performance revolves around three basic elements:

- Broad deployment of IoT: Gathering data from across the global supply chain via smart sensors and smart devices;
- Engineering Systems: Data is integrated with intelligence to detect, analyze and predict outcomes to everyday manufacturing challenges;
- Integrated Intelligence: Enterprise-wide intelligence where all data including enterprise level systems are completely interconnected across the entire ecosystem.

The objectives of Pharma 4.0 are ambitious in that the intent is to make the leap from a reactive framework, historically achieved using automation strategies and

technologies, to a predictive framework based upon analytics to allow us to anticipate and address potential challenges in the overall supply chain. While the focus of Pharma 4.0 is the manufacturing supply chain, the principles are being applied in a much broader fashion across the entire drug development life cycle.

Internet of Things (IoT) and Data Management

The IoT is one area where we are seeing an expansion of the principles as early as drug discovery. Table 1 below summarizes some of the key areas where IoT is deployed across the drug development life cycle and supply chain, extending from drug discovery all the way to post commercial pharmacovigilance.

Table 1- Applications of IoT across the Drug Development Life Cycle and Supply Chain

Drug Discovery and Development	Manufacturing and Supply Chain	Patient Access
• Wearable devices for subjects to do real time reporting • Monitoring and reporting of data from clinical sites, subject screening and real time reporting	• Serialization (AIDC) • Real time logistics visibility • Smart warehousing and route management • Predictive maintenance • Yield Optimization	• Wearable devices • Smart pills • Compliance and usage tracking

Supply chain visibility remains a very big challenge for pharma and biotech. The ability to anticipate failures or address excursions in real-time has always been the end game. Like any process, the supply chain has its own unique sources of variability. Whether that is a result of human interaction or mechanical failure, the ability to monitor, measure and ultimately predict excursions which are not part of the normal process control requires real time or near real time measurement capability. IoT solutions today include sensor network technology coupled with intelligent data analysis. Compliance with the FDA Unique Device Identifier (UDI) and the Drug Supply Chain Security Act (DSCSA) is a significant driver for deploying IoT within the supply chain. Manufacturers, including both drug sponsors and Contract Manufacturing Organizations (CMO), needed to comply with the act by November 2018, a delay of one year from the original target. Compliance was defined as an implemented solution to create a unique Global Trades Item Number (GTIN), serial number, lot number, expiry date in human readable format, and GS1 compliant data matrix code. Looking only at the U.S. market, this is a significant technical challenge, especially from a database management perspective. When you look at a global marketplace and supply chain in which more than 70 different serialization standards and regulations exist, it is easy to see how a patchwork solution architecture would not be viable in the long term.

Accessing Data, Unlocking Information

Much of pharma's data today is trapped in isolated islands of automation and databases. This has been one of the first challenges faced by the industry attempting to step into Big Data Analytics. Disparate data captured in separate database silos dramatically complicates any predictive analysis and severely restricts the potential for any new and innovative analysis. If the goal is to have a complete 360o view of all relevant data and their relationship to each other across your business, patients, supply chain and development pipeline, then we need an architecture that can easily handle all types of data. With data in silos, and despite many attempts at solving it, the problem has become worse, not better. Data integration has proven to be the most challenging problem in IT, and existing data integration products and strategies are not working. Most organizations have a similar looking architecture – a bunch of operational "run the business" systems, utilizing a suite of extract, transform, and load tools (ETL) to feed data in order to "observe the business" data warehouses. In recent years, new sources of data like IoT feeds, message feeds, Artificial Intelligence (AI), and Machine Learning tools have made the problem more complicated.

Today, ontological databases have matured to a point where they can address the overwhelming challenges of managing and analyzing siloed, disparate data. There

are technical solutions that let you bring the data in "as is," curate it, apply security and governance, and make it accessible for analysis as needed. These solutions are flexible enough to avoid having to model everything at once, and you don't have to change it manually every time the data or your business needs change (it is done instead using ETL). These platforms are designed to give the business, architect, and developer what they all want, which is:

- The ability to load data as is – Instead of waiting on complex ETL, data ingestion is immediate. There is no need to define a schema in advanced.
- Unified platform – Instead of stitching together a bunch of separate products, everything is already unified in an integrated and single platform that provides a consistent, real-time view of data.
- Smart curation – Instead of worrying about mapping schemas together, integrating a Master Data Management (MDM) tool, writing custom algorithms, etc. these solutions have integrated tools designed to manage the curated data.
- Advanced security – Instead of disjointed data lineage, the database tracks that metadata right alongside the data itself. Instead of worrying whether to lock data up or risk sharing it, these systems have highly granular, tight control over exactly what data gets shared with whom.
- Simple development – Instead of waiting for ETL to complete or learning some proprietary language, developers start building data services application program interfaces (APIs) as soon as the initial data is loaded.

These systems now provide pharma with the potential for a single portal and interface to all potential data across the entire business value chain. Most importantly, it doesn't require disassembling any of the solutions that have been put in place. The reluctance to migrate away from legacy systems is one of the biggest organizational hurdles faced by cross-functional data management initiatives. Look for Big Data initiatives within the industry to shift to these solutions in the next three to five years.

Artificial Intelligence (AI)

Few areas of innovation have had as broad a potential impact as AI. If you think of the IoT as connecting devices in order to gather data, then AI makes the decisions based upon that data. As such, the applicability of AI is not limited

Note: Many companies span multiple drug lifecycle stages and data types, therefore relative positioning is indicative
Source: L.E.K. research

to the shop floor or the manufacturing supply chain. Figure 2 shows the broad applicability of AI across the entire pharma and biotech value chain:

Potential applications of AI span the spectrum, from drug discovery and molecule identification to post-approval pharmacovigilance. Almost every major market in the world and many secondary countries have formal AI strategies in place or underway.

Broadly speaking, the term AI applies to any technique that enables computers to mimic human intelligence. To fully understand the applicability of AI it is important to look closer at the two subsets of AI; Machine Learning and Deep Learning. Machine Learning is exactly what it sounds like; the application of targeted statistical techniques that enable machines to improve upon tasks with experience. Machine learning has been used in combination with well-established techniques such as "fuzzy logic" to build a set of rules that allows equipment to consistently improve its performance against a predefined set of objectives as it gathers data. Facial recognition is one example of this application.

Machine learning is not only being used on the shop floor to optimize performance, there are applications of machine learning being applied in drug discovery to improve the success rates of new drug therapies and drug modalities as they move through the clinical pipeline. A recent MIT[1] study published in April 2019 concluded that after analyzing more than 21,000 clinical trials between 2000 and 2015, only 13.8 percent of drugs successfully pass clinical trials. It would not be hard to say this is not a sustainable performance in the face of the downward pricing pressures across the globe. One large pharma organization is using machine learning to improve their molecule selection process. By building large libraries of digital images of cells treated with different experimental compounds, they are using machine-learning algorithms to screen potential compounds faster with a higher rate of success.

Another potential blockbuster application of AI is the treatment of complex diseases that have multiple modes and mechanisms of action, such as autoimmune diseases like Multiple Sclerosis (MS) or ALS. Typically, current research targets one gene anomaly or defect. By using AI, it may be possible to identify multiple genes that influence the disease and devise drug therapies against multiple targets..

Another interesting application of AI is happening in terms of clinical treatment. Some cancer treatments are toxic and require adjusting the dose to maximal delivery as the patient's treatment progresses. This is called Dynamic Dosing, and it is a complex treatment regimen. AI can be used to continuously identify the optimal doses of each drug to result in a durable response, giving each individual patient the ability to live a free and healthy life.

Deep Learning

Deep learning is the other subset of AI, composed of algorithms that permit software to train itself to perform tasks, like speech and image recognition, by exposing multilayered neural networks to vast amounts of data. One of the areas that is ripe for deep learning lies in establishing the capability to easily collect natural language-derived data. For example, evaluating patients against the inclusion/exclusion criteria for clinical trials. Identifying patients who satisfy the inclusion exclusion criteria is one of the key aspects of constructing a viable controlled clinical study, and for most clinical studies, any time recovered in the enrollment timeline can translate directly to time-to-market. Patients just need to answer a few simple questions on its search platform and they will receive a list of suggested studies they may be eligible for. Usually, when drug developers submit details of their new trial, most of it gets entered as structured data in formats such as drop-down menus. This data is easy to record and analyze by computers. However, patients' eligibility criteria get entered into free text fields where they can write anything they like. Traditionally, interpreting this data was near impossible for a computer to "understand." AI, specifically Deep Learning algorithms, can read this unstructured data so the computer can assign appropriate clinical trials.

Extending this concept to the treatment of patients, AI is being applied to analyze structured and unstructured clinical data, including doctors' notes and other free-text documents. Clinical data is separated into key elements while also protecting sensitive health information. The AI application then extracts thousands of these clinical data points to create a multi-dimensional profile. Doctors and researchers can then use these profiles to find suitable candidates for a clinical trial.

Blockchain

Blockchain's lineage is in cryptocurrency. The primary requirement for buying and selling cryptocurrency is security, not speed or efficiency. Blockchain creates a digital ledger of all transactions that may take place in the supply chain. The application of Blockchain in Pharma is still in the investigative phases. One application that is being adopted by the global supply chain is the concept of smart contracts. A smart contract is a computer protocol intended to digitally facilitate, verify, or enforce the negotiation or performance of a contract without third parties. In this format, contracts could be converted to computer code, stored and replicated on the system, then supervised by the network of computers that run the blockchain. This would also result in ledger feedback such as transferring money and receiving the product or service. International organizations, including pharma, governments, and banks are turning to blockchain to ensure and enforce the terms of a contract.

Several areas where blockchain has shown utility include:

1. Verifying the authenticity of returned drugs
2. Utilizing the DSCSA serialization requirements and medical device UDIs to establish a digital provenance and chain of custody for drugs and devices – addressing the counterfeit problem worldwide.
3. Enforcing supply chain logistics requirements. The fully integrated enterprise, utilizing IoT to track critical parameters such as temperature creates a digital ledger, which, if violated, would immediately alter the terms of the engagement by the carrier and or supplier.
4. Informed consent is a mandatory requirement for any trial in the U.S. and internationally. The use of blockchain will ensure all components of the consent process are compliant and adhered to.

Have We Put The Cart Before the Horse?

One of pharma's greatest foibles as an industry has been the penchant to focus on the wrong things. We saw this with Process Analytical Technology (PAT), where we focused on the design and implementation of the technology and ignored the impact of foundational material characterization and supplier control. We saw it with Lean and Six Sigma, where the emphasis on the tools and certifications in the absence of the cultural leadership components relegated these Operational Excellence philosophies to simply a suite of tools, rather than a holistic approach to business performance. Pharma 4.0 has the potential to fall into the same trap. The focus on technology in the absence of understanding the basic question to be answered can derail a cross-functional initiative in the blink of an eye.

There is no doubt society is becoming increasingly digitized, and this can be a good thing—with improved efficiency, enhanced quality, and better company compliance with ever-increasing, data-related regulatory requirements. There is no shortage of technologies but choosing the one that is going to have the greatest positive impact on your company, in the area that you most need it, is an obvious crucial decision. With production data now available for the asking, executives rightly wonder about how to begin. Which data would be most beneficial? Which technologies would deliver the biggest return on investment for a company, given its unique circumstances? Which data leakage threats are causing the most pain? This last question has made the headlines with high profile ransomware attacks on Merck that affected the company's operations worldwide.

Industry confronted this basic question with its first foray into big data analytics. The first step to identifying a

strategy and solution is to understand what success looks like. Is the resulting analysis intended to be predictive, descriptive, diagnostic, or prescriptive? The answer to that basic question will dictate the path forward and lead to the solutions to be considered.

References

1. R. Cross, Drug development success rates are higher than previously reported, https://cen.acs.org/articles/96/i7/Drug-development-success-rates-higher.html

Additional questions

Q) The table spanning the use of AI across different parts of drug lifecycle stages was very enlightening, but in which part of the drug lifecycle do you think AI will have greatest effect (and why) over the next 3 years?

A) No doubt we will see broader adoption of IoT on the shop floor and in the distribution portion of the supply chain in the short term. The biggest impact operationally, I believe, will be seen in the clinical trial management stage of the drug development lifecycle, over the next five years, with the potential biggest industry impact being in the molecule selection and design component over the decade.

Q) What are the drag factors slowing adoption of AI in the next 1-3 years?

A) There is limited understanding and SMEs of applied AI within our industry. We are seeing a smattering of folks with a focus on life sciences stepping into the space to capture the opportunity, given the potential for AI's direct impact on the bottom line. The challenge with anything new in our industry is that the organizations selling into life sciences don't know drug development and the drug sponsors interested in AI don't really understand AI, so they cannot direct the solution provider very effectively. As this knowledge gap dissipates through experiences on both sides, more effective pilot projects and solutions will be developed and brought to term.

Q) Will AI helping innovators in drug discovery advance more promising lead compounds to transformative rates of success (effective therapies making it to patients)? How long will this take to achieve realistically?

A) Absolutely. You will see major change in the next decade in the U.S. and EU, as these are the most mature regulatory frameworks in our industry. We have already seen a major spike in biotech associated with more cost effective and just plain effective tools, such as CRISPR, NGS, ADC's and CAR-T platforms. The impact to patients will be tangible as we are already seeing with innovative therapies. If we can harness AI to improve our evaluation and molecule selection criteria then there is no doubt that we will be able to bring new effective drug therapies to market faster and potentially cheaper.

Q) What could the role be of AI and data analytics in improving yields in pharma manufacturing in the next few years? Do you think the current system of route scouting early in development will limit its success (i.e. drug makers commit to using inefficient process and are reluctant to change the process later, as they fear this will slow-down approval)?

A) You will see a major push from machine learning, IoT, and technology which is deemed "Pharma 4.0-ready." The reluctance to change is rapidly diminishing given the FDA's and EMA's initiatives to move towards a scientifically-based definition of product quality.

Q) How would manufacturers need to adapt to implement dynamic dosing / how much more could this improve patient therapy efficacy?

A) The reality is that each individual responds to an oncological treatment differently. Historically, dynamic dosing has been used to reduce toxicity, but there have been successful studies in which AI was successfully used to optimize the treatment for hard-to-treat cancers. As in any optimization strategy, the key is to measure those parameters that are critical to the treatment output. For cancer therapies where the physiological endpoints are clearly understood and agreed to in the field of treatment, you have a very clear opportunity to optimize

with AI. The timing could not be better, with the approval of CAR-T drugs that dealt with the issue of demonstrating process robustness for new personalized medicine therapies.

Q) By what year do you foresee AI truly opening up doors in treating complex diseases with multiple modes and mechanisms of action? (Make possible to identify multiple genes that influence the disease and devise drug therapies against multiple targets)?
A) It is fair to say we will see significant changes in treatment therapies by 2040, where AI will be standard practice in the design of drug therapies, their processes and in the treatment of disease.

Q) Do you think AI and machine are a classic case of Amara's law ("we tend to overestimate the effect of a technology in the short run and underestimate the effect in the long run")?
A) It certainly fits the bill and our industry is one of those with an extraordinarily short attention span and institutional memory. However, if regulatory expectations continue to evolve and escalate, then there will be sufficient motivation for the industry to revisit the potential. Amara speculated that at 15 years you reach an inflection point in terms of realizing a technology's potential. That seems to fit our industry to a T, if you look at PAT and QbD..

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Chaos to Continual Improvement: Path to Harmonization

Introduction

After taking a break in 2018, in part to make sense of why chaos with continual improvement juxtaposes in the highly regulated environment, I am pleased to contribute to the 2019 CPhI Worldwide report. This report builds on my previous two contributions to CPhI Worldwide reports, 2016-2017 (1-2). The following musing seeks the emergence of a "Butterfly Effect" around two, not so "strange attractors," real-world satisfaction in pharmaceuticals and professional development in the sector. These attractors are intuitive; "common sense." But can be in a "blind-spot"- and with a globalized supply chain, often in need of a reminder.

Consider the headline of a report published on August 30, 2017, in Bloomberg, "With US generic drug market in chaos, Indian upstarts rise" (3). Juxtapose it in a broader, geopolitical context, "these are no ordinary times. It will not be business as usual in a world of disarray," noted Richard Haass in 2017, president of the Council on Foreign Relations (4). No relation between the two? Alternatively, not my responsibility, or what can I do? Let us think again; we all must care and take responsibility for the part we play.

Disarray is a state of disorganization, and it is occurring in systems above our quality management system. How will this disarray affect what we do in our organizations? Disorganization can sometimes be a step in the process that changes an existing organization or order. It can be confusing to most and induce fear of unknown – what new order? It creates confusion and injects insecurity, and it creates uncertainty. To maintain an effective quality management system, professional development and real-world satisfaction are two essential topics for active considerations, especially now in a rapidly transforming world, for the success of individuals, corporations, and the sector.

Chaos is not "disorder," and in drawing this distinction, I posit 'chaos to continual improvement' is a path forward, which the pharmaceutical sector should consider. How is this path different, and what steps would we need to take, for example, to leave behind unpredictability and move towards predictability, are some of the questions considered in this report. The ensuing musing is in the context of hurdles in adopting the principles and recommendations in the guideline "Q12" proposed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) (5).

Background

Chaos and complexity theories are concerned with the behavior of dynamic systems, i.e., the systems that change in time. Chaos is a system whose outputs are unpredictable due to extreme sensitivity to starting conditions, often referred to as the "Butterfly Effect," and patterns emerge around "strange attractors." This description can be traced to a 1972 talk entitled "Predictability: Does the flap of a butterfly's wings in Brazil set off a tornado in Texas?" by Edward Lorenz, at the American Association Advancement of Science meeting in Washington DC (6).

Chaos is a science of process rather than a state, i.e., of becoming rather than being (7). In the book entitled, "Order Out of Chaos: Man's New Dialogue with Nature", Ilya Prigogine, and Isabelle Stengers trace the gradual emergence of the conception of order and chaos and layout their argument why entropy is the price of structure, and that we grow and develop "in direct proportion to the amount of chaos we can sustain and dissipate" (8). Ilya Prigogine received the 1977 Nobel Prize for Chemistry "for his contributions to non-equilibrium thermodynamics, particularly the theory of dissipative structures. (9)."

Challenges to Continually Improve in the Pharmaceutical Sector

CAPA, corrective actions and preventative actions, are essential to maintain the current (validated) state, necessary for product life-cycle management, but CAPA is not a continual improvement. Current Good Manufacturing Practice (CGMP) regulations expect effective investigations of deviations to identify root-cause of variations in "approved" drug products and "validated" processes. The 2017 CPhI report discusses a case example of Amgen breaking the 2-3 sigma barrier to reduce the error rate to 3.4 errors per million opportunities or "six sigma" (2). This case is remarkable because not many companies have achieved this level of progress. Despite this distinction, the regulatory constraints placed on companies such as Amgen and others are virtually the same. Logically, this should change.

The proposed ICH Q12 seeks to improve predictability and facilitate efficient management of post-approval CMC changes across a product lifecycle. It also provides a step towards continual improvement that can be managed within a company's quality management system.

