Prospects, Analysis and Trends in Global Pharma

Industry Expert Panel Submissions

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

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Part 1.

Quality and regulation
Adherence to the Current Good Manufacturing Practice (CGMP) Regulations in the 21st Century

Introduction

At the beginning of the 21st-century, the US FDA launched initiatives to contribute in several ways to improve efficiency and reliability of pharmaceutical operations, and then via ICH these efforts were extended internationally. Operational challenges continue to be visible in external failures such as drug shortages, recalls, Warning Letters and Import Alerts; and the FDA has recently taken additional steps to achieve the goals it had outlined in the 21st Century initiative. Over the past couple of years, a growing cluster of deviations - breaches in the assurance of data integrity - have gained prominence, in part due to improved detectability, and this has led to an erosion of trust.

Why is compliance with the Good practices such as a significant challenge? Reflecting on insights accumulated over the past two decades, from when at US FDA to currently in the private sector, suggest that we – as a community of professional practitioners - are not adequately accounting for certain human behaviors in our business and regulatory practices. This article seeks to improve awareness of this urgent and pressing need, and it invites a discussion on ways to improve human-centricity in the pharmaceutical industry’s operational practices. Additionally, progress and trends in Process Analytical Technology (PAT) and in the adoption of pharmaceutical Quality by Design (QbD) methodology, that are part of the solution, are discussed.

Human factors need to be more closely considered in designing manufacturing processes – using behavioural economics will help improve practices Industry is often trapped in a “file first, figure it out later mindset” and simply try's meet standards not improve quality.
Compliance or Adherence to CGMP Regulations: Choices of words matters

The words we use influence the way we think, organize information, make decisions and the way we behave. Consider two commonly used words in our vocabulary - compliance and adherence. In pharmaceutical operations, compliance is used to describe the behavior of following written instructions or operational routines (SOPs). In healthcare, the noun adherence is preferred to describe the behavior of following written instructions for taking medications (prescriptions). In the CGMP context would you consider compliance and adherence to be synonymous?

On the US-FDA website, it is stated that Adherence to the CGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications to adequately control manufacturing operations9. In this context is adherence synonyms with compliance? Alternatively, is it a subtle reminder of an important principle?

Note: The noun adherence is related to the verb adhere, meaning "to stick"; faithful support for a cause. Compliance is what you do when you try to fit standards set down by someone else. The act of submitting; usually surrendering power to another.

In healthcare, the noun adherence is preferred because compliance suggests that the patient is passively following the doctor’s orders and that the treatment plan is not based on a therapeutic alliance or contract established between the patient and the physician10. Adherence to medications is squarely in patients’ self-interest.

The rate of adherence to prescriptions, particularly in chronic conditions, are dismal10. Changing this behavior is incredibly difficult; as if humans have an innate immunity to change11:

“…. when doctors tell heart patients they will die if they don’t change their habits, only one in seven will be able to follow through successful…Our individual beliefs – along with the collective mindsets in our organizations – combine to create a natural but powerful immunity to change.”

Robert Kegan and Lisa Lahey11

So, should it surprise us that deviations from established pharmaceutical operating routines (SOPS) are widespread (12) and such a significant challenge?

So why did the FDA write-up on CGMP9 use the word adherence? It is to emphasize that adherence to CGMP regulations provide ample flexibility to design and implement policies and procedures. Such systems are required to assure the identity, strength, quality, and purity of drug products in any facility and should account for, among other things, specific human factors therein.

It is the responsibility of management and leaders of a company to design and implement processes and procedures that are easy to comply with and, yes, joyful. Unfortunately, in some companies, Quality Management System (QMS) is just a folder of policies and procedures; often put together using a ‘cut-paste’ approach; i.e., without design or system thinking. Such disregard can eventually trigger a regulatory demand for CGMP remediation; sometimes with the help of external CGMP experts (“Doctors”-remember compliance suggests that the patient is passively following the doctor’s orders10. Are we not underestimating human immunity to change11?