Post-approval changes in chemistry, manufacturing, and controls (CMC), particularly those that require a "prior approval supplement," are long-drawn-out and expensive. Surely, needed in some situations but broadly burdensome.

Many regulators assume that the "locking" the CMC information and knowledge shared in an original regulatory application is useful means to maintain control. This assumption does not account for entropy and discounts the negative impact of "fixed" processes on practical CAPA and process efficiency. That this assumption, in and of itself, can also pose a risk to quality is not recognized explicitly.

Implementing some of the principles outlined in ICH Q12 is marred by legacy regulatory requirements in the ICH regions. As noted in ICH Q12, aspects of recommendations related to Product Life Cycle Management are "not compatible" in all "ICH regions." What about other regions which are a significant part of the global supply chain? In a world of disarray, is it rational to expect the tensions and misalignment among national policies such as the "Established Conditions" to resolve shortly?

Layers of legacy regulations and guidelines point to one thing – we must take a different stance so that what we know in our current guidelines can be translated into practice. Isn't this challenge to harmonization indicative of a gap in our collective development, in our "suitability and capability" to" the amount of chaos we sustain and dissipate"?

Minding the Gap: What we know and what we can implement

The ICH Q12 acknowledges that - "experience with the implementation of recent ICH guidelines has revealed technical and regulatory gaps that limit the full realization of more flexible regulatory approaches to post-approval CMC changes as described in ICH Q8(R2) and Q10 Annex I (5)." So, what are we planning to do differently to fill this gap? Another guideline?

Now speaking broadly, are we not continually discounting the emphasis needed on the ability of industry and regulatory professionals to solve problems in the real-world; that is in the real world of an "experience economy" (10), where how we feel matters more and adherence to prescriptions and compliance with SOPs is getting more and more difficult; a topic discussed extensively in my 2016 CPhI report. As noted in the 2016 report - to "get-it-right" in the 21st Century, let's remember Einstein's challenge that we will never solve the problems of tomorrow with the same order of consciousness we are using to create the problems of today! Surely harmoniously advancing the continuing education and training of industry and regulatory professionals are necessary, but not enough. Increasing attention is essential in adaptive learning to overcome our "immunity to change" - which stems from a change- prevention system, feeling system, and knowing system, (1).

While at the US FDA in 2005, my viewpoint suggested that "the symptoms observed in the current pharmaceutical system is, in part, a reflection of the current state of the pharmaceutical science education system. It is fragmented and diffuse (e.g., few focused university programs, diverse in-house on-the-job training, and casual for-profit educational programs). The academic, pharmaceutical science programs have limited resources and are burdened by a [retail] practice environment that restricts their ability to generate knowledge with broad applicability. Much of the focus today, especially in pharmaceutical industrial operations and associated regulatory functions, seems to be based on a "documentation and checkbox" approach, in which deviations are a source of significant inefficiency and contribute to cross-disciplinary and cross-organizational circular arguments of art versus science. A reactive decision-making system, in turn, works to undermine the credibility of the pharmaceutical industrial community. The current pharmaceutical science educational system is in dire need of transformation to ensure that we continue to meet our public health and security objectives efficiently and to maintain a highly competitive environment for the US pharmaceutical industry" (11). Then I had argued for the nation to invest in a "Comprehensive Pharmaceutical Engineering Education and Research System." In this report, I call for engineering science.

Progress, in the context of continuous manufacturing, is reflected in its societal acknowledgment and support in the section "Domestic Manufacturing and Export

efficiency of the US law, the 21st Century, Cures Act (12). Furthermore, efforts to develop another guideline ICH Q13, Continuous Manufacturing of Drug Substances and Drug Products, announced (13).

Engineering Science: Butterfly Effect and Emergence

So how do I "feel" about this progress? Surely, we should celebrate achievement but not blindly. In no way do I wish to undermine the importance of this proposed ICH Q13 guideline when I say I am tired of waiting for another guideline. If guidance were the solution, the world would not be in disarray.

Transformation to continuous manufacturing is a process, not an outcome, and it requires time, pharmaceutical engineering know-how, and resources. Do we have these in an amount to make a difference for the challenges we confront now – affordability and availability of medicine? Continuous manufacturing is a significant part of the solution. We must also improve the assurance of quality in traditional manufacturing.

Strange Attractors and Butterfly Effects

In the current experience economy, two "attractors" –

experience and variable human development appear to be creating undesirable Butterfly Effects. That is, more and more are dissatisfied and exhibit immature behaviors. If, as pharmaceutical professionals – required by regulations to be good practitioners, we cannot counter this negative sense, disarray can infuse in our organizations too. To combat it and perhaps begin to reverse it, we must make satisfaction and professional development, not so strange, "attractors" in our management systems and create a desired Butterfly Effect – via a fractal approach, empowering all professionals simultaneously to contribute to improving the effectiveness of our quality management systems.

The CGMP Warning Letters and precautionary product recalls that used to be routine announcements in the 20th century now go viral and are endemic on social media. We must recognize that randomized controlled clinical trials with controls such as double-blinding and placebo arm only account for expectancy effects such as placebo and nocebo effects in the clinical trial. These expectancy effects are more prevalent in the real world, and today we have no choice but to research the real-world impact of placebo and nocebo effects. In this paradox, we should also verify our assumptions that we may be considered as our "prior knowledge" and consider "New Prior Knowledge" needed for Therapeutic Equivalence with the necessary assurance in the 21st century (14).

Emergence becomes an Emergency

The emergence of a new kind of pharmacy one that tests every batch it dispenses is an example of a new source of "emergency" in the pharmaceutical sector (15). Regardless of how this trend progresses, continues, and grows, it is a "canary in the coal mine." The media response of the sector to this new pharmacy model was chaotic, confused, and disorderly. Some chose to act, make sense, and then respond as is typical in chaos, while others remained silent (16).

The response to the on-going "Vaping Crisis" in the US also illustrates this challenge – some States opted to ban (act) first, whereas federal agencies such as the FDA focused on probing to make sense before responding (17). This incident also points to a more significant difference between nations within the "ICH regions," such as the USA and the UK. In the UK, tobacco harm reduction is a policy stance, whereas, in the USA, adoption of harm reduction has been slow broadly and specifically as it pertains to needle exchange to prevent the spread of HIV in drug abusers, and in the ongoing opioid crisis (18). Should pharma adopt a harm reduction stance? A topic, perhaps for another report.

Now circling back to where we stared – "With the US Generic Market in Chaos, Indian Upstarts Rise" we make better sense of what is chaos in the context of steps we routinely take in to make decisions pertaining to many generic development projects and their regulatory submissions (Abbreviated New Drug Applications or ANDAs) - act, sense, and respond translates to as; i.e., file first, wait for FDA response to make sense, and respond to deficiencies noted by FDA. Will then, ANDA's submitted by Indian upstarts and approved by FDA, reduce the likelihood of emergencies? I hope so.

Let's not discount the other staring conditions that can make pharmaceutical system performance unpredictable– pharmaceutical raw materials and pharmaceutical professionals. Beyond impurities in starting materials, excipient functionality, and physical attributes of raw, in-process materials and products continue to pose challenges. Similarly, we lack standardized or harmonized assessment of education, training, and experience (e.g., as in the US CGMP regulations at 21 CFR 211.25). Wonder how we progress beyond publishing harmonized ICH guidelines? Alternatively, how much did we improve?

Engineering Science

In 1955, the American Society for Engineering Education (ASEE) identified six engineering sciences: mechanics of solids, fluid mechanics, thermodynamics, transport phenomena, electromagnetism, material structures and properties that share the fundamental laws and principles of the physical sciences (20). The Engineering Research Center for Structured Organic Particulate Systems redefied pharmaceutical powders, granules, and tablets as s system (21). Later, ASEE also suggested a seventh candidate for engineering science: information theory (20) to connect the information to materials to abstract knowledge from physical characteristics of a system to improve the functions it performs By design, engineering sciences are integrative because they recognize that a complex system demands knowledge in several disciplines and several organizations as in a pharmaceutical corporation over the lifecycle of products. Education and training for pharmaceutical scientists would benefit from Team Science, which is the theme for the National Institute for Pharmaceutical Technology and Education or NIPTE (14).

The notion of pharmaceutical engineering science holds promises to progress the transformation of education and training for industrial pharmaceutical professionals. It is also needed to improve knowledge generation and management for" New Prior Knowledge" (14) that can help to ensure a sound foundation to progress the US FDA's proposed Knowledge-aided Assessment & Structured Application (22).

Have you observed how we generate power from our knowledge? Based on my experience, we generate the power of knowledge via applications. In an implementation, our theories and practices interact. How we manage this interaction determines the outcome — allowing us to objectively assess the business processes adapted for a new application in the context of the results we knowledge and progress.

We embody knowledge in our new or emergent practice. A new practice is characteristic of few individuals who experienced a new application. With practice, over time, when we share it with others in an organization, we use tools such as SOPs, training, etc., to make it a "Good Practice" – Via calibrated routines (SOPs) that are designed to be reproducible and repeatable with for a committed level of education and training. When we identify and remove "special causes" of deviations in our practices, we hone-in on most optimal practice recommendations. When its value and limitations become self-evident in the context of intrinsic "common causes," it is ready to be shared broadly as a "Best Practice." Thinking about "good" and "best" practices more precisely would be useful.

Emerging Practices to Good Practices to Best Practices

Historically we, in the pharmaceutical sector, have not felt a need to distinguish between types of systems and practices. We lump our discussions under "Good Practices" and Pharmaceutical Quality System without considering the nuances of different systems, predictability of cause and effect relationships, and types of practices. I posit that in the 21st century's experience economy, it is useful to use more precise vocabulary and distinguish between types of systems and practices as we chart our journey from chaos to continuous improvement.Table 1 is a list of four systems, selected aspects of our stance in these systems, and their characteristics relevant to this discussion. This information is from (23), a relevant article that and readers are encouraged to review. How "emerging," "good," and "best" practices related to characteristics of complex, complicated, and simple systems are also apparent in this table.

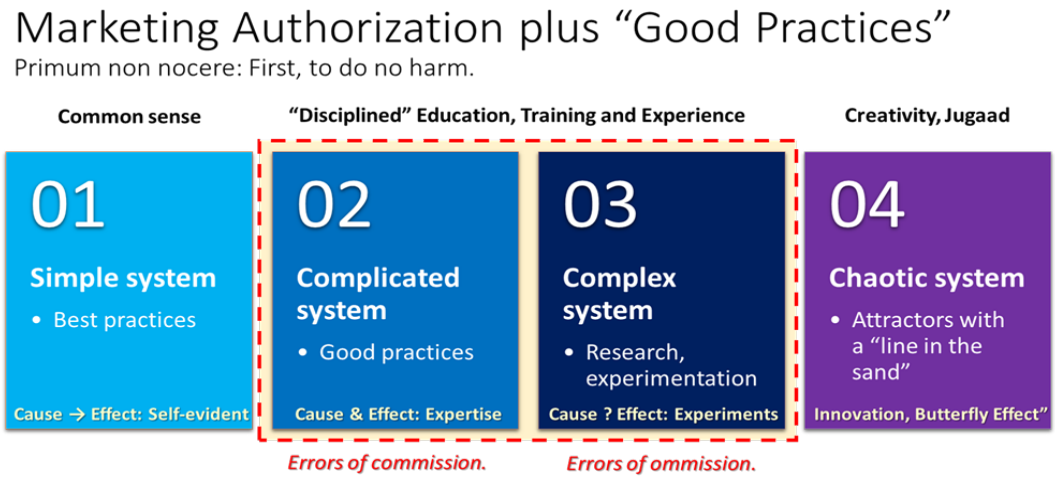
Table 1: Systems, Predictability, and Practices

System	Cause and Effect: Predictability? Stance?	Characteristics
Chaos	Unknowable, not predictable due to extreme sensitivity to starting conditions (Butterfly effect). Patterns form around "Strange Attractors" (e.g., Regulatory defaults such as 10X scale-up factor, 180-day exclusivity) Stance: Act, Sense & Respond	High turbulence, so pattern-based leadership. Provide clear, direct Communication.
Complex	Unknown without research and experimentation can be predictable after knowledge acquired via experiments. Stance: Probe, Sense, Respond	Pattern-based leadership to guide "Emerging Practices." Research & Development. A need for creative and innovative approaches.
Complicated	Known unknowns, i.e., expertise needed to understand cause-and-effect relationships (transferred from R&D); more than one right answer possible. Stance: Sense, Analyze, Respond	Fact-based management. "Good Practices" such as calibrated, reproducible, and repeatable routines or SOPs.
Simple	Self-evident, without specialized expertise. Known knowns. Stance: Sense, Categorize, Respond	Empowerment of staff, use of "Best-Practices" with recognition of their value and the limitations.

More precise vocabulary can help us understand and inform others on types of errors (of commission and omission), appreciate systems, communicate more effectively with customers, and to build consensus. It should also help to improve the timber and consistency of our One Quality Voice. In Figure 1, the four systems are arranged linearly as separate compartments for illustration purposes only.

In the real world, our systems are "ecological," we live and work in these systems, they overlap and intertwine, and our inability to recognize their characteristics is a source of disorder. In recognition of the distinction between chaos and disorder, we appreciate different types of systems and consider taking a stance that is more appropriate in various systems to make more rational decisions.

Figure 1. Four Systems: "Wise executives tailor their approach to fit the complexity of the circumstances they face" (23)



Risk, Knowledge, and Satisfaction Management

The journey from chaos to continual improvement, included (i) push towards automation (e.g., continuous manufacturing) to drastically reduce human operational errors; an aspiration, in the long run, and (not or) (ii) recognize satisfaction management, in the context of professional development, as an enabler of the pharmaceutical quality system. Note – this discussion is not a call to modify ICH Q10; it is for consideration for all of us, without the need for a new guideline.

Risk Management

Table 2 provides a mental model to align our stance for risk-management in chaos and complex systems along slide the risk-management approach (e.g., ICH Q9) for a complicated system that is familiar to most.

ICH Q9 guideline (24) defines risk in terms of harm and probability of its occurrence in pharmaceutical manufacturing, which is a complicated system and expected to operate predictably in a state of control via compliance with SOPs, broadly Good Practices. However, at higher levels – at the senior management and public health policy level, which operate with higher uncertainty, the risk is best considered in terms of impact, threats, and vulnerabilities. That is, in chaos and complexity, "Risk = Impact x (Threat x Vulnerability)."

When interfacing, interrelating, and interacting with other systems such as the social system, we must recognize the asymmetries of information, knowledge, and understanding. We must expand our awareness of potential impacts rapid changes in the social, economic, political, and technological domains can have on us in the context of our professional and corporate suitability capability. It is essential to pay attention to changing patterns (e.g., changes in adherence rates, social media posts, etc.) that relate to the evolving expectations and need for assurance of quality population and healthcare providers.

Table 2:Aligning risk management in complex and complicated systems.(illustrative)

Disaster	Impact	Threat	Vulnerabilities			
Natural	All local systems	Life & Infrastructure	Facility & headquarter location			
Geo-politics	Global systems	Disorder, recession, institutional ineffectiveness	Spread across the global supply chain			
Regulatory	Disharmony: Local - ICH	License to market	Risk to Quality	**Risk Management (e.g., ICH Q9)**		
				Detection	Occurrence	Severity
Patient-centric	Lose trust, anxiety, fear	Increased in complaints and adverse effects Nocebo effects Lower adherence rates	"NTI" drugs Generics Biosimilars "Value-based pricing" contracts			
Supplier (if no system failure)	Process suitability & capability	Increased OOS	Legacy products			
Process	Time to market and market presence	Warning Letters, Import Alerts	Legacy products New products, not "QbD."			

Knowledge Management

We acquire knowledge in applications that solve a problem. In an application theory and practice, interact, and outcome of an application provide an objective means to assess the validity of practice in the implementation of new knowledge. Attention on errors of omission in the practices emerging in research and development and errors of commission in good practices established in operations are essential aspects of knowledge management, as shown in Figure 1.

In addition to the knowledge acquired during product and process development, we generate knowledge from investigations related to market complaints, deviations, and Out of Specification Observations (OOS) – when we are forced to ask why "5" times to generate operational knowledge. In an "FDA Approved" and "Validated" functional system, one would expect a few errors - of omission and commission. However, when these errors keep reoccurring, even after "retraining the staff," it should signal we are no longer operating in a complicated system. Recurring errors suggest ineffective CAPA – not getting to the root-cause; hence, the system may not be complicated, as it exhibits complexity.

Rigorous scientific investigations (OOS and deviations) and CAPA are steps leading to a door that opens on a path to continual improvement, which can only occur in a complicated system when both regulatory and industry professionals have a similar understanding of the underlying cause and effect relationships, and it can happen in a simple system when objectives and their results are self-evident.

As noted in Q12 effective knowledge management, beyond making rational decisions, is essential to improve transparency, to "Do and Tell," and to strengthen the interrelations between professionals in different organizations (e.g., R&D and Operations and CMC Review and CGMP Inspections). Continual improvement truly can only begin when all professionals are suitable and capable of ensuring that pharmaceutical processes are stable and capable.

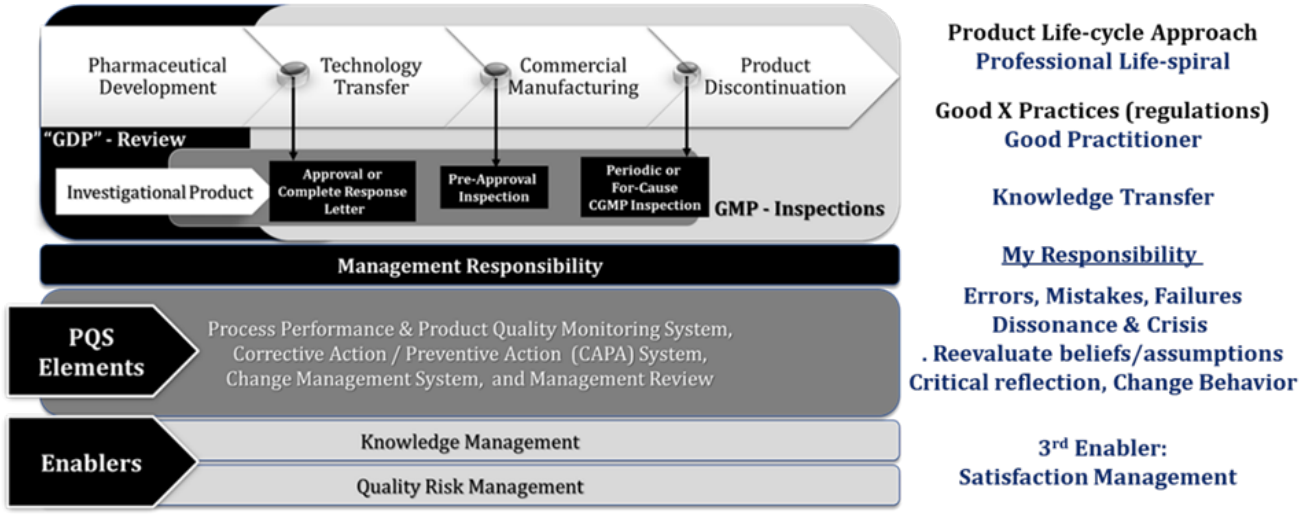
Fear of errors makes it difficult to "Do and Tell" and hinders continual professional development. The inability to rigorously investigate deviations and OOS makes a human error the root cause. The validity of CAPA remains an open question, particularly when the same errors reoccur. Removing fear and mastery is crucial for professional

satisfaction, and satisfaction management of customers and co-workers is a critical enabler of our journey to continual improvement.

Satisfaction Management

Continual improvement is intentional, i.e., planned to (i) increase knowledge and understanding of materials we use, and improve our processes to provide the assurance patients expect and need, (ii) reduce variance from our targeted objectives, (iii) improve efficiency, and (iv) reduce costs. Continual improvement must satisfy patients, professionals, and profit considerations.

Figure 2. ICH Q10 (25) with Satisfaction Management as an Enabler for guiding development of a "Continual Improvement Plan" with specific focus on Continuous Professional Ddevelopment.



Satisfaction can be considered as the difference, Δ, between an expectation and the observed outcome. The Δ is dynamic and changes as expectations change. The journey can begin only when a process is demonstrably stable and capable. However, to get to process stability and capability requires the suitability and capability of professionals to detect, correct and prevent errors and deviations. Today many corporations struggle to do so and must depend on external consultants for CGMP remediation. CGMP requirements are foundational. Ideally, all professionals should be self-author improvements to the SOPs they have to comply with, and they should understand how they can conduct rigorous investigations and be aware of CAPA effectiveness. These aspects can be incorporated in a pharmaceutical quality system, as shown in Figure 2, and various elements listed should interrelate with corresponding parts in other business systems such as the HR system and incorporated in corporate policies. External consultants can help in these transitions by changing their stance – helping their clients be self-authored.

Continuous Professional Development & Continual Improvement Plan

To give others assurance, we first must be self-assured. Self- authorship is a step to self-assurance; it can be objective and measurable. A Continual Improvement Plan (CIP) that incorporates elements of Continuous Professional Development (CPD) based on self-authorship can be objective and practical. What is or should be CPD? I suggest we consider CPD is to go beyond traditional education & training to be self-

authored in what we know and how we know it and be self-transforming in filling gaps between what we know and what we can implement. CPD requires us to feel the need and know the ways to leverage our collective experiential learning and understand the context of our abstract nouns such as "quality" and assurance. It is about increasing our "Order of Consciousness" per constructive development theory discussed previously (1-2).

CPD involves the notion of "life-spiral" management for continual advancement, a different mindset than life-cycle management. Product life-cycle management with "Annual Product Review" in conjunction with a CIP and CPD can convert life-cycle to a life-spiral.

Professionals at all levels self-authoring improvements to current SOPs and new SOPs they must comply is an import step in their professional development. Doing so increases awareness and provides a path to be

self-assured. A simple framework for a CIP grounded in professional development, illustrated in Figure 2, which is an adaptation of the ICH Q10 model (25). The element of "professional development" is represented as "My Responsibility" and "Satisfaction Management," an enabler like knowledge and risk management.

Summary

This report recommends that we pay attention to differences in chaos and disorder, systems, and practices. Doing so can help us to more efficiently fill gaps between what we know (as in guidelines) and what we can implement in practice. It suggests and explains why "chaos to continual improvement" is a path forward worth considering. On this path, we appreciate better different systems and practices to modify the stance we take on risk and knowledge and improve appreciation of the need to adopt the not so strange "attractors" - satisfaction and professional development in practice, informally and formally (e.g., corporate policy), and facilitate planning for continual improvement. The foundational element of a corporate continual improvement plan is suggested to be individual continuous professional development plans for all pharmaceutical professionals in the industry and regulatory agencies. The report, in the context of a world in disarray, narrates considerations on how to progress with an eye on real-world challenges. The two tiny and not so strange attractors, satisfaction, and professional development selected in this report can be easy to dismiss, and many may dismiss this report. The few that do pay attention can generate the desired Butterfly Effect to change their world of pharmaceuticals and beyond; bon voyage!

Additional Questions

1. If guidance alone is not the solution, where in the industry should leadership for new professional development come from?
From within, the pharma sector attracts highly educated and talented individuals. Nurturing their development is a corporate responsibility. Many corporations are fulfilling this responsibility. Others that do not pose a risk which they can and must mitigate. There are examples of innovative proposals and products progressing forwards before guidance is established. Mechanisms exist for meetings with regulators - pre-IND, end of Phase II meetings, complex generics, and biosimilar development meetings, etc. Surely, guidance documents help to streamline and improve process efficiency. But waiting for regulatory to "tell how to develop a product" is not a good sign and a risk factor that should be recognized.

2. Continuous professional development implies a moving ground for both agencies and the industry. Do you think this will present challenges in objective assessment?
No, the question of objective evaluations is raised in the absence of adequate professional development. How is an accurate assessment possible without professional

development? Even the CGMP, the US regulations at 21 CFR 211.25, require "education, training, and experience" – so shouldn't we be asking - where are objective standards to assess what is "adequate"- education, training, and experience?

3. If we cannot regulate in continuous improvement, do you think it will require another major industry incident before the FDA looks at a fundamentally new approach on how to improve pharmaceutical practices?
Why can we not? We are doing so already with current or "C" in CGMP via observations and warning letters. In an experience economy with emphasis on "real-world evidence," we need to do better, minimizing what erodes assurance that our system intended to provide. In a world that is in disarray – we cannot and must not let "another major industry incident" occur on our watch..

4. In 5 years, how do you think the industry will have developed in its approach to continuous improvement and regulatory guidance?
Many companies already have, and more can be expected to have progressed significantly. In my CPhI 2017 report, I illustrated a case example of Amgen. The sector is a mix of large and small corporations, and my concern is for and with companies that are "star-ups" and others who may not have the resources needed to progress beyond "tell me what to do." .

5. Do you think the industry needs to drive this change rather than regulators?
Industry, regulators, suppliers, etc., are all part of the same "ecological" system, and each must drive this change from within each organization. It cannot and should not just be regulators. The regulators and industry can work to progress meaningful performance metrics and industry taking responsibilities for developing standards per a process such as ANSI Essential Requirements: Due Process Requirements for American National Standards.

6. Would the industry benefit from some type of new continuous improvement organization, perhaps one that could generate a flow of ideas between industry and regulators, taking a longer term view of the industry, and how we could simplify regulations and give the industry the confidence to try improved practices?
What will help is the education system nudging the industry and regulator to do better and offering support via their targeted research to fill gaps, "New Prior Knowledge" is one example and creating opportunities for continual professional development with certification in the context of a community of knowledge. The notion of academia as the "Third leg of the Stool," nudging and supporting the industry and regulatory agencies to do the right thing was voiced by Dr. Woodcock (Director CDER, FDA) at the 2017 NIPTE Conference; see: HTTPS://WWW.SLIDESHARE.NET/A2ZPHARMSCI/ NIPTE-FOR-PHARMACEUTICAL-TECHNOLOGY-EDUCATION-2018

7. Do you think automation and/or AI could help the free industry to pursue more efficient methodologies? If yes or no, what do you think will be the impact of these in 5 years' time?
Yes, automation and AI will begin to play a significant role but predominantly in the "brand" sector. I wouldn't be surprised if some "brand" companies will also advertise to consumers in the USA that they provide higher assurance of quality via "continuous manufacturing." Why should they not leverage factual information? A reason for writing this report is that we must also raise the assurance of quality and Therapeutic Equivalence of generic drugs with traditional manufacturing (e.g., via feedforward and feedback PAT based controls to address sensitivities to starting conditions that can make the current system chaotic).

8. What is your single biggest prediction for the next 1 – 5 years?
I expect increasing pollical push and regulatory and industry efforts to growing efforts to reshoring "modern" manufacturing to the USA and increased emphasis on professional development as a factor in facility risk classification system.

9. What do you think is the greatest threat to industry or patients in the next 1 – 5 years?
Continued erosion of trust patients and public have in our collective quality management system, particularly in Therapeutic Equivalence of generics and interchangeability of biosimilars. Continual erosion in the assurance of quality contributes to making insurance of healthcare more unaffordable for more of a population than it is today.

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Pharmaceutical Quality: Concepts, Misconceptions, Realities And Remedies

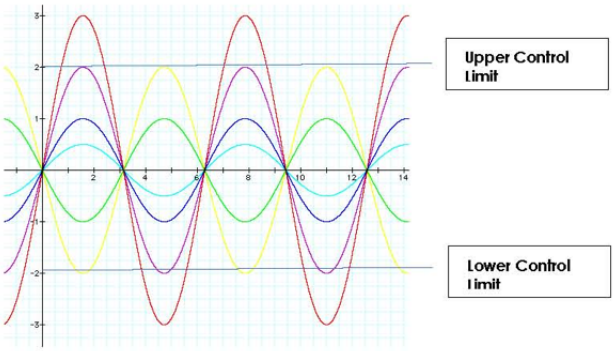
Introduction

Pharmaceutical quality, especially for generic drugs, has been and is going through its cyclical ups and downs. Discussion heats up and then goes dormant until the next major quality issue appears. One would expect that every pharma manufacturer (API and their formulator) will be on their toes and prevent regulators from issuing 483 or equivalent citations and news reporters from writing about out of compliance issues. Unfortunately oversights at companies keep occurring and the press are forced to report this.

There are many cases but a few have been highlighted from Heparin (1, 2, 3), Ranbaxy 2005 (4, 5) and most recently Valsartan (6). We all know there are multiple other incidents and negativity rears its ugly head. Delays and lethargy of regulators compromises public health (7, 8). Pharma companies, it seems, are immune to every controversy. This sometimes leads to the feeling that their cheer is higher revenue and higher profits rather than higher and more consistent quality. Any negativity is considered par for the course and will come to pass with time. Their thinking "less than quality happens" and "patients die eventually so why worry" should not be a normal demeanor. Quality is good for the companies but if their product/s deviate out of desired specification range, unless caught, are seldom admitted, admitted after the fact, or with reluctance.

Quality of a pharma product generally follows a Sine curve, (9) with specification amplitude being between the upper and lower control limits. Developed countries set the limits for their drugs. It is necessary that companies adhere to these limits. Since these limits are tighter than the developing countries, many question tougher standards. Manufacturing would be greatly simplified if there was one standard across the board.

Figure 1: Product Quality Range



Product quality to most of us reflects a company's integrity, intelligence, knowledge and ability to manufacture products that are the best in their class. The irony is that cost to achieve first time quality is very low or nothing if done right the first time (10). Properly designed and executed manufacturing processes are supposed to deliver

quality products. The recurrence of quality issues (deviation from established specifications, lack of data integrity and cGMP practices), especially in pharma, have a common theme. They are a reflection of shortfall in company's integrity, management, knowledge and manufacturing practices. Every oversight can result in an issue.

It is critical that we understand pharma's manufacturing landscape as it effects product quality. Every company knows what is needed but the ultimate question is "do they produce repeat quality product that meets established specs using cGMP practices?"

In drug manufacturing there are two components (API or formulations) and their sequential execution is necessary to produce a dose. Before we discuss manufacturing process preferences, it is helpful if we understand what is a batch and/or a continuous process. This review could be considered unnecessary by some, but they have quality implications. They are elaborated. It is always good to re-visit the established definitions for different processes. There is no financial relationship with any company.

Financial Model:

Companies have to follow criterion that gives them acceptable financial return. It is also applicable to Pharma's older cousin fine/specialty chemicals. However, Pharma's profitability criterion, my conjecture, is based on how to maximize profits irrespective of the processes used. I believe that their criterion of maximizing revenue and profits is based on exploiting the emotional need of humans to extend life. Lack of affordable drugs for masses have forced companies to increase revenue and profits through year over year price increases. Pharma has not explored increased profitability through continued process improvements and my conjecture is that the regulators are the obstacle in this process. Cipla (11) did dent the established model some. In the long run it was a blip. Companies from the developed countries have made sure such perturbation does not happen again (12).

Again, pharma's profit model is based on tradition of capitalizing on a financial opportunity rather than based on manufacturing excellence, my conjecture. The current practice may have been derived from initial limited and dire need for the brand drug. Once the drug is widely sold, tradition of multiple manufacturing sites (inefficient processes) similar to when the drug had limited distribution has continued. It seems value of alternate or efficient processes has not been explored. As explained later, too many API producers and formulators could also be part of the current quality variations and problems.

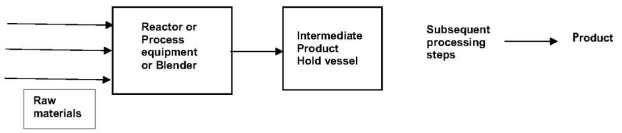
Process Selection:

It is necessary to understand the manufacturing process selection methodology. Reaction chemistry, formulation recipe, product demand and overall economics dictate process (batch or continuous) selection. This is not a new revelation. Selection processes in the chemical and petrochemical industry have been discussed and taught in chemical engineering curriculums as early as 1926 (too many references to cite). In the current pharma business model, batch or continuous manufacturing should influence revenues and profits but they do not because the process selection criterion is not based on economics or technology. It is based on exploitation of patient emotions and need to please shareholders.

Batch Process:

There is an established definition for batch process (13). Figure 2 is a simple schematic. It is noteworthy that in such processes it is critical and necessary to have storage space/ tanks/vessels where the intermediate products are held before the next processing step.

Figure 2: Schematic of a Batch Process :- INTERMEDIATES HELD FOR FURTHER PROCESSING



Batch processes are stop and go and many different processes and products can be fitted in the same equipment (14). They provide flexibility. Invariably intermediate products are tested to assure the process is working as planned. If a processing step does not produce the desired quality product, such intermediate holding tanks (or other tanks) can be used to rework the intermediate to produce specification product. One way or the other this practice increases product cost either through intermediate inventory related costs or re-work or disposal. Cash flow is impacted. All added costs are passed on to the customers.

Continuous Process:

Continuous processes have an established definition (15). Figure 3 is a generic schematic of a continuous process. There are two distinct differences between a batch and continuous process. In continuous processes flow of materials does not stop during the operating year [24x7x50=8,400 hours] except for the necessary downtime for maintenance or planned shutdown etc. which generally is as short as possible for economic gain. Each selected process is based on the reaction or formulation chemistry/ method and financial justification. In addition, each process is designed to produce a single product or an exactly similar product. There is no intermediate product hold tank/space in any continuous process. This is the most critical aspect of the process. Since the process is producing product every operating second, its quality cannot deviate outside the upper and lower quality limits at any instant. Feedback control loops that are well established and practiced maintain quality regimentation. Since the process is time-independent, in-line testing gives an instant image of the process. Deviation outside the control limits (Figure 2) means product is not meeting specs and will result in significant financial losses. Batch processes are a stop and go operation.

Figure 3: Schematic of a Continuous Process :- NO INTERMEDIATE PRODUCT HOLD

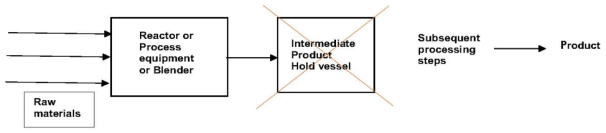
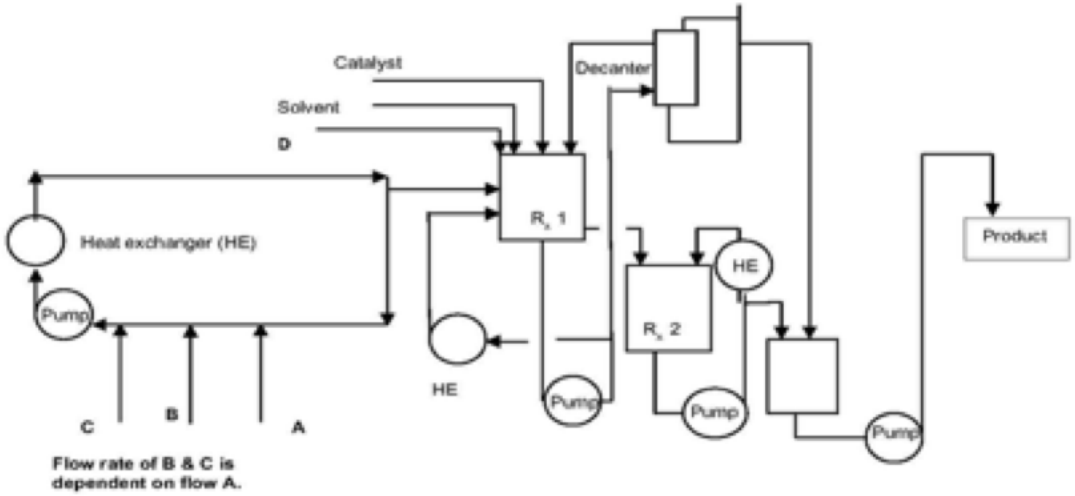


Figure 4 is a schematic of a real continuous process. It operated about 7,500 hours per year producing the same fine/specialty chemical. Again, we have to recognize that chemistries of API are similar to their older cousins – fine/specialty chemicals. The only differentiation is that API have disease-curing value whereas fine/specialty chemicals don't.

In Figure 4 process chemicals A, B and C are introduced at a predefined rate based on demand in a pipe flow reactor, reacted and continuously pumped to Reactors 1 & 2 where chemical D is introduced and reacted to produce the product. Chemicals A, B, C, D, Solvent, and the catalyst are fed in to the system 24x7x50 hours per year. Stoichiometry was precisely controlled using existing process controllers. Product was withdrawn from the reaction system continuously. This process is one example

of many continuous processes that have been commercial since early seventies. Thus, continuous processing/ manufacturing is not a new technology but is being touted by many as NEW (FDA and others who are equipment suppliers rather than actual practitioners).

Figure 4: A Continuous Flow Process Schematic



Batch Vs. Continuous Process:

It is necessary to understand why batch processes are the preferred processes for the manufacture of APIs and their formulations. Pharma, it seems, due to its own volition has never considered alternate manufacturing technologies. It is sad but it seems it is due to its sustained profitability even in quality by analysis regimentation.

Selected process, their method of execution and equipment do influence product quality unless an effort is made to have an exact replica or dedicated equipment. Even then, there can be a batch to batch variation at the same company. Understanding of equipment, raw materials and execution method influence quality. Judicious review of product demand is necessary.

Improved quality is being touted from continuous process vs. batch processes. That is true if there is such a process for the manufacture of APIs and their formulations, which would produce the same product about 7,500 hours per year. However, volume is needed to have a steady run from the same equipment. If the process is stop-and-go, it is no different from any batch process. In addition, a significant understanding of chemistry, component interaction and execution control is needed. This can present formidable and different challenges for API manufacturing and their formulations. If all was easy then continuous manufacturing – especially for formulations – would have been adopted in pharma manufacturing 60+ years ago.