Broader adoption of PAT-based continuous manufacturing system by brand and by a couple of major generic and CDMO’s should be more prominently evident in the next three years.
Reasons for medication non-adherence?

A considerable amount of research has been conducted to identify correlates and predictors of adherence and nonadherence. It would be useful to summarize what we have learned and consider its relevance to non-compliance with SOPs in pharmaceutical operations. The table below lists five interacting dimensions of non-adherence and draws a parallel to factors relevant to the failure to comply with SOPs. Clearly, the list of factors (Table, below) is not comprehensive; it is only to highlight some similarities between the two challenges.

Patient-Focused Manufacturing, Quality, and Regulatory Solutions

The FDA initiative on Pharmaceutical Quality for the 21st Century aimed, in part, to reduce the reactive aspects of regulatory compliance ingrained within the system. Although there is some progress – many challenges remain. Early in 2016, the FDA’s new Office of Pharmaceutical Quality was stood-up, and it is expected to achieve, more comprehensively, the goals outlined in the FDA’s 21st Century Initiative. The FDA has noted some challenges that have continued:

1. Product recall and defect reporting data demonstrate unacceptably high occurrences of problems attributed to inherent defects in product and process design
2. Alarming shortages of critical drugs over the past few years
3. Rapidly growing numbers of Post-Approval Supplements; which inhibit industry’s ability to optimize and improve
4. Current regulatory review and inspection practices continue to be “one size fits all”; i.e., not considering specific risks to the consumer from product failure modes
5. There are no formal benchmarks for the current state of pharmaceutical quality; inadequate quality surveillance adds to the challenges that make it difficult to make decisions on risk
6. Inspection and Review functions remain disjointed; inspections not well-connected to knowledge gained from product application review and vice versa.

In the Federal Register Notices dated March 12, 2015, the US FDA announced its participation in a conference entitled “Mission Possible: Patient-Focused Manufacturing, Quality, and Regulatory Solutions.” It should be obvious that patient-focused manufacturing, quality, and regulatory solutions demand an adequate emphasis on staff/operator-centric quality management system, policies, and procedures. Are we adequately emphasizing staff/operator-centric quality management system, policies, and procedures? Not adequately.

A case in point is our casual attitude towards the regulation 21 CFR 211.25...education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Shouldn’t staff and their supervisors reliably comply with written SOPs when provided with appropriate education, training, and experience? Given that, pharmaceutical processes are required to be “validated”; complying with SOPs should yield predictable outcomes. How often does it occur? 70-90% of the time? That is not often enough!
Table. Five interacting dimensions of non-adherence (13) and some parallels to factors relevant to CGMP non-compliance.