Brand drugs, due to their high prices, have limited demand for the API and its formulation. As the demand increases, additional API and formulation sites are used to meet the increasing demand (7). Once a drug becomes generic, many companies enter the landscape (Table 2). Each uses a batch process even if there is a high demand. This is discussed later. Tradition prevails. e.g. Johnson & Johnson's McNeil lab (when it re-did its Tylenol formulation plant), chose batch production when it, due to its high product demand, could have easily used continuous process (16).

Drug dose and product demand determine API and formulation needs (17). Table 1 illustrates API and tablets

needed to satisfy the needs of 50 million patients per year. If principles of economics and chemical engineering were applied, the most likely needed API (dose 1 milligram) could be produced in a single plant. Formulation of this API could also be done at a single plant requiring multiple parallel formulation lines operating year-round. For a 50 milligram dose a single plant using a continuous process would suffice the global API need. However in reality, multiple plants are used to produce the API and their formulations. This is an extremely important fact as quality from each (API and their formulations) facility can vary even if every plant was an exact replica of each other. This is due to myriad factors (people, raw materials, equipment and even execution).

Table 1: Theoretical API and Formulation needs

Patients	Mgs	#/yr.	API, Kilo/ year	Tablets/yr.
50,000,000	1	365	18,250	18,250,000,000
50,000,000	50	365	912,500	18,250,000,000

Table 2 is an illustration of reality for some of the widely used selected drugs. Process economics should dictate process selection but that is not the reality. Fundamentals of engineering and economics are not applied for manufacturing selection guidance. It is interesting to note that Pfizer produced 200 tons of Atorvastatin API at three sites (8) but now it is being produced at 44 (17) sites and is being formulated at over 800 sites (different companies). Every product will not be exactly the same. We can all draw our own conclusions about batch to batch and site to site quality variations. Another interesting fact we have to recognize is that the FDA (or another regulatory body) does not have adequate manpower to perform even risk-based inspections just for these six drugs, my conjecture.

Based on the number of sites (17) (Table 2) that are being used to produce the API and their formulations, any experienced engineer/entrepreneur could conjecture that accepted principles of process selection are not being used in API production and their formulations. The only explanation for the large number of sites clearly suggests that the involved companies producing the API and their formulations are quite profitable even when they do not have the most economic processes. They will also have quality variability. One way to assure profits is taking short cuts whatever they might be. Marginal quality might be easier and cheaper to achieve than to comply with USFDA quality requirements. As long as quality is close enough, the product can be shipped to many countries. It is my conjecture that such practices can overflow to the developed country shipments.

Table 2: Number of sites for APIs and Formulations

Drug	Number of API Sites	Number of FDF Sites
Ciprofloxacin	22	536
Atorvastatin Calcium	44	865
Omeprazole	87	768
Modafinil	29	70
Metformin HCl	77	752
Metoprolol	41	338
Total	300	3,329

Again, rationale for so many API and formulation producers is "PROFITS". Reverse calculations illustrate the profit math. Ciprofloxacin, an excellent in-demand antibiotic is used as an illustration. Table 3 is quick back of the envelope analysis. A series of articles(18) further illustrate the point. It is interesting to note that Ciprofloxacin API used to sell the drug in India indicates API price of about $16.40 per kilo. Export price ranges between $26.00--$46.00 per kilo (19), a significant incentive and margin at API seller level which prompts many to produce this and other APIs. As indicated earlier these API producers most likely do not have economic processes and quality is tested in rather than built in with high probability of significant quality deviations. No one should be surprised if there are multiple quality levels of the same product at the same site.

Table 3: Reverse Calculation Illustration

Ciprofloxacin, 500mg tablet	Rupees/ tablet	$/tablet, exchange rate Rs. 69/$
	Selling price in India	
Selling price in India is used to reverse calculate API cost	3.75	0.054
API reverse calculated cost 85% is used as profit margin, seller margin, formulation profit margin and costs	0.56	0.0082 [=$16.4/Kg.]

US selling prices (20) vary from $0.28 to $4.77

Given the current profits landscape, many companies will enter to fill the need. As stated earlier to assure profits, it is

very likely that shortcuts will be taken and quality could be compromised. Many companies believe that about 80% of the population does not need drugs of USFDA standards. Their thinking is 98% is good enough then why 100% (USFDA standard) is needed. Such thinking is a reflection of a company's integrity and ethics. Such thinking prevails in companies who do not have total command of their operations and will sooner than later be cited by regulators.

Pharma companies have not explored increased profitability through continued process improvements and my conjecture is that the developed country regulations are the obstacle in this process. Too many filings are needed to comply with current regulations. Companies might not have the time to improve processes also. Thus, continuous process improvement effort is minimal at best.

Possible Solution:

Ethical practices, integrity and quality products are expected from companies. Every company that produces health-related products e.g. drugs, has to make sure that the products meet established quality specifications and follow cGMP practices (21). Data integrity must be paramount as well. Companies have to have complete command of their operations. Their ethics and integrity are at stake when they produce any drug. If they cannot comply with such expectations, my conjecture is that they should need not be in this business. They have to ask themselves the question "would they or their next of kin consume the products they produce?" It is imperative that for quality they live by "Do or Do Not, There is no Try---Yoda". It is incomprehensible when companies operate outside the specification limits they had committed and agreed to in the first place.

Companies very well know that non-compliance with USFDA regulations will have negative consequences besides bad publicity. They will have to spend monies for remediation. Doing things right the first time has minimal financial costs but somehow, they miss this important fact.

With the USFDA being short-staffed, my speculation is that even the "risk-based inspections" might not be sufficient to catch less than quality/cGMP producers. Some companies have and will figure out the system and take advantage thereby jeopardizing safety and the health of many. If that is the case, it may be necessary to change the prevailing regulatory landscape.

Under the current regulations, producing companies are given an opportunity to correct their non-compliance. Companies could be abusing this privilege. Repeat offence companies (7, 22) are still in business. Ranbaxy stayed in business for many years (8). Pharma lobby's behavior, siding with less than quality manufacturers, should be considered shameful and unethical.

FDA needs to change the rules of the game. It seems FDA/regulators are afraid of ensuing shortages that could result. Repeated non-compliance to FDA's requirements and guidelines should be a cause to forbid shipments to the United States. It is my conjecture that API manufacturers and their formulators in China and India have taken advantage of lack of sufficient producers in the developed countries and some might have "take it or leave it" posturing. Developed country regulators have to take a tougher stance (8). With many API producers (17) of the same product, it is very likely that that each has an inefficient and the cheapest process with harmful impurities. In order to maximise their profits, formulators and PBMs are most likely purchasing the lowest cost API and formulations and might not be totally aware of the impurities and their consequences (22).

A combination of polite and drastic pathways need to be used by the regulators to convince manufacturers to abide by the current regulations and quality standards. Companies could be given single site exemption with the stipulation that they deposit $200,000 (refundable) after the first deviation from FDA's expectations. A second offence on the same site should be the cause for forfeiture of the deposit and the company should be barred from exporting their product to the United States. I call this "one strike and you are out as in the game of cricket" – a simple and clear strategy.

The FDA has taken bold and drastic steps to withdraw ANDA approvals in the past but they have not been

publicized much (23,24,25,26). Recently the FDA withdrew ANDAs approvals for Apotex (27), essentially stopping their exports to the US market. The USFDA should withdraw ANDAs from the companies if they have not produced the product at the declared site for more than one year (28). They have no clue if approved ANDAs are being produced. Basically, the FDA has a big stick that it has not used properly. Maybe it is time to use it as often as possible. There could be some shortages, but they could become an opportunity for others.

Companies, who have considered FDA to be lax, need to wake up and produce quality products. Their business future could be in jeopardy. Thoughts discussed above could be part of the going forward strategy. If promulgated, pharma companies that comply with USFDA standards will benefit from higher profits that will come from better technologies that will be the result of consolidation, economies of scale and competition. Regulators should facilitate "continuous improvements". It is imperative that companies don't abuse the trust and privilege.

Going Forward:

Pharma landscape needs to be reviewed and changed to assure quality drugs from the get go. I believe regulators themselves are reluctant to adopt "continuous improvement" in their own operations which they expect companies to practice. They need to practice what they preach (28). The FDA, instead of preaching QbD (quality by design), needs to practice it. It relies of QbA (quality by analysis).

The Current ANDA filing process is complex as most of the application involve multiple reviews and submissions taking as much as three years (29). The FDA's ANDA approval process should be such that any application filed by its own personnel should be approved by a fellow reviewer on the first review in 90 days (30, 31). If it cannot be, that suggests that the ANDA filing and approval process needs to be simplified and perfected. Complexity of the current process is confirmed by the recent Government Accountability Office (GAO) Report (29). Since certain drugs are given an expedited approval (32), it suggests possibilities of 90-day approval is possible, if an effort is made.

ANDA applications that can be reviewed and approved in 90 days will demand that companies filing such applications have a complete command of every facet of the manufacturing, product quality, labeling and whatever else is needed by USFDA. Many will say "this cannot be accomplished". Such conjecture is unfathomable from successors of a generation that can send a human to the moon and bring him back.

Table 4: ANDA Approvals and Withdrawn

FY	APPROVALS	WITHDRAWN
FY 2013	440	107
FY 2014	409	179
FY 2015	492	170
FY 2016	651	248
FY 2017	763	214
FY 2018	781	606
FY 2019 (May 2019)	814	295
TOTALS	4,350	1,819

Table 4 from US FDA (CDER and OGD) (33) illustrates ANDA approvals and withdrawals. A clarification on withdrawals (are these withdrawals by FDA only or companies only or a combination?) has been sought. My conjecture is that most of the withdrawals are initiated by the company. These numbers are not publicized. It is also interesting to note that the number of ANDA approvals per fiscal year (Table 4) is significantly higher than the numbers published (31, 34). The GAO (31) report suggests that about 80 ANDAs are approved per year. Why not have 160 ANDA approvals per year? Such numbers are not out of the realm of reality if the FDA can simplify the ANDA filing and approval process. It will take effort. There will be significant internal resistance. Approval of a product and its manufacturing process is equivalent to a binding contract between two parties (manufacturing company and FDA). If a company does not live up to its contract, then the FDA should exercise its power to withdraw the ANDAs. The USFDA has a stealth weapon, withdrawing approved ANDAs, but has been reluctant to use it. Recently they have used it (27) and publicized it. It is an indication of wall handwriting to the companies to get

their act together if they want to be player in the developed country markets. No one, including the legislators, should be surprised that ANDA withdrawals could become frequent to stop less than quality drugs being offered to the populous. The EMA and other regulators have similar options. ANDA withdrawals could lead to temporary shortages but could be an opportunity also.

The US FDA should also refrain from telling/suggesting companies the types of manufacturing processes (batch or continuous) companies that they need or should practice. Regulators should focus on making sure companies have robust and repeatable manufacturing processes through continuous improvements. They, as suggested earlier, should facilitate the filing and approval process (31). Companies justify every investment and are responsible for their product and its quality. If they don't know what is necessary to produce quality products and are reluctant to follow FDA guidelines that are necessary to export products to the regulated markets, they should not be in the business. Only the best of the best should produce drugs.

The Possibility of companies losing their profitable markets will force them to stay on top of their product quality through economies of scale and better manufacturing technologies. If they succeed, their revenues and profits will improve. In light of regulators withdrawing ANDAs or potentially imposing fines for repeat violations, companies have to re-look at their operations and technologies. Some might have to consider "does it pay them to be in the business".

Companies have choices to make but supplying drugs that do not meet established quality and regulatory standards should not be the choice.

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CPhI insights

Part 2.

Biologics (capacity and biosimilars)

informa markets


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Mammalian Biomanufacturing Industry Overview

Trends Overview 2019-2023

- Demand for biologics manufacturing by volume is projected to reach over 4,200kL, a 5-year growth rate of over 10% per year (just over 2,500kL in 2018).
  - If Alzheimer's drugs and PDL/PDL-1 checkpoint inhibitors are approved, demand could be much higher, resulting in capacity shortages.
- Global biologics manufacturing capacity will increase to 6,400kL by 2023 from nearly 4,400kL in 2018
  - CMO/hybrid companies increase their control of capacity from 28% in 2018 to 36% in 2023
  - By 2023, Europe will have capacity equivalent to North America. Capacity in Asia continues to grow.
- Half of products in late phase development (Phase 2, Phase 3) can be met by a single 2,000 or 5,000L bioreactor.
- Overall capacity should experience some loosening in short-term constraints but may tighten after 2023. With the majority of capacity remaining in-house, it may be difficult for companies with products in development, but without internal manufacturing, to access capacity at the right time and under the right terms.

Abstract

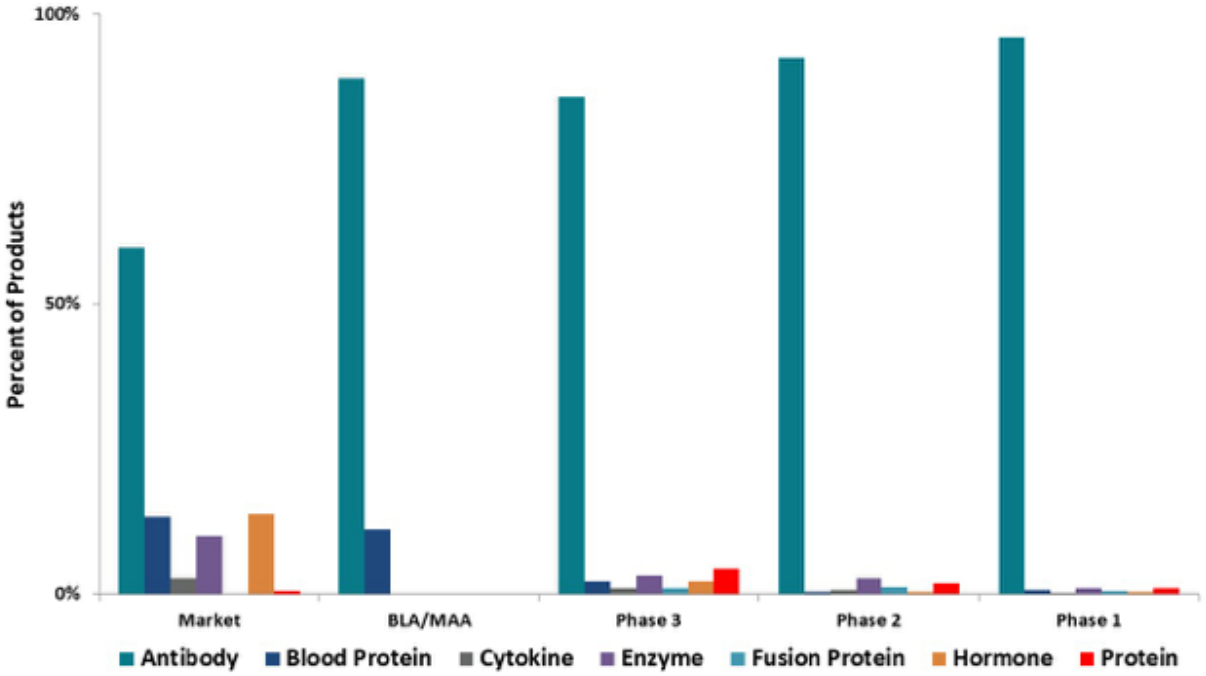
Biologic-based drugs are an increasingly important part of the portfolio growth strategies for pharmaceutical and biopharmaceutical companies. As the number of commercial products and pipeline candidates grow, key issues facing the industry include the current and future state of biomanufacturing capacity,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

Article

Since the approval of the first recombinant therapeutic antibody, OKT3, in 1986, biopharmaceutical products have become a larger percentage of overall pharmaceutical company revenue. In 2018, the sales of the top five selling recombinant proteins (Humira, Keytruda, Herceptin, Enbrel, Avastin), all antibody products, totaled just over $48B. The compound annual growth rate for antibody product revenue, which include naked monoclonal antibodies, Fc-fusion proteins, antibody fragments, bispecific antibodies, antibody conjugates, and other antibodyrelated products, was approximately 20% from 2004 to 2014. However, this growth has slowed to the mid-teens in the recent years due to the maturation of many products and emerging alternative therapeutic modalities. Also, it is difficult to sustain such growth rates as the overall market size increases.

To provide context around this growing segment of the pharmaceutical market, BPTG's proprietary bioTRAK® database of biopharmaceutical products and manufacturing capacity estimates that there are nearly 1,400 biopharmaceutical products in some stage of clinical development in the United States or Europe. The majority of these products, nearly 85%, are produced in mammalian cell culture systems. We evaluate the distribution of mammalian products by product type and phase of development to further refine the biopharmaceutical manufacturing market. 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 at nearly 60% and are the largest product type for all phases of development, with the early stage pipeline consisting of nearly all antibody products. 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 needs 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. Our future product growth estimations 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.

The projected treatment population size is estimated based on price per mg and sales. Combining the population with the yearly per patient dosing, we forecast the kilogram quantities required to meet demand of each product for the next 5 years. These kilogram quantity forecasts can be converted to liter quantities for each product using cell line expression level and overall purification yield estimates. These estimates are based on industry benchmarks 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 assumption when calculating future demand.

Figure 2 shows the projected kilogram quantities of product needed to meet annual commercial and clinical demand for all product types produced using mammalian production systems. In 2018, approximately 25 metric tons of product were required. 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 approximately 25 metric tons in 2018 to nearly 50 metric tons in 2023.

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

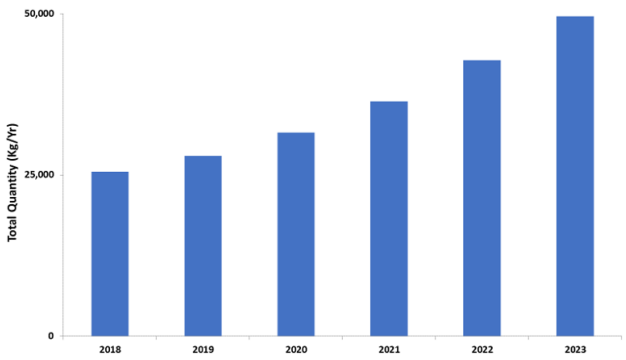
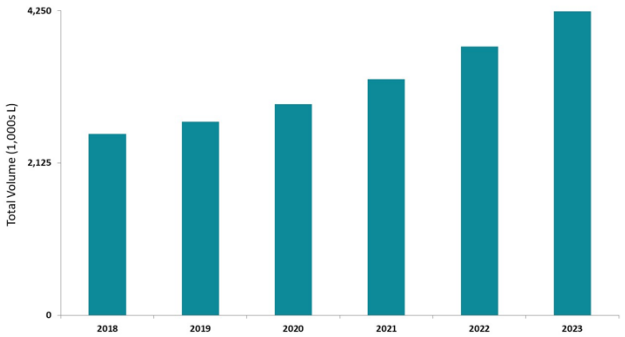


Figure 3 shows the projected volumetric capacity needed to meet annual commercial and clinical demand for all product types produced using mammalian production systems. In 2018, the annual volumetric requirements were just over 2,500kL, while in 2023, the volumetric requirement is projected to be just over 4,200kL, a 5-year growth rate of 11%.

Figure 3: Estimated Volumetric Capacity Needed to Meet Product Demand



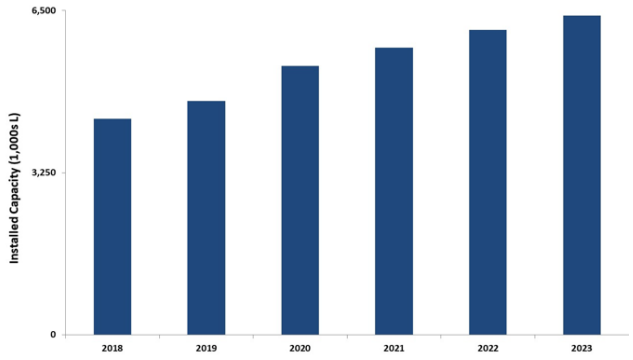
As with any forecasting model, our assumptions are based on the mostly probable scenarios and include estimations for biopharmaceuticals which are being developed for certain large patient population indications such as Alzheimer's disease, or broad cancer treatments like PDL/PDL-1 checkpoint inhibitors. Should several of these large-demand products obtain regulatory approval and adequate reimbursement by healthcare oversight organizations (i.e. US Pharmacy Benefit Managers, the UK's National Institute for Healthcare and Excellence (NICE)) or become part of a managed entry agreement between a company and public payer of a social or national health insurance system, 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 decrease in demand for some biopharmaceutical manufacturing capacity. Among these are the industry's 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. Given the projected increase in volumetric demand over the next 5 years, the industry is cognizant of 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 fluctuations over time, regulatory and reimbursement issues, and competitive factors.

To understand how the industry is positioned to meet these product demands, we estimated the 2018 mammalian cell culture supply to be nearly 4,400kL and predict it to grow to nearly 6,400kL by 2023, a 5-year growth rate of 8% (Figure 4). However, not all capacity is equally available throughout the industry. In 2018, product companies (i.e., companies focused on product development) control over 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. The distribution of capacity changes slightly in 2023, with product companies controlling 65% of the installed capacity, while CMO capacity increases 6% and hybrid companies remaining stable with a 1% increase.

Figure 4: Mammalian Manufacturing Capacity



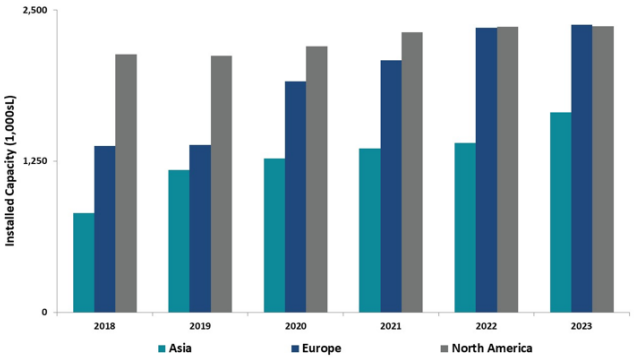
While product companies control the majority of cell culture capacity, the distribution of this capacity is highly concentrated within ten companies, as shown in Table 1. Capacity for companies not ranked in the top ten is distributed among nearly 130 companies in 2019, and nearly 135 companies in 2023. Currently, nearly 65% of the capacity is controlled by ten companies; in 2023, this changes to less than 60%. Based on substantial capacity investments, Celltrion and WuXi Biologics will displace Merck KGaA and Pfizer from the top ten.

Table 1: Control of Manufacturing Capacity

2019 Rank	2023 Rank	Company	Company Type
1	1	F. Hoffmann-La Roche	Product
2	4	Samsung Biologics	CMO
3	2	Lonza Group	CMO
4	3	Boehringer Ingelheim	Hybrid
5	7	Johnson & Johnson	Product
6	9	Amgen	Product
7	6	Sanofi	Product
8	10	Novartis	Hybrid
9	-	Merck KGaA	Hybrid
10	-	Pfizer	Product
-	5	Celltrion	Product
-	8	WuXi Biologics	CMO

Figure 5 shows the geographic distribution of the manufacturing facilities. In 2018, nearly half of all mammalian capacity is located in North America, followed by Europe and Asia. Over the past five years there has been modest capacity growth in North America and Europe, with significantly greater growth in Asia. By 2023, with significant growth rates projected in Asia (~9%) and Europe (nearly 15%), North America and Europe will have equivalent capacity. The capacity growth in these areas, particularly in Korea and Singapore as well as Ireland, are likely 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 2018 kilogram demand for the top five selling antibody products totaled nearly 6.8 metric tons. The demand for the more than 90 remaining marketed antibody products combined was approximately 15 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 nearly 60% of these products in development 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.

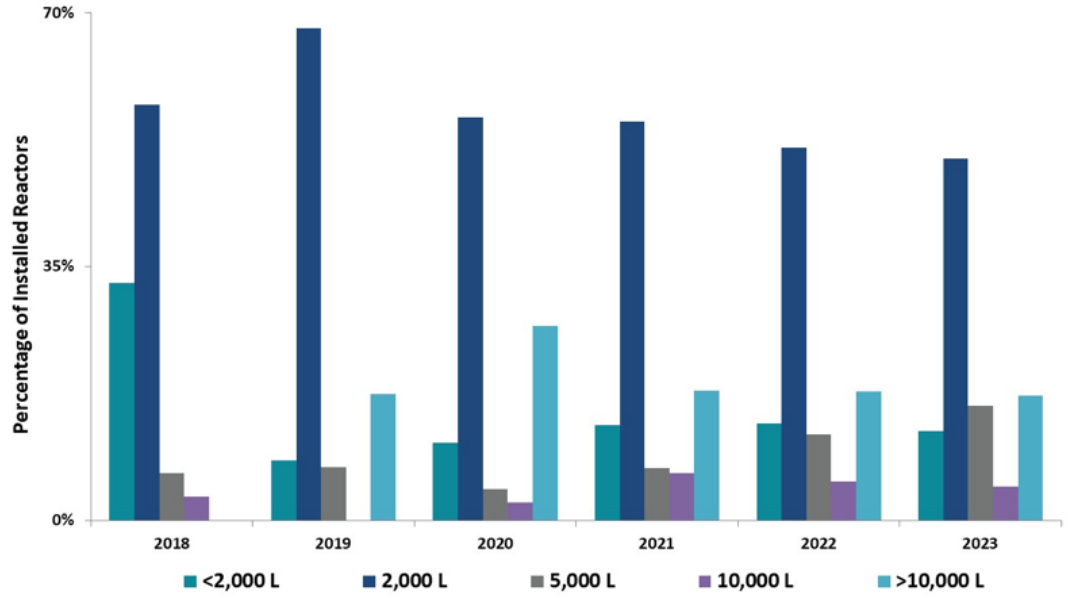
A closer review of future projected commercial manufacturing demands for products in Phase 2 and Phase 3 clinical development reveals half of the products can likely be met with a single 2,000 or 5,000L bioreactor assuming 18 batches per year per bioreactor, with a 90% success rate for batch manufacturing (Table 2). However, this does not mean that large scale capacity is no longer needed. Our model predicts that the remaining half of products will need bioreactor capacity of 10,000L and greater to meet the forecasted 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. As an example, a single 2,000L bioreactor is capable of manufacturing 39% of the products in Phase 2 and Phase 3, while a trio of bioreactors at this scale would be capable of manufacturing over half (54%) of the products in development.

Table 2: Percentage of Product Demand Met by Bioreactor Scale

No. Bioreactors	2,000L Bioreactor	5,000L Bioreactor	10,000L Bioreactor	>10,000L Bioreactor
1	39%	11%	11%	39%
2	47%	14%	12%	27%
3	54%	14%	11%	21%

If we analyze the cumulative number and scale of bioreactors coming on line between 2018 and 2023 at the <2,000, 2,000, 5,000, 10,000 and >10,000L scale (Figure 6), it is evident that the majority of the bioreactors projected to come on line are 2,000L. Nearly 20% of the bioreactors are at a scale of 10,000 or greater. Manufacturers understand the capacity demand scenarios and are installing capacity to meet these anticipated demands.

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 terms. North America currently 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 2023, 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. The type and scale of capacity being installed will also be important as the demand for 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 reflecting the demand profile, we are focused on 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 patients.

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Biopharmaceutical Therapies And Biosimilars: Not Your Father's Medication

Introduction

The pharmaceutical industry for many, many years has meant "small (usually synthetic) molecules," mixed with various non-active materials and put into capsules, (or, in the old days) rolled into pills, or pressed into tablets. While synthesizing the APIs (active pharmaceutical ingredients), formulating the dosage forms, and analyzing the materials at every stem of the lifecycle was not always trivial, it was relatively straightforward.

The tools used for analyzing/controlling each step were, in many cases, already in labs across the world. Since the early commercial production tools were, by today's standards, very, very slow, in-process tests need not be fast or sophisticated. Indeed, the vast majority of solid dosage forms were "immediate-release" tablets or capsules that depended upon the gelatin-solubility for release of the API. Later, time-release dosage forms were subjected to the same in-process tests as immediate release forms: hardness, friability, disintegration, and weight variation.

All this was fine when a single-punch press (and later, somewhat larger units) were used, producing hundreds of tablets per hour. Since final testing was "sufficient" for safety and efficacy, the 20-30 final doses tested (or an assay of a composite) were considered fine. After all, the batch-style of production took weeks for a single lot to be made, so who cared if it took (several) days to analyze it? So, as production methods grew faster and faster, the industry was saddled with 1950's style in-process and final lot analysis techniques. The best impetus to "modernizing" the way we monitor and analyze and, more importantly, control our production was the PAT Guidance of 2004. (If you aren't familiar with this Guidance, please Google it.)

The Guidance (and successive Guidances from USFDA, EMA, and ICH) supported better and more control of a process through modern technology. The extension of analysis/control to process applications meant simply waiting for faster and better computers to be made available, sufficiently complex software to be written, and the engineering of smaller, faster, and more accurate measurement devices. Beginning in (roughly) 1990, several companies began developing the tools needed (one example was the cooperative effort between Pfizer, UK and Zeiss, Switzerland, to develop the first wireless, in-place NIR spectrometer for blend uniformity measurements… in real time). The acceptance of this tool by FDA opened the floodgates for new equipment and peripherals.

Traditionally, the making of a small molecule dosage form has two distinct segments: synthesizing the API, and generating the solid dosage form. The former is essentially

organic chemistry, while the latter is (or should be) based on materials science, i.e., mixing and tableting. However, with the development of wireless spectrometers (largely Near-Infrared), continuous monitoring and feed-back (control) under PAT, new approaches are coming to market. A decade or so after the introduction of PAT/QbD (Quality by Design), we see more and more real-time release of final dosage forms, not to mention the growing presence of continuous manufacturing (CM). So, it would appear that solid dosage forms are well on there way to QbD and, eventually, where warranted, continuous manufacturing.

These (and similar) tools have been in existence for organic (API) synthesis reactions much longer than those of tablet production, simply because the organic synthesis reactions take place in non-aqueous solutions, amenable to spectroscopic (IR, NIR, Raman) controls. Parameters like viscosity, temperature, refractive index, and other physical measurements were easy to measure in an organic solution.

However, expecting us to simply apply these same control technologies to biopharma products would be naïve. There are some fundamental, basic differences between the two paradigms. Instead of a controlled synthetic organic reaction in a chemical reactor, the manufacturing of biologics (monoclonal antibodies, recombinant proteins and DNA, vaccines, etc.) relies on complex cellular bio-systems with high sensitivity to their environment and feeding regiment in an aqueous matrix, not simply controlled by well-established principles of organic chemistry.

The production of large molecules by microbes and mammalian cells requires the control of numerous processing parameters

The production of large molecules by microbes and mammalian cells requires the control of numerous processing parameters such as nutrient concentration, temperature, pH, gases, agitation, and so on. The host cells, the product(s), the by-products (i.e., lactate, ammonium, and CO2) and the growth medium constitute a complex mixture with many of the chemical species present in a bioreactor at levels undetectable by many analytical tools, including NIR spectroscopy. [Many materials are not strong absorbers of IR or NIR light, i.e., ammonium [NH4+ and H+ ions, so their effects on other molecules and water are followed by Chemometric methods.]

The production of large molecules typically follows a two-step process. First, the microorganisms produce the molecules of interest. Then, the molecule is purified from the growth medium, cells, viruses, and other impurities. Most of the published work involving NIRS and other popular process controls has been for the large molecule production, so I will not address the cleanup process here.

The biopharma manufacturing process routinely relies on the in-line and in real-time measurements and control of parameters such as pH, dissolved oxygen, and CO2 – both dissolved and in the headspace, which impacts cell viability. Nutrients (i.e. glucose) need to be measured and controlled throughout the duration of the batch production and byproducts (i.e. lactate, ammonia) need to be monitored. Until recently, manual sampling and off-line measurements with fundamental primary analytical methods were the predominant control procedure. However, the use of in-line spectroscopy as a process analytical tool to monitor and control these bioreactors has seen a significant increase over the last decade.

All impurities in APIs are critical, but with biological impurities (often proteins, not seen previously), the stakes are potentially higher. Not only are there potential long-term carcinogenicity and mutagenicity dangers, but, with unknown proteins, there are also potential immediate allergic reactions. Assuming there are no immediate reactions, there are still the potential long-term potential harmful effects, depending on the therapy for which the biological is being used. If the drug is used in a one-time application, such as heparin for a cardiac event, there would not likely be a chance for the minor impurities to do much harm. On the other hand, long-term use of a bio-drug such as insulin, which is used for decades, would allow even the smallest impurity the time to do harm to the patient.

One might assume that a company that develops an NDE (new drug entity), based on a bioprocess, will spend years assessing potential harmful effects. Between the time involved in development of the API (protein, etc.), all

the clinical trials, and subsequent stability studies while in production, it would be expected that the initiator company would have accumulated a large portfolio on all the potential by-products and, later, the break-down products of the drug substance and its synthesis route. However, as with generic competition for small molecules, there has arisen competition from secondary companies, producing the "same" active molecule, but from a different synthesis/bio-expression route.

Now, a biosimilar would have, by definition, less time for any potential side-products to be evaluated before marketing, often with abbreviated clinical trials before release/marketing. While the major active ingredient may be identical to the patented one, any biological process expresses numerous proteins, each particular to the mode of expression. When all is said and done (excluding potential lawsuits for patent-infringement, etc.), the most problematic feature of any biosimilar will be the exotic side products and potential side effects. Again, excluding copyright infringement possibilities, several Guidances and policies of the USFDA also add to the complexity of making and selling biosimilars.

When you include the provisions of the QBR Guidance, for example, it becomes more arduous. The "Question-Based Review" (Question-Based Review (QbR) for Generic Drugs: An Enhanced Pharmaceutical Quality Assessment System) has as one of its main thrusts requiring ANDAs (Amended New Drug Applications, which, unfortunately, would include biosimilars) from disparate companies follow a common form for style. Previously, when each of the large number of generic companies submitted their documents, each used their own internal style. This resulted in reviewers at the USFDA having to navigate dozens of different types of applications, causing long wait times for the generics to get a yes/no answer on their new product's fate. [Imagine an English teacher allowing each student to write a term paper in his/her individual manner… chaos.] This style requirement, alone, made the Guidance an excellent idea and, like a class receiving a term paper assignment, they all understood what was needed and in what order it should be presented. This did, indeed, speed up review times.

Unfortunately, it also included some responsibilities for the generic company that were new to them. The responsibility for the purity of the product was extended to both earlier and later than had been the case previously. The existing responsibility was to "simply" produce a product (often covered by a monograph in the USP) that met the requirements of purity, assay, disintegration or dissolution times, and so on. Prior to QBR, it was sufficient to depend on the CofA (certificate of analysis) for purity, potency, etc. of an active pharmaceutical ingredient (API)… with a biosimilars, a mere CofA would have never been a good idea.

Unfortunately, it also included some responsibilities for the generic company that were new to them.

But, under new Guidances (both FDA and ICH), the generic drug companies (including CMOs) now need to be familiar with the synthesis route for the API such that they can prove (validate) that their incoming RM testing and stability-indicating assays can identify and quantify any breakdown product from the synthesis of any of API, no matter the synthesis route by which they were produced. This also extends to stability programs: each analysis method MUST be capable of finding and quantifying materials from the breakdown of the dosage form APIs; however they are produced.

This means a constant feedback loop between suppliers and the company's labs, such that any analytical method can separate any and all potential by-products (from synthesis) and any and all breakdown products from stability samples. Now, in a "normal" or traditional generic company or contract manufacturing facility, there are a number of trained analytical chemists, allowing the methods to morph to the specificity needed. It only adds a small amount of labor and time to the existing workload when small molecules are involved.

However, when it comes to biological or biosimilar production and sales, all bets are off. Whether the CMO is producing a biological product that was the "original" (under contract to the patent-holder) or generating a product that is "similar," the process is far more complicated than merely mixing powders and compressing a tablet or encapsulating the mix into a capsule. Understanding the effects of an API on the final dosage form is even covered in ICH Q11:

"The identification of CQAs (critical quality attributes) for complex products can be challenging. Biotechnological/biological products, for example, typically possess such a large number of quality attributes that it might not be possible to fully evaluate the impact on safety and efficacy of each one. Risk assessments can be performed to rank or prioritize quality attributes. Prior knowledge can be used at the beginning of development and assessments can be iteratively updated with development data (including data from nonclinical and clinical studies) during the lifecycle. Knowledge regarding mechanism of action and biological characterization, such as studies evaluating structure-function relationships, can contribute to the assessment of risk for some product attributes."

This control/understanding of biologicals for the companies who have developed the drug is difficult enough, even with a large number of biochemists, molecular biologists, analytical and QC chemists. For smaller companies (both producers of the bioproducts and the generics who package them as dosage forms) largely used to performing small molecule analyses, this makes the task even more difficult. Clearly, any company producing a biosimilar would need the facilities of the major company that originally discovered and produced the first bioproduct.

So, in short, biologicals are the next great step for the pharmaceutical industries. The double-edged sword is that, as the molecules become more and more complex, our need for control and understanding becomes greater. The potential for curing exotic diseases and helping humans has become greater, but (as they say in Marvel movies) "with great power comes great responsibilities." Our quality programs will need to become many times more stringent and carefully designed.

But, the future with biopharmaceuticals is far brighter than without them.

Additional Questions

Q) What lessons could the biosimilars industry learn from the small molecules sector?
This is somewhat complex. Several lessons may be learned:

1. The biopharma industry, in general, can use a broader range of disciplines. Small molecule manufacturers have analytical, QC, engineers, and so forth, while biopharma has nearly the same level of expertise at all stages of development through production.
2. Traditional technologies need to be updated to both different, newer technologies (NIR, Raman, etc.), but faster instrumentation, equipped with stronger algorithms (Chemometrics). [This will necessitate more and more diverse personnel.]

Q) CQAs have gained a good deal of attention in small molecules recently do you think the risks are currently under reported?
One problem is that we base everything on what we believe is a "good" product… based on limited clinical trials and limited production runs. Even if we apply PAT/QbD to the production, we seldom perform more clinical trials to reaffirm that the CQAs are truly CQAs.