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Factors (Adherence)</th>
<th>Factors (SOP Compliance)</th>
<th>Dimension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health-care System &amp;</td>
<td>Lack of awareness and knowledge about adherence</td>
<td>Lack of awareness and understanding about reasons for, and rate of, SOP non-compliance</td>
<td>Quality Management System &amp; Management Factors</td>
</tr>
<tr>
<td>Team Factors</td>
<td>Suboptimal communication between patients and health professionals</td>
<td>Suboptimal communication between staff and management</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lack of clinical tools to assist health professionals in evaluating and intervening</td>
<td>Lack of process analytic tools (e.g., optimal control chars) to identify, understand,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>in adherence problems</td>
<td>correct and prevent SOP non-compliance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Knowledge of health literacy issues</td>
<td>Knowledge of why CGMP is relevant and why SOPs are difficult to comply with</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lack of behavioral tools to help patients develop adaptive health behaviors or to</td>
<td>Lack of behavioral tools to help staff develop adaptive CGMP behaviors or to change</td>
<td></td>
</tr>
<tr>
<td></td>
<td>change maladaptive ones</td>
<td>maladaptive one</td>
<td></td>
</tr>
<tr>
<td>Patient-Related Factors</td>
<td>Lack of information and skills as they pertain to self-management</td>
<td>Lack of knowledge and skills as they relate to self-management</td>
<td>Staff related factors</td>
</tr>
<tr>
<td></td>
<td>Difficulty with motivation and self-efficacy</td>
<td>Difficulty with motivation and self-improvement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lack of support for behavioral changes</td>
<td>Lack of support for behavioral changes</td>
<td></td>
</tr>
<tr>
<td>Therapy &amp; Condition</td>
<td>Dose frequency and the incidence of side-effects</td>
<td>Workload pressures and rates of facility management neglect (e.g., planning)</td>
<td>Plant &amp; Process Related Factors</td>
</tr>
<tr>
<td>Related Factors</td>
<td>Disease-specific demands, symptoms, and impairments</td>
<td>Process complexity, instability, and inadequate education training &amp; experience</td>
<td></td>
</tr>
<tr>
<td>Social and Economic</td>
<td>Poverty</td>
<td>Remuneration is consistent with responsibilities. Fear of job loss</td>
<td>Social &amp; Economic Factors</td>
</tr>
<tr>
<td>Factors</td>
<td>Access to health care</td>
<td>Access to top management</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Illiteracy</td>
<td>Education, Training &amp; Experience</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cultural beliefs about illness and treatment</td>
<td>Cultural norms and beliefs about pharmaceutical quality &amp; CGMP</td>
<td></td>
</tr>
</tbody>
</table>

When a manufacturing process is not predictable; human error is (almost often) the immediate “cause” and which requires no further thought (what is the root-cause?). Sufficient correction then generally is to: retrain or to modify a SOP and retrain.

When this occurs repeatedly - either an operator loses his/her job, or it can open the door to individual and/or systematic set of irrational behaviors, and sometimes this leads to breaches in the assurance of data integrity.
Confronting our Immunity to Change

The immunity to change was described by the following three dimensions:

1. Change-prevention system
2. Feeling system
3. Knowing system

Employee empowerment is in need of attention (Feeling system). It begins with senior leaders making adherence to CGMP regulations and compliance with SOPs the Normal thing to do, Easy thing to do and also Rewarding (See Figure below). Junior employees are looking towards the leaders to guide and support them.

Employee empowerment is in need of attention (Feeling system). It begins with senior leaders making adherence to CGMP regulations and compliance with SOPs the Normal thing to do, Easy thing to do and also Rewarding (See Figure below). Junior employees are looking towards the leaders to guide and support them.

Good practices include management actions to provide support, resources, asking questions to ensure optimal design and effective implementation of SOP’s which should be designed conjoint with targeted training. Given a set of starting conditions (e.g., raw material COA, and equipment), a complicated process should be reproducible, and deliver results expected (we are in Operations not in Research mode). Processes that do not – are complex.

Interactions and emergence characterize a complex process. Following a SOP will not reproducibly achieve expected results. Right-first-time (RFT) rates for pharmaceutical processes can be small (i.e., suggesting process complexity).

A failure rate of 5% should not be considered small – because in certain environments (e.g., a weak culture of quality) batch failure can have a devastating impact on behavior. Management which does not openly acknowledge the need for high RFT rate (during development) is perhaps trapped in “file first and figure it our later” mindset. Then when they do not recognize the actual RFT (whatever it might be) during routine operations (the change-preventing system), it can lead to rationalization within an organization. Phrases such as “this is FDA approved” or “process is validated” when heard in company discussions should raise a red flag!

The knowing system (epistemology; how do you know what you know?) is critical. It calls for leaders to ask the right question at the right time. Traditional regulatory defaults such as a scale-up factor of 10X, three batches for...
Process qualification, can be an easy reminder to ask the right questions; how do you know that 10X is the optimal option for a particular product/process? The knowing system should cover the entire life cycle – from proper development and regulatory review to effective process validation, technology, and knowledge transfer and continued process verification. The knowing system should include a special reminder to improve awareness of how adherence to CGMP and compliance with SOPS addresses residual-uncertainty.