Q) How do you think regulators will react – try to standardize approaches over the next 1-3 years (from EMA and FDA to NMPA, etc)?
They have been "peeking over each other's' shoulders" when writing guidances and rules… modeling rules for linearity, noise, etc. for spectroscopic and any method based on Chemometrics. Using the ICH (International Council of Harmonisation), in which all the Agencies are voting members, most newer documents mirror each other. This will, at least, lead to commonality.

Q) In five years' time how do you think regulation of biosimilars will evolve / how should it evolve?
I believe (hope) that a better definition of what a biosimilar is and what tests must be performed. Since the bio-API is expressed via a different life form (bacterium, etc.), the minutely small side-products will, by necessity, be different from the initiator product. (If it were made in the same manner, from the same bio-reactor, it would

violate patent law.) What will, I feel, happen will be that biosimilars will eventually have to undergo the same clinical rigors as the initial product to be proven as safe as the initial material.

Q) Do you think new therapies like RNAs/ oligonucleotides coming to market are perhaps safer as they act upon genes rather than altering them (sitting somewhere between NCEs and biologicals) – what challenges will they face?
These are exciting and have proven effective (in many cases). The up-side is that these therapies don't interact (mostly) with other organs like a small molecule API of chemotherapy, which is designed as a poison, but we hope the cancer will absorb it faster than other (healthy) cells. The down-side is that the search for these therapies is slower and more expensive for "rare" diseases (few patients), making the cost per patient far higher. They will go forward, but may well need government assistance to succeed in a large fashion.

Q) (controversial question) do you think biosimilar production for new and more advanced therapies might be better conducted in the west until risks are understood?
That is based on a preconceived idea that "western" pharmaceutical companies are superior to developing countries. I have no doubt that countries such as China and India have the technology and expertise to conduct the proper R&D.

Q) How do you see the role in the massive growth?
If you stillmen biosimilars, I see slower overall growth, after a flurry of introductions, unless they are proven both safer AND less expensive than the initial offerings. Due to the expense of R&D for the initial products (and small-ish market), if a research company cannot make back its expenses, work will not grow quickly in the area… it is, after all, a for-profit business, not a charity or government agency.

Q) Are you confident the 'battleground' has now shifted to biologics (i.e. we are reaching the end of the development cycle for solid dose drugs with PAT and continuous processing), or is there more still to be done?
Not yet, but the gauntlet has been thrown to the fee of big Pharma. We may believe that, for example, continuous manufacturing may be highlighted in conference proceedings and journals, but, in reality, a very small number of manufacturing sites and products are produced by this methodology. [Not always from lack of desire, but there is still a shortage of trained personnel with practical knowledge of the technology.]

Q) Have we made enough progress with 3D printed formulations and individualized dosage forms? Do you see a breakthrough coming if so when?
Two years ago, at the IFPAC conference, one company from India presented its product (already approved by FDA) that was made with a 3-D process line. Yes, it was for smaller, specialized dosage forms, but the ability to produce commercial product has been demonstrated. Back as far as 1999, there were people at Purdue Pharma looking at encapsulating an antagonist in the OxyContin tablets via 3-D printing. At that time, it was far too slow and expensive to pursue, but 20+ years has moved it to a reality.

You can never "predict" a breakthrough, but need/desire is a strong motivator for development. It would not be a wild prediction to assume that five years from now will see an impressive number of 3-D printed (specialty) dosage forms for products, using multiple layers, osmotic pumps, etc. as a means of controlling the release of the API(s).

CPhI insights

Part 3.

Biologics (advanced therapies and China)

informa markets

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Trends in Chinese Biopharmaceutical Manufacturing, Contract Manufacturing and Innovation Opportunities over the next 5 years

Introduction

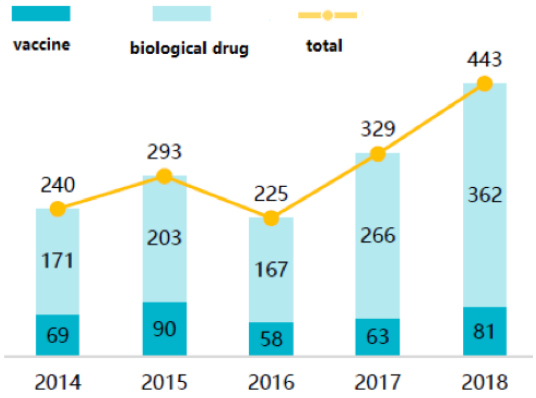
During the past decade overall growth in China's bio-processing capacity has been particularly impressive, albeit from a low baseline. With loans, grants, as well as cheap lease of land from both central and local governments, bio-manufacturers in China are orienting themselves to be major players in GMP manufacturing. China now has over 50% more facilities than India, and, according to our Top1000bio.com website, has over 8% of global capacity, although the average facility size is significantly smaller than in India or Western markets.

It's an exciting time for the industry; barely a week passes without news of construction of a bio-processing facility being put into operation in China. This includes domestic biopharmaceutical companies as well as contract manufacturing organization (CMO), especially as regulations are changing so third-parties can manufacture biopharmaceutical supplies. Domestic biopharmaceutical companies, especially those with late-stage clinical projects or biological therapeutics on the market, are also building or expanding in-house bio-processing facilities. Henlius Pharma, a mAb developer led by returnee scientists, started a second bio-production site in Shanghai in 2018 (1). From our recently released study, Advances in Biopharmaceutical Technology in China, 2nd Ed (2), we found that some of the new facility construction and expansions reflect the demand for biologics for domestic consumption, while other facilities are beginning to develop manufacturing strategies for GMP production for major markets, with capacity involving commercial scale stainless steel and single-use bioreactors.

Trend 1: Spike in Biological Therapeutics Development Drives Bio-processing Capacity in China

The past decade witnessed the rapid growth in the sales in China of biopharmaceuticals, with a compound annual growth rate (CAGR) of > 15% versus < 4% in the developed countries (3). China is the most populous country in the world and home to the largest patient groups, with a growing economy with GDP second only to US. The rapid urbanization in China as well as greater access to national healthcare insurance, has made China the world's 2nd-largest market for pharmaceuticals in 2017 at $122.6 billion (2).Though chemical drugs and traditional Chinese medicine both poses robust growth, it is bio-similar therapeutics, especially that of mAb therapeutics, whose growth is especially impressive. China biologics markets have grown from under $1 billion in 2012 to a projected $50 billion in 2021 with a CAGR of 16% (2).

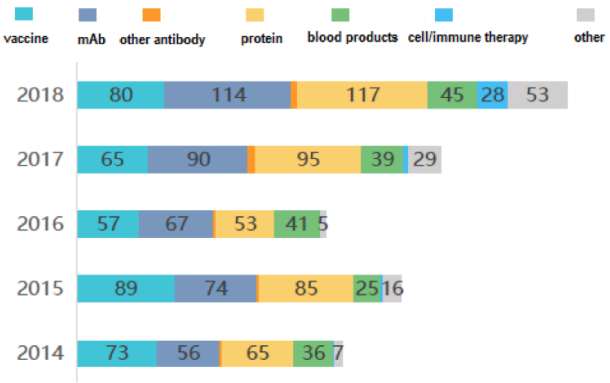
Figure 1 Growth in Biological Therapeutics Projects in China 2014-2018 (3)



Source: 2nd Ed., Advances in Biopharmaceutical Technology in China, 2018, BioPlan Associates, Inc. Rockville, MD. USA

Since the first launch of made-in-China mAb therapeutics in 2005, China has experienced a spike in mAb drug development in recent years. BioPlan's internal studies have shown that over 250 mAb therapeutics are under clinical development in China, with CD20, HER2, EGFR, VEGF, TNF-alpha as the hottest targets. This wave of mAb therapeutics development was initiated only around a decade ago, with the majority of developers starting their mAb development within the recent 5 years or so. Regulatory authorities in China has just started giving green lights to this wave of mAb projects, as the last 7 months has witnessed three PD-1 mAb therapeutics made by domestic companies been approved, but the peak has certainly not arrived yet. New investments are still coming into this sector. In February 2019, China Antibody just completed a round of pre-IPO financing worth perhaps hundreds of millions of dollars, and hardly a month passes without news about new companies being founded with a focus on mAb therapeutics. BioPlan's internal research has also shown a consensus that in the next 5 years China will see at least 10 mAb therapeutics from domestic companies getting BLAs, with the more optimistic projection at over 50 or so. There is also consensus that China will need at least additional 100,000 L in bio-processing capacity annually in the next decade.

Figure 2 IND Distribution of Biologics between 2014-2018 in Different Classes (3)



Source: 2nd Ed., Advances in Biopharmaceutical Technology in China, 2018, BioPlan Associates, Inc. Rockville, MD. USA

Trend 2: Contract Bio-manufacturing on the Rise

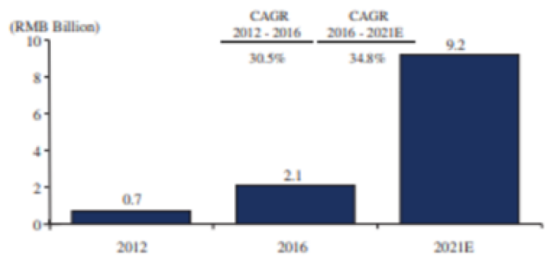
As the development of a new drug as well as the establishment of GMP compatible R&D and manufacturing facilities requires huge investment, big pharmaceutical companies need to use professional R&D service-outsourcing to help them effectively reduce costs while enhance efficiency. For some emerging markets (e.g., China and Singapore), local CMOs not only can make up for the shortage of the big pharmaceutical companies' self-owned resources but can also establish new production chains for them. Small biotechnology companies, which

usually cannot afford to build the necessary manufacturing facilities with limited resources, would have to rely on outsourcing of manufacturing to CMOs, who have mature supply chains and the capacity for production of therapeutics.

In the past decade, China's biopharmaceutical service market shows exceptionally strong growth potential though its history is relatively short

In the past decade, China's biopharmaceutical service market shows exceptionally strong growth potential though its history is relatively short. While ten years ago it is hard to find one competent biopharmaceutical service company in China that could meet the basic requirements for a Western client, now China is home to many excellent Chinese biopharmaceutical service companies including WuXi Biologics, MabPlex, CMab and JHL Biotech, Inc. From 2012 to 2016, China's biopharmaceutical service market had grown rapidly at an annual growth rate of nearly 30%, with the market's size growing from CNY 700 million in 2012 (~USD $104.7 million) to CNY 2.1 billion in 2016 (~USD $314 million) and anticipated to reach CNY 9.2 billion (~USD $1.4 billion) in 2021(Figure 2)(2).

Figure 3 China Biopharma Outsourcing Service Market Size



Source: 2nd Ed., Advances in Biopharmaceutical Technology in China, 2018, BioPlan Associates, Inc. Rockville, MD. USA

Regulatory reforms are also bringing growth opportunities to the outsourced service industry. With both global and domestic demands on the rise, Chinese regulatory authority has made strategic moves to boost the outsourcing sector. In 2016, China started a pilot program named Market Authorization Holder (MAH) program, under which Holders of a CFDA biologics approval number are required to market the therapeutic product and take the responsibility for them while having the option to either manufacture the drugs products on their own or use contract manufacturers instead. The MAH breakthrough first starts a pilot run in 10 provinces and municipalities and is now re-affirmed in the 2019 version of Drug Administration Law. According to statistics from Liberation Daily, till the end of May 2017 there is a total of 381 applications of MAH and Shanghai alone sees 16 applicants of MAH for 24 drug projects with 18 contract manufacturing partners (4). Mr. Li Zhiliang, CEO of Autek Bio, stated that at current stage China has over 50% idle capacity in bio-manufacturing while this percentage is below 30% in US/EU. He expected the implementation of MAH to significantly decrease idle capacity, leading to a cost reduction and increased productivity (2).

Local government support also contributes to the growth of the outsourcing sector for biopharma industry. Industry insiders have mentioned multiple cases of municipal government providing cheap lease of land or other forms of subsidiary for CMO companies; for example, in November 2018, with support and subsidiary of local government, Wuxi Biologics started construction on a Biologics Manufacturing Center of excellence (MFG8) in the city of Shijiazhuang, Hebei Province. The new Biologics Center with 48,000L bioreactor capacity, one of the largest global facilities using disposable bioreactors will be built to meet cGMP standards of the United States, the European Union, and China (5). Without such support from local government, it would be not that easy for CMOs to expand their capacity in China.

Trends 3: Single-use Bio-production Becoming 'Mainstream' in China

While in the past, almost all Chinese biopharmaceutical companies relied on stainless steel bioreactors for production, the new wave of biologics development goes hand in hand with single use technology. The industry is making progress with substantial investments in bio-processing, while many of the facilities under expansion have plans to incorporate some of the most advanced technologies, including modern single-use technologies

(SUT), and modular strategies. For example, on June 28th, 2016 Pfizer China broke ground for its first biologics production facility in China, which is fully based upon GE's single-use technology in a KuBio™ modular facility. JHL Biotech, the biologics CMO founded by veterans from Genentech, also attributes its fast-track opening of Wuhan base to the KuBio™ modular factory (1). Dozens of domestic biopharma companies are using single use bioreactors or are constructing single-use technology based facilities as it provides a faster track for project development.

The case for single use bioreactors is particularly strong for two groups of companies: early stage mAb developers or biologics contract manufacturers. For mAb developers, single use technology offers the key advantages of less capital investment during project development stage as well as time-reduction in facility construction. As most mAb developers in China are working on biosimilar/ biobetter version of mAb against several established targets including TNF-alpha, PD-1, Her-2 or EGFR with usually multiple companies for each target, the time to clinical development can mean life or death for a project. Though the regulatory authority in China used to be quite lenient with domestic generic makers, many analysts believe that it may become stricter in the future with the on-going healthcare reform. As a result, the late comers may be denied market access for their antibodies. Less capital investment during development is also extremely important for the small to medium sized biotech companies, as more often than not they are cash strapped without enough resources for facility construction. Biologics CMOs is another group of staunch supporters of single use technology. The well-known biologics CMOs in China, including Wuxi Biologics, JHL Biotech, MabPlex, all use single use bioreactors. As a CMO will serve multiple clients, cross-contamination becomes a high-priority concern and single use technology can provide a perfect solution to them as it completely eliminates the need for cleaning. With both mAb development and outsourced bio-manufacturing on the rise in China, there is no surprise that single use technology is getting more popular, enjoying double digit (some even project over 30% CAGR) growth in recent years.

However not everyone agrees that single use technology can keep this momentum of growth in the next decade. First there is concern that this wave of mAb development may ebb in the next few years, as investment into this sector may drain up as investors find out that the return of mAb therapeutics in China is not as high as they have expected. Meanwhile as more mAb projects are coming to clinical stage, their developers may prefer stainless steel bioreactors due to cost concerns when they are considering building their own commercial scale facilities. Though the MAH reform has opened the door for commercial scale outsourcing in China's biopharma industry, domestic companies still have a strong tendency to keep manufacturing as their core competence. Many of the VC-backed developers would seek IPO, and Chinese investors are known to value fixed assets such as land, facility over IP and product portfolio. We see many developers outsource pilot-scale production but would plan to build their own facilities when their project goes to late clinical stage. When Chinese developers build commercial scale facilities, they witness a high preference of stainless steel bioreactors over single use ones. Therefore, there are industry-insiders who believe the growth rate for stainless steel bioreactors may go up while the market for single use technology cools down in the next decade.

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New Developments in Bioprocessing Development & Manufacturing

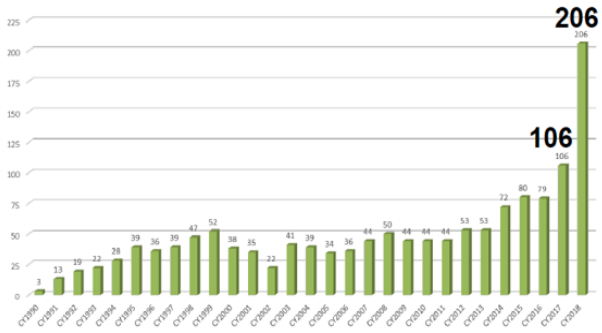
Introduction

Biopharmaceuticals are continuing to grow at rapid pace, most recently accelerating even more so due to the keen interest in cell and gene therapy. In this article my focus will be on several key growth areas of the field, focusing on aspects of development and manufacturing. The article will build on my earlier one a year ago on top trends in bioprocessing[i].

Cell & Gene Therapy

This relatively new area is the "hottest ticket in biopharma town". Thanks to some impressive successes in both cancer and rare-disease therapy, and now four (4) FDA approved therapies, companies are scrambling to enter this market. Development and manufacturing facilities for cell and gene therapy are in great demand, as shown by the recent billion-dollar premiums paid by pharmaceutical and contract-services companies to acquire such capabilities. Examples include Roche's acquisition of Spark Therapeutics ($4.3B), Catalent's of Paragon Bioservices ($1.2B), ThermoFisher's acquisition of Brammer Bio ($1.7B), and Celgene's acquisition of Juno Therapeutics ($9B). There has also been a surge in activity at FDA in this area, with Investigation New Drug Applications skyrocketing from 106 in 2017, to 206 in 2018, to over 800 so far in 2019[ii] (Figure 1).

Figure 1: IND Applications in Cell & Gene Therapy to FDA by year.



Notwithstanding the excitement in cell and gene therapy, there is a general realization that the field needs to move toward industrialization and beyond

bench-scale processing. One of the key challenges, however, is that the major progress has been in autologous therapies, which involve treatment of an individual patient's own cells. With this approach one needs to scale-out rather than scale up, with multiple lots for multiple patients, each in its own equipment. This approach has been facilitated by the widespread availability of single-use technologies for bioprocessing. Nevertheless, it does involve additional expense and processing compared to scaling up lots each of which can treat multiple patients, which is the typical arrangement for biopharmaceutical therapies such as monoclonal antibodies and other recombinant proteins[iii].

Cell and gene therapies typically involve both more manual labor than do recombinant proteins and also scientific personal with specialized skill sets. Automation and robotics are being applied to help reduce manual labor, but the demand for scientists with training in cell and gene therapies far exceeds the supply. Universities such as the New Jersey Institute of Technology are partnering with companies in the field to set up such training at specialized institutes[iv] to address this need.

Intensified Processing

This concept broadens the active trend towards continuous processing to include any steps that accelerate a process such that more of a given biotherapeutic can be produced in less time. This includes using intensified perfusion bioreactors, earlier pioneered by DSM Biologics and now actively pursued by many companies. In this type of process, cells are grown to a very high cell density through optimized feeding strategies and product continuously harvested utilizing an alternating tangential flow (ATF) such as developed by Repligen.

Other companies have intensified their fed-batch bioreactors by utilizing a small, high-density perfusion seed bioreactor inoculate a series of production, fed-batch bioreactors[v]. This process replaces the multiple scale-up steps typically needed to generate inoculum to start the production bioreactor with a single ongoing perfusion bioreactor that keeps generating inoculum for a series of bioreactors. Thanks to the high density possible with perfusion, cells can be inoculated at a higher starting density, saving time in the production reactor as well.

On the downstream side, faster protein purification is being enabled through several innovations in chromatographic separations. First, there have been advances in the capacity of membrane-based separation technologies whose rapid exchange kinetics allow for faster processing[vi], such as those originally from Natrix Technologies but now offered from Millipore Sigma[vii]. More recently companies such as GE Healthcare have been developing a new generation of separation modalities based on nanofibers[viii]. These provide very high flow rates and capacities, such that multiple very short cycles can be run up to the cycle lifetime of the support (150-200 cycles). This enables single-use even for expensive affinity supports such as those with Protein A used to bind antibodies selectively. Essentially the affinity support becomes a fixed material cost for each run, rather than a large, upfront cost that is slowly depreciated as long as the product remains in the portfolio[ix]. This is exciting since so much is spent on Protein A resins during clinical development for products that may never be commercialized. While the technology is still being developed for manufacturing scale, it is available for bench-scale evaluation[x].

A new generation of separation modalities based on nanofibers provide very high flow rates and capacities... short cycles can be run up to the cycle lifetime of the support (150-200 cycles)

While chromatographic resins have continued to increase their capacities, especially for affinity supports such as Protein A, a more recent development from Purolite has been application of a new agarose manufacturing technology to produce highly uniform beads. The resulting resin has high capacity even at high flow rates (2 min residence time), due to the improved flow properties of the uniform beads. Furthermore, the flow properties

also facilitate the removal of impurities such as host-cell proteins (HCP), such that less washing may be needed. Both the faster flow rates and easier removal of impurities shortens the processing time, thereby intensifying the process[xi].

Another innovation using standard chromatographic bead technology involves the use of variable load rates on short (10 cm) production columns. The concept is that flow rate is maximal during the beginning of the feed, and then is sequentially tapered off to slow flow rates as the column capacity is reached. The result is achieving a higher dynamic capacity for the resin to more closely approach the static capacity. Furthermore, due to the short length of the column, each column cycle is shorter allowing multiple cycles in less time. While column capacities are not quite as high as the multi-column, simulated moving bed (SMB) type of approach, it is much simpler and less expensive to implement. There are some caveats to this approach, including the need to pack the short column carefully to ensure even flow distribution and to measure column packing efficiency at both high and low flow rates[xii].

Finally, the non-chromatographic purification technology of selective precipitation is being reconsidered in light of both higher product harvest titers and continuous processing. A recent study[xiii] evaluated the in-line precipitation of a monoclonal antibody using zinc chloride and polyethylene glycol (PEG) solutions. This was followed by washing of the precipitated antibody using tangential flow filtration (TFF) and re-solubilization to effect substantial purification (90% removal of HCP) and high yield (97%). Although performed at bench scale, this methodology shows promise for further development and scale up.

Biosimilars

The development and production of biosimilars has been moving steadily forward, with much greater progress in Europe and outside US. Techniques for process intensification are being applied to biosimilars as well, as seen by the first biosimilar produced by continuous processing receiving approval to begin clinical trials[xiv]. Drug developers and manufacturers have worked closely with regulatory authorities to produce the "highly similar" biologics intended as biosimilars. Thus, the principal hurdles are no longer scientific, technical or regulatory for most biosimilars. In the US, the main hurdles to market have been political and legal due to "patent walls" and litigation. For example, many biosimilars have received FDA approval in the past two years but are delayed in marketing due to delays negotiated with the companies who produce the reference or innovator drugs[xv].

Conclusion

The development and manufacturing of more efficient bioprocessing has been moving biopharmaceuticals rapidly toward industrialization. While recombinant proteins have had a substantial head start on new therapies such as cell and gene therapy, my expectation is for rapid growth and advancement in this area as well. Finally, biosimilars have reached a point where development and manufacturing are no longer the principal hurdles to market and adoption.

Additional Questions

1. In the years ahead, with over 800 IND for Cell & Gene therapy, do you foresee capacity shortages (i.e. not enough CDMOs to support the numbers of promising candidates coming through the pipeline)?

There is already a shortage of CDMO services for this type of work. The high valuations shown by recent acquisitions of CDMOs, such as Brammer Bio and Paragon Bioservices, bear this out. I expect the shortage to continue for the next few years until more development and manufacturing scientists are trained in this new discipline and CDMOs expand their offerings.

2. What do you think the manufacturing for Cell & Gene therapy market may look like in 3 years' time?

It will continue to be tight as demand is extraordinary.

3. In five years' time, do you think we will be in a place where biologics manufacturing, due to new technologies, will be substantially more cost effective than it is today?

Yes, as most of the advances from new technologies are more efficient and cost saving. Furthermore, economic pressure from biosimilars will push manufactures of these types of therapeutics towards lower costs.

4. What do you think are the manufacturing implications (caused by the large pipeline) of cell and gene therapies over the next 1-3 years?

I expect that there will be some realignment for manufacturing in the areas of cancer and rare-disease therapies in terms of a greater focus on cell and gene therapies for these indications, rather than recombinant protein therapeutics.

5. Do you think we'll see a notable rise in continuous processing for biosimilars in the next couple of years, and if so – Why?

I think the rise in continuous processing will be incremental and ongoing, rather than dramatic. There is such an established base of batch-based manufacturing that will temper wholesale movement towards continuous processing.

Economic pressure from biosimilars will push manufactures of these types of therapeutics towards lower costs

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CPhI insights

Part 4.

Contract services, new modalities and breakthroughs

informa markets

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Increase in Drug Approvals and Priority Review Shows the Future Is Bright for the CMO Industry

Introduction

New drug approvals are on the way up, as the FDA approved 11% more innovator therapies in 2018 compared to the previous year, spelling good news for both marketing authorization holders (MAHs) and CMOs. Data also show small and mid-cap pharma companies especially are increasingly turning to outsourcers to manufacture newly approved drugs.

In 2018 the FDA approved 137 NDAs and BLAs including New Molecular Entities (NMEs) and new formulations of older drugs, according to the GlobalData Drugs database. This figure represents an 11% increase over 2017 (122).

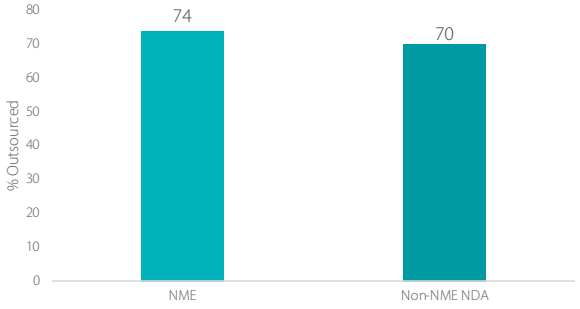
Overall, 57 NDAs were manufactured by contractors in 2018. In 2018, 51% of NMEs were outsourced, compared to 33% of non-NME NDA products.

The share of solid dose NMEs outsourced in 2018 stands at 52%, similar to the 2012–2017 average. However, outsourced injectable approvals slightly increased to 44%.

There were 22 dose CMOs that garnered contracts for NME products in 2018, with Catalent and Patheon (part of Thermo Fisher Scientific) topping the list with five and four contracts, respectively.

Mega cap bio/pharma companies received 17 approvals in 2018 (12% of all NDAs). The overall number of approved mega cap-sponsored NMEs remained fairly stable over the last decade, as did mega cap companies' propensity to outsource the manufacture of these drugs. NME outsourcing by small and mid-cap companies has markedly increased in 2018 compared with the 2013–2017 approvals average.

Outsourcing Propensity for Small Cap Pharma Companies, 2009–2018



Source: GlobalData Drugs by Manufacturer (Accessed July 19, 2019) © GlobalData

As shown in the figure above, small cap pharma companies outsourced dose manufacture for 74% of NMEs and 70% of non-NME NDAs, which highlights the high level of dependence of small pharma on dose CMOs. The rate of outsourcing for the more innovative NMEs is slightly higher than non-NME NDAs, which shows that small cap companies are less likely to have the expertise and/or technology to cope with manufacturing more innovative products. Out of the top four dose CMOs, Catalent was most dependent on private, mid, and small cap companies, whereas Patheon, Baxter, and Vetter manufactured most of their novel product approvals for large and mega cap companies in the past decade.

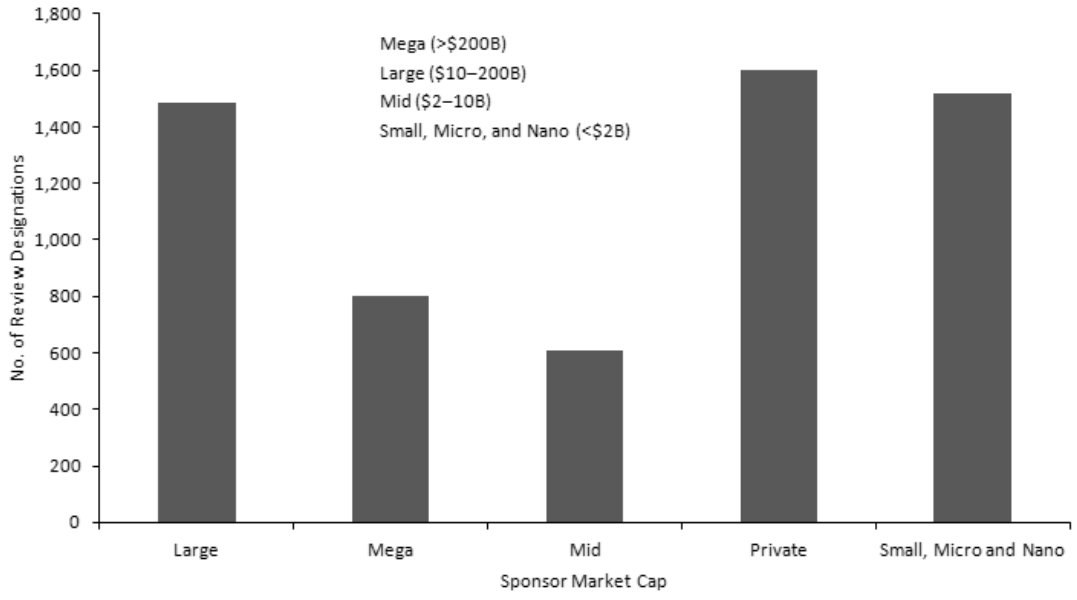
Priority Review and Other Accelerated Designations

NDA approvals were particularly high in 2018 for small cap pharma companies, which sponsored 43% of NDAs, according to the GlobalData PharmSource Trend Report CMO Scorecard: Outsourcing of NDA Approvals and CMO Performance – 2019 Edition (March 2019). As small biotech companies with limited budgets begin to dominate the industry, FDA special designations, especially Priority Review, can provide valuable revenue streams of up to $350M in cash to small and mid-sized biopharma firms. A Priority Review designation means the FDA's goal is to take action on an application within six months (compared to 10 months under standard review). A Priority Review designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.

The FDA is awarding increasing numbers of Priority Review vouchers, according to GlobalData's Regulatory Milestones Tracker database, which shows the number of Priority Reviews has risen by over 900% since 2012. Although this has decreased the sales price of Priority Review vouchers to an average of $80M in recent years, in the context of small biotech companies, $80M is no "small change", and Priority Review vouchers continue to be a very useful fundraising tool.

For these cash-strapped companies, the revenue from these designations' traditional benefits of extra regulatory help: regulatory-based incentives such as faster review and increased communication with the FDA are only useful if the company can afford to develop a drug.

Number of FDA Review Designations Awarded Between 1985 and H1 2019, by Sponsor Market Cap



Source: GlobalData Regulatory Milestones Tracker database (Accessed July 5, 2019) © GlobalData

In 2018, 34 Orphan-designated drug NMEs were approved, the highest between 2009 and 2018; this represented 53% of all NME approvals. Of these approvals, 65% were outsourced, the strongest outsourcing propensity for orphan NMEs since 2014. Mega cap companies sponsored five Orphan NMEs, and only one of these had commercial dose outsourced. However, this drug (Pifeltro) was dual sourced and therefore was also being manufactured in-house. Orphan disease development is one of the most lucrative therapeutics areas, with accelerated/flexible development timelines, additional exclusivity, tax breaks, and the possibility of premium pricing due to low competition.

Orphan disease development is one of the most lucrative therapeutics areas, with accelerated/flexible development timelines

There were 23 NMEs approved with Fast Track status in 2018, significantly more than the 18 in 2017. Of these products, 16 (70%) were outsourced, which is an increase over the five-year average (2013–2017) of 58%. Between 2016 and 2018 there has been an increase in the number of Fast Track drugs approved. The number of NMEs approved with Breakthrough Therapy Designation (BTD) in 2018 declined from 2017, with only 14 approvals recorded for 2018. However, outsourcing percentages of BTDs have never been so high since the program began in 2013 to expedite clinical development of drugs that demonstrate significant improvement against marketed therapies for the treatment of a serious or life-threatening condition.

There was considerable overlap between Orphan, Fast Track, and Breakthrough Designations, with numerous NMEs approved in 2018 receiving all three designations. The number of pipeline drugs being assigned these review designations overall has been increasing over the last decade. While these designations do not guarantee regulatory approval and will form part of the clinical trial attrition rate, this can be viewed as a further positive sign that the market approvals with these designations will continue to increase. GlobalData's Product Database contains a Likelihood of Approval tool that uses a model including drugs approved in the past 10 years, drugs that have failed during clinical development in the past 18 years, and drugs that are currently in development, to predict the Likelihood of Phase Transition and the Likelihood of Approval for drugs seeking US approval only.

Containment Substance Manufacture

Around 60% of high-potency APIs (HPAPI) developed are for oncology; containment facilities are in high demand and will be increasingly so in the future as the oncology drug development pipeline continues to grow. NME approvals that required manufacturing containment rose significantly from 2017 to 27 products in 2018, of which 32% were outsourced. The category was driven by the approval of no less than eight protein kinase inhibitors and six cytotoxic drugs during the year. In general, the number of high-potency drug approvals has increased over the last decade, which may be a positive sign for CMOs as small and mid-cap companies lack the expertise for regulatory compliance and high containment facilities, and seek to outsource NMEs requiring special handling. The increase in NMEs requiring containment has been driven by a rise in oncology kinase inhibitor drug approvals. CDMOs that provide contract HPAPI manufacturing services must be prepared to adopt, improve, and implement new protocols, equipment, training, and technologies to meet increasingly stringent risk reduction and regulatory compliance in HPAPI manufacturing.

Large CMOs have made significant recent investments in high-potency manufacturing, including Ajinomoto Bio-Pharma Services (B/POR, March 2019), Hovione (B/POR, March 2018), Lonza (B/POR, March 2019), and PCI Pharma Services (B/POR, November 2017). Controlled-substance manufacturing has seen similar interest, with investments by PCI Pharma Services (B/POR, March 2019); Noramco (B/POR, November 2018), which has also invested recently in controlled-substance manufacturing (B/POR, March 2019); Johnson Matthey (B/POR, October 2018); and Catalent (B/POR, June 2018).

Catalent also completed the second phase of a $5.5M expansion at its Kansas City, Missouri, US, clinical supplies facility. The CDMO has increased its controlled-substance and controlled-temperature storage capacity at the site. The first phase boosted its highly potent, cytotoxic, and cold storage clinical packaging capabilities; this latest expansion, completed in May 2018, includes a 3,600 square foot Drug Enforcement Administration (DEA) Schedule I and II controlled-substance vault, 450 controlled-temperature pallet locations, 500 high-density storage locations, and a new sampling room.

Priority review therapies and other accelerated drugs are more likely to be contract manufactured than products that go through standard review

Priority review therapies and other accelerated drugs are more likely to be contract manufactured than products that go through standard review. Historically, dose manufacture for 70% of accelerated drugs has been outsourced versus an average of 45% for all drugs. Both small and mid-cap companies are more likely to outsource their dose manufacture than large and mega cap companies due to a lack of in-house manufacturing capabilities and/or expertise. Therefore the rising number of priority review designations and small cap companies gaining FDA approvals can only be a positive sign for dose CMOs. High containment substance equipment and facilities are prohibitively expensive and require a high level of expertise, and with increasingly stringent regulations as well, these forms of manufacture are also more likely to be outsourced. Overall there are great opportunities for innovative CMOs that are able to adapt to manufacture increasingly complex drugs and produce drugs within shorter timelines required by certain increasingly used regulatory designations.

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Patient Centricity: The New Nexus For CDMOs

A Patient-centric journey through the pharma supply chain

In the last decade we have a seen a progressive trend across the pharmaceutical industry, with big block-buster drugs gradually becoming less prevalent and a shift towards smaller volume therapies, often for niche patient cohorts. This trend has primarily been driven by the fact that much of the easier, less complex drugs have already been made, with research now looking at more complex compounds and orphan designations. But whilst this change has been necessitated by the discovery pipeline, it has also brought about a new age of more targeted therapies, and in some cases, even personalized approaches and this has profound supply chain implications[i]. The net result of these changes is that the patient is becoming much more central to development as therapies target smaller patient cohorts[ii].

Running parallel to this development, we have seen the patient experience in clinical trials become an important consideration, with adaptive trials and patient engagement and retention tools becoming increasingly common[iii]. Originally this had the vision of ensuring compliance and robust data in trial design, but the industry has shifted quickly up the value chain so that patient, healthcare provider and sponsor can have access to vital information through a mixture of patient selected devices, and eCOA tools[iv].

Accelerating this development was the enactment of 21st Century Cures Act – which has placed an acute emphasis on patient centric development, personalized medicine and increasing utility of real-world evidence. Understandably, patient-centricity has also gained considerable traction in adherence for commercial products and we have seen great strides made by both packaging and delivery device manufacturers. The patient here is rightly now viewed as the direct customer innovator companies are designing products for, and therefore, the user-experience in real-world settings is equally as important as traditional therapeutic efficacy – any therapy is fundamentally only as good as its correct and timely use by patients.

A third key development that has brought the industry to the nexus of a new age is the tremendous desire now coming from patients for greater knowledge about their own care, access to their own data, and transparency in the therapies they receive. The engaged patient is taking back control of their own treatments and using

a combination of apps, remote healthcare access and the internet of connected things (IoT) to better manage their conditions – from simple tools for calorie counting through to complex devices that monitor dose, response and lifestyle factors.

But the future of this concept is transferring it through all parts of the pharmaceutical supply chain and the industry must move beyond working in silos – it's also why Piramal has moved ahead of the curve to become a patient-centric CDMO. But before exploring the implications of this shifting approach, we should take a step back to consider what it means to be patient centric.

A recent study published by Astra Zeneca yielded a collaborative definition of patient centricity as "putting the patient first in an open and sustained engagement of the patient to respectfully and compassionately achieve the best experience and outcome for that person and their family"[v]. This definition does not solely come from industry, but was driven by direct consent from the end-users themselves – the patients. It is important to note this distinction: in order to be truly patient-centric in thought and deed, one must hear *directly* from the patient.

So with this definition in mind, we explore the potential impact on the CDMOs that support the industry's efforts by efficiently helping discover, develop, manufacture and test new or improved drugs. Every dose decision taken in development, choice of delivery vehicle, administration instructions and packaging all have a direct impact on the patient.

Patients represent the ultimate beneficiaries of these services, and we must place their needs at the heart of the conversation. Understanding their needs – and building an organization that is dedicated to addressing them – is the core of patient centricity. This concept holds true regardless of whether the organization is a pharmaceutical company, biotech, healthcare service provider, digital patient engagement specialist, CRO or even a contract development partner.

For CDMOs like Piramal, this means a new mindset and culture for the organization defined by a fundamental objective of reducing the burden of disease, and how we approach developing and commercial drug substance and product. At every level, the internal staff must transform their identity, shifting from self-identifying as a manufacturing company to thinking and acting like a service company. Of course, the company will still produce products, and it must remain driven to deliver for its customers. But the emphasis shifts from what those products are in and of themselves, to what the products can do for patients. Only by adapting this sentiment as an ethos can an organization become truly patient centric.

At a practical level this means we need to deliver new engagement schemes throughout the workforce so that employees understand the importance of what they do, and how their efforts have a real-world impact on patients. So for example, at the project initiation stage, teams should be briefed on the therapy area, patient population and the impact of the drug. Then to empower employees to meet the people the product will help, patients are brought in through customers to share their journey about how the drug has helped them.

One key initiative that we have pioneered at Piramal to deliver this type of true patient centricity is the creation of Patient Awareness Councils across global sites. These new bodies comprise cross-functional executives and employees, and they act as the patients' advocates and ambassadors for patient centricity through development and commercialization. Their role is exploring in detail the impact of manufacturing choices, development criteria and approaches have on the patient. Moving into the future, they will have an extremely important role to play in every project, and are tasked with creating, managing and monitoring the best practices for applying patient centricity to the entire organization. Ultimately, the goal is to drive patient centricity from the bench to the plant.

This concept is extended to after visits and increasingly we will see 'patient profiles' being brought into the CDMO space – which are essentially daily maps of the patient's experience to better inform the drug development process. It's a key part of the team's discussions with patients, as we want to get a closer picture of the patient. At present, these types of initiatives only run in commercial drugs, but it won't be too far in the future to see this type scheme delineated into early phases of development. Moving forwards, this will also mean creating new guidance – developed with advocacy groups, ethics & compliance, as well as legal – for

employees on how to interact with patient groups. The challenge is to accept that this approach takes time, because it is a change in culture and in the 'way we work' running through the business even into the manufacturing teams.

In other parts of the industry we have seen Patient Advocacy Training groups created – e.g. Sanford Research Institute introduced the Patient Advocacy Certificate Training [PACT] course – and our hope is that the industry will embrace these to ensure it has the right culture and philosophy to achieve true patient centricity[vi].

The definition of patient centricity, as defined by the aforementioned Astra Zeneca study, requires pharma to 'put the patient into your working standards'. So for Piramal, this means ensuring that the patient first approach also extends into how we as an industry react to helping patients get access to the therapies they need.

As an example, a customer recently approached us to manufacture a drug for an orphan indication that affects just 3 patients per 100,000 births. Therefore, the volume requirement was very low, and it did not make commercial sense for the (Lexington) site to manufacture the injectable drug. The treatment was targeted towards a pediatric population, with a genetic disease that greatly shortened life expectancy. There was no other treatment available on the market for this disease, but in our endeavor to make this treatment available for pediatric patients, we agreed to partner with the customer to manufacture and supply clinical batches of this injectable drug and went on to support commercialization of the drug. In the future, we will see more examples of this, as CDMOs back up their patient centric credentials with a commitment to doing the right thing by patients, even in cases of little or low profit. Similarly, putting in place patient centric cultures within the workforce at CDMOs. So for example, when the FDA recently approached our customers to increase production of a generic injectable drug used in the treatment of a variety of cancers – due to issues with another manufacturer – we immediately stepped up production. Adapting the site for higher volumes, the team worked additional shifts to accommodate the extra batches that were required to fill the gap. So, patient centricity is not just about tangible factors, but also recognizing that the responsibilities we have extend beyond the delivery of pharmaceuticals, and we have a duty to adapt to the wider conditions facing our patients.

Drug Discovery

Another area that, even just a few years ago would have seemed unlikely, is the growth of patient and charity organizations directly funding discovery programs of biotechs and early stage researchers. Understandably, these groups have an acute focus on patient centricity, and in the future, they may take a more active role in the supervision of outsourcing with the goal of delivering the greatest cost benefits and, more importantly, partners that offer the Investigational New Drug the best possible chance of success.

Transparency

Running parallel to the patient centric approach we are taking, there is the trend globally of the 'informed patient' – people want far greater depth of information than before, and not just on clinical trials data and side effects, but also running into the manufacturer's reputation for quality. What started as a trend out of the internet that was breaking-down the traditional silos of medical information has now shifted to a focus of life cycle impact of medicines. This trend has been accentuated by many of the FDA infringements seen in the last few years, and a growing awareness of the role that outsourcing plays in the patient supply chain. Whilst scandals like adulterated heparin undoubtedly cast a long shadow on the industry, the move towards full patient transparency in the supply chain is shining a new light on good manufacturing practice (excuse the pun). In the future, it may become

greatly more common for license holders to share and celebrate the manufacturing records of CDMO partners. An early example of this type of trend can be seen with the recent serialisation initiatives in both Europe and the United States. These are already delivering much greater trust, and it is translating through to the patient as there is greater visibility on every drug's journey - it can be tracked moving between manufacturer, distribution channel and all the way to pharmacy[vii].

What the patient will want to see is the best possible regulatory standards are adhered to, but also, that their therapies are made with partners that look to go beyond these standards using approaches that included PAT, QbD and continuous processing. Undoubtedly, the future will see patients taking an increasingly active interest in exactly how, when and where their vital therapies are discovered, developed and manufactured.

Environmental footprint

We are not there just yet, but the next natural evolution of this trend will be for the patient to be assured that not only are their therapies safe and effective, but they have also been made with minimal environmental impact in mind, from reducing the number of process steps and hazardous chemicals to the safe disposal of waste products. It does not take one to look too far into the future for us to envisage the use of some kind of environmental certification to be placed upon CDMOs that could translate through to patient packaging. Certainly, in devices and packaging, the industry is already heavily advanced on its journey towards extrapolating not only its immediate environmental challenges, but the full life-cycle impact[viii].

Conclusion

The implications for pharma of patient centricity have been well documented but what is under appreciated is the new significance it will bring to bear on the CDMO sector – especially with the new types of drugs coming through the pipeline. So rather than being fundamentally a b2b facing proposition, increasingly, contract service providers will view the patient as the end consumer – and never 'just someone we simply sell to'. This will be a relationship built upon mutual understanding and partnership. The pharmaceutical supply chain is increasingly opening-up and the patient must be placed at the center of industry efforts. Increased transparency and a new age of dialogue between manufacturers will increase trust, help us achieve better efficacy rates and, most importantly, develop better medicines for the patients we serve globally. Questions no one thinks to ask today (e.g. 'how are my drugs manufactured', 'what is the supply chain process' and even 'its environmental footprint') will be key parts of the supply chain and patient engagement package in just a few years' time. At Piramal, we are striving to be a key driver of this transformation and we are working with forward looking pharma partners and patients about how we can together begin delivering a better kind of healthcare. This is the future we envisage, one in which, above all else, we recognize the responsibility we bear should be solely to patients. We are at the nexus of a new age, whereby patient centricity will become the integral philosophy around which we design all services even technical approaches – from implementing dosage form and delivery, packaging and logistics right through to meeting regulatory standards and good manufacturing practice.

Patient Centricity to the Core at Piramal

As a global organization with sites in Europe, North America, India and China, it's vital for PPS to instill a patient centric ethos that transcends cultural boundaries with the fundamental objective of reducing the burden of disease. At every level of our organization, we put patients first.

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Newer drugs will require a new way of manufacturing centered on the patient; the 'patient centric CDMO' is the future

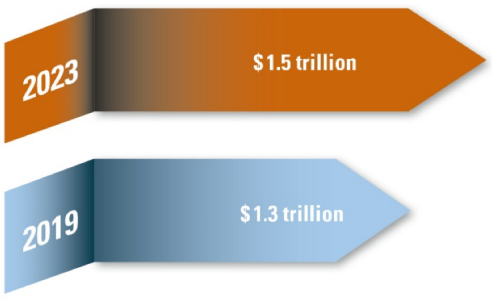
Introduction

When road conditions change, it is time to check your roadmap. Today, our global healthcare landscape is undergoing such a change. Ever-more complex drugs, new therapeutic approaches and technologies, pricing issues, and differing trade strategies in an industry with integrated global supply chains are but a few of the changes placing revised demands on all players in the healthcare industry, including solution providers. It is time to take a new look at the roadmap. In addition to delivering high-quality products and services, flexibility and an open mindset are decisive attributes necessary for reaching destinations successfully.

A changing industry with stable growth

We are in the midst of a growth phase in global healthcare. Recent data show that spending on new medicines is projected to reach approximately $1.3 trillion in 2019. By 2023, that number is projected to exceed $1.5 trillion[1]. Global pharmaceutical and biotechnology markets, in particular, also reflect a strong future potential with 3-6% annual growth projections continuing until 2023[1]. While those figures reflect a positive trend for the industry as a whole, they are first and foremost indicative of the impact on the future of medicine and the patients who will benefit from new products and innovations.

Global Spending on Medicine



The US pharmaceutical market is expected to remain the key future growth driver, outpacing the global market itself. However, while the US leads in the sale of injectable products, China is a key parenteral drug market from a volume perspective. But drug pricing is an important leaver effecting markets and sales volumes that will continue to play a key role in industry growth, regardless of geography. This is of particular importance when we consider that within the next five years net drug prices are likely to increase in the USA by only 0-3%[1].

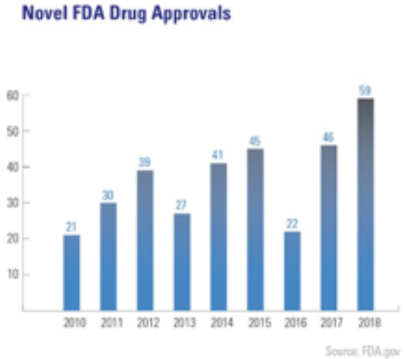
However, new biologics entering the market often have tremendously high prices, which are obviously incurred by the user of the medicine or health insurance funds. So what we are now seeing is that these medications, more than ever before, have to offer robust proof that they are able to deliver significantly improved outcomes. Thus, optimizing the cost of development and manufacturing will be a key comment in remaining competitive, and the industry will have to show genuine innovation.

As a result, we anticipate that there will be a continuing diversification of innovators, with greater numbers of emerging biotech companies launching new medicines in the years to come. This is based on shifts in their business strategy, striving to maximize financial returns to investors. And, it is supported by the fact that they are well-funded with venture capital in today's time of low interest rates. Similarly, their big pharma counterparts often now prefer to partner with emerging biopharma companies or encourage incentive-based agreements rather than outright acquisitions. For big pharma, the mitigation of risk while maintaining tighter control over operating costs and margins is paramount.

Nevertheless, numerous merger & acquisition activities within the industry will certainly continue, primarily driven by larger companies seeking to strengthen and expand their own product offerings.

New therapeutic approaches and drug substances will be a key to success

Given the growth in the global healthcare market, it is no wonder that this has led to an increase in the number of new drug approvals as well. In 2018, the US Food and Drug Administration (FDA) approved 59 new drugs, surpassing the exceptional levels of even the previous years - of these, 40% were for injectable drugs[2]. In fact, as of 2004, the FDA had already approved more than 200 injectable drugs. From a scientific novelty perspective, 2018 saw the premiere of three new substance classes or targets among injectable approvals – the first small interfering RNA (siRNA) drug[3], the first G protein-coupled receptor-targeted (GPRC) monoclonal antibody[4], and the first monoclonal antibody for the treatment of HIV-1 infection[3].



While seeing this positive news for new drug approvals, particularly injectables, it needs to be stated that a significant change is taking place within the industry: the market size for many drug products is getting smaller. Today, ever-more targeted medicines are being developed that are designed for smaller patient cohorts. Thanks to newer, more precise diagnostic tools, scientists are creating new research approaches that allow the physician to select a therapy or treatment protocol based on a patient's specific physiological profile. This pathway can not only help minimize harmful side effects and make more successful outcomes possible, but also, it minimizes the required amount of drug to be administered within the medication plan. But critical to this process is to start the development approach for these new types of drugs in a highly targeted, patient-centric manner. Compared to the past, it is far more important to understand a patient's medical journey and treat it in a holistic manner. The downside is that targeted medicines manufactured in smaller amounts will raise important questions for healthcare stakeholders regarding cost and accessibility. From a pharma or biotech company's perspective, the development costs

for this kind of medicine are often similar, however, the potential patient group is smaller, consequently increasing the price per patient.

A look at new treatment options reveals that breakthrough therapies for medical needs are quickly on the rise. Looking at the injectable market, in particular, nearly 40% of breakthrough therapies are monoclonal antibodies (mAbs), most of which are used to treat cancer and orphan diseases. Presently, the oncology pipeline includes approximately 750 drug candidates in late-stage clinical development, with approximately 70-90 oncology products to be potentially launched within the next half decade. By contrast, approximately 60 oncology drugs were launched in the preceding five years[1].

Beyond oncology, diseases such as diabetes and other chronic ailments will continue to increase, which is creating expanding requirements on secondary packing services of drug products - such as, to take just one example, the assembly of self-injection devices. There are even signs that new drugs could emerge for a range of other diseases with large unmet needs, including Alzheimers. Other notable areas include first-time treatments for diseases like nonalcoholic steatohepatitis (NASH), neuromuscular disorders, and targets for cell and gene therapies[1].

Given this scenario, it can be expected that the pursuit and adoption of approaches to allow for personalized medicine will continue to play a major role in the pharma and biotech industry, and will affect all relevant players – from discovery and development to the commercialization stage.

Make way for digitalization, data and intelligence

The business of data and intelligence is a topic receiving a great deal of attention and one that will continue to evolve, primarily due to new approaches in the area of digital health. As with other industries, the role of big data and artificial intelligence in healthcare is increasing. They provide the tremendous therapeutic opportunities to capitalize on a patient's own datasets and provide insight across entire populations. The full impact of these changes is yet to be harnessed, but this is also why we can expect specialist companies from across the information technology space continue to apply their approaches in healthcare - often in partnership with established healthcare companies or as part of other healthcare applications. Again, this provides initial market access whilst mitigating risk.

Many companies around the world are engaged in developing innovative solutions in the area of digital health, including the application of ever more patient friendly technologies. For example, the evolution of connected smart devices will offer additional possibilities for the exchange of data. Meanwhile, a growing number of mobile apps are being submitted to the FDA for clearance and approval. Essentially, these apps are a 'prescription digital therapeutic', representing an entirely new and emerging way of patient treatment. These are technologies greatly contributing to an enhanced patient monitoring, compliance and adherence, and the long-term effects could be even greater than we yet realize.

Combined, these new approaches may also contribute in a very positive way to the discovery and development of medicines, providing new insights.

Various effects on the business of a CDMO

For Contract Development and Manufacturing Organizations (CDMO) these changes mean they must innovate alongside customers, and be able to deliver for both large and small pharma and biotech companies.

The demand for specialized services in those areas is supposed to continue to grow, which will have particular ramifications for the supplier side. In addition, a record level of funding was raised in 2017/18 by emerging biotech companies and, as a result, they are amply endowed with the necessary funding for their pipelines. Part of their development spending is funneled through different

service providers. Based on these facts, CDMO's today continue to benefit from a strong market environment[5].

As noted, overall drug products are becoming ever-more complex to develop and manufacture. That is why companies often outsource these drugs to specialized service providers in order to access external expertise, technical and process know-how. CDMOs are focused on being solution providers, therefore the relationships in most cases are strategically-focused rather than tactically-focused. This includes the central benefit of sharing expertise in both directions. Customers often have in mind the total cost of ownership calculation. And they look for long-term partners to fulfill their manufacturing needs with skills that involve speed, flexibility, the usage of innovative approaches, and a high level of expertise for complex compounds. With the globalization of the pharmaceutical business and the resulting complex supply chains, pharma and biotech companies have come to rely on expert partners that are able to deal with this multidimensional level of complexity. Decisive success factors therefore include a global reach and network, specialist departments and state-of-the-art equipment and processes.

Regardless, whether customers ask for a fully integrated service or for individual development, manufacturing or packaging services, it is essential that solution providers remain at the ready to take on new, sometimes challenging tasks quickly and have the expertise to offer added value in order to deliver an integrated approach to pharmaceutical development. Next to the high quality of deliverables it is this specialist expertise which can add value to both the project and the whole drug product. This approach is oftentimes helpful for sponsor companies in order to shorten their lead times while maintaining successful results. Sponsors look for partners with the ability to improve efficiency and provide consultation that enables complex drugs to reach the market quickly and reliably, rather than provide a type of standardized service.

Also, partnering with companies offering complementary expertise will likely offer a promising contribution to support modern drug development and manufacturing. This can mean working in teams comprised from various companies that are able to address todays and future complex market requirements.

Additional Questions

Q: Increased use of personalized medicines means increasingly personalized dosing and packaging – how will Pharma and the CDMO sector need to adapt to this, and how will contract providers help reduce the costs per patient?

A: This will in fact create a significant change, compared to today's market. Drug product manufacturers along with their associated suppliers of machines and consumables will have to respond to more specialized, lower volume manufacturing with more automated systems designed to reduce API losses. We also see packaging suppliers creating new drug-delivery systems designed to meet new specialized treatments. These systems consider small manufacturing batch sizes, larger injection volumes, as well as longer applications such as new "on body injectors" systems.

For the "real" personalized medicine per patient, where each therapy is tailored specifically to an individual's own genetic profile, new logistics and manufacturing systems will be required. Such systems will have to allow for the creation of API in small scale and possibly, be directly integrated at the filling site. However, we believe that for the main disease indications, today's existing types of therapies will remain standard procedure. For many diseases individualized personalized medicine is still someway off from becoming clinical routine.

Personalized medicine as a concept is an approach to avoid unwanted costs for the healthcare system and insurance payers by not prescribing expensive medicines for "non-responders". However, since each unit has to be individually produced, there is very little manufacturers can do to prevent the rising costs of manufacturing. Drug owners will need to realize profit margins on smaller unit sales, that are driving up costs per unit for individually affected patients. Digitalization and Artificial Intelligence (AI) innovations may help manufacturers and their partners enhancing overall productivity and improve cost effectiveness in the future.

In summary

An evolving and thus changing landscape in the healthcare sector has led to the need for all players in the industry to rethink how they will navigate for success. It can be expected that customers will ask for increasing support from their partners than ever before. These collaborations span broad support in the complex drug development and manufacturing process combined with reliability during technical transfers, as well as improvements along the lifecycle of their complex drug products. No doubt, what will make for a successful CDMO other than the important aspects of quality, experience and a fitting service portfolio, is having a customer and patient-centered attitude at the core of its daily activities.

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