Getting it Right-First-Time in the 21st Century

The FDA “getting-it-right” is critical; in particular with its emphasis on One Quality Voice. Commitment to achieve the goals of the 21st Century initiatives requires concerted efforts in multiple dimensions – on the stubborn immunity to change (as discussed above), our methodologies and our technologies. Progress in these three dimensions is palpable.

Integrating Generic CMC review within OPQ/CDER/FDA is already changing the questions to sponsors; questions on patient-related-failure modes and manufacturability are now more prominent and a surprise for some companies. Issues now being raised by FDA during CMC review - on product failure modes and manufacturability - is a signal that the methodology for Quality by Design should be a more serious focus during development and, perhaps, a strong message against the practice of “file first and figure it out later”. If this trend continues (and regulator heterogeneity sufficiently minimized), it can offer a significant competitive advantage for those companies that have advanced their business practices to implement QbD methodology (e.g., as per FDA PAT, ICH Q8-11, and Process Validation 2011 Guidelines) efficiently in their development program. The business impact should be most significant for new drugs categorized as a Breakthrough (where product development and CMC review can often be on a critical path; time crunch), Complex Generics, and First Generics.

The FDAs strong support for application of new technology in pharmaceutical manufacturing – particularly as it pertains to the continuous production of pharmaceutical is broadly evident. The Summary Review of Regulatory Action on Vertex’s NDA 20603814 provides a hint as to why marking this approval in 2015 the ”Tipping point” would not be an exaggeration.

“Quality-by-Design (QBD) process for the development of the product, manufacturing process, and control strategy. A fully continuous drug product manufacturing process was applied to the manufacture of the product, which is a unique and a new process”

A new manufacturing process included in an NDA submission is a pleasant surprise, indeed! Moreover, it also provided for a rapid QbD development of product, manufacturing process and control strategy! These two aspects, taken together, justify the label – Tipping point. The ability to manufacture continuously (24/7) is important but which, I suggest, is a business decision.

The NDA 206038 implicitly provides reassurance that PAT based manufacturing and control strategy can address several ontological and epistemological gaps that exist today (in FDA’s Inactive Ingredient Guide, USP and broadly). PAT provides a way to measure, monitor and control physical quality attributes such as excipient functionality, and, offers efficient solutions for many frustrating issues such as blend uniformity testing.

Vision 2020 appears to be on track; significant business opportunity is within grasp in the next 3+ years. This includes technical capabilities to get pharmaceutical manufacturing right the first time. Perhaps, the growing number of cases of breaches in data integrity help here by reminding us that we are prone to our cognitive biases and blind spots; more so because we can not dismiss the possibility that the growing number of cases may just be due to improved detectability. This realization should prod us to overcome immunity to change, pay more attention to human factors and to do so look for practical solutions in disciplines such as behavioral economics to improve our practices.
The lure of the rapid, comprehensive QbD development of solid dosage forms, process, and control system in a PAT-based continuous manufacturing system is an attractive option for both industry and regulators. Fully integrated drug substance and product continuous production systems are also expected to gain momentum. Improved assurance of quality, smaller footprint, material saving and a relatively lower environmental impact are among the important reasons why adoption of these systems will increase with continued regulatory encouragement. Broader adoption of PAT-based continuous manufacturing systems (which need not be 24/7 operations) by brand and by a couple of major generic and CDMO's should be more prominently evident in the next three years.

Perhaps a bigger incentive may turn out to be the “C” in CGMP which has started to trend in the direction of process control, statistical confidence, and continued process verification. When process stability and capability are important factors in an FDA’s risk-ranking of facilities, it would be a significant driver for “Six-Sigma” level of assurance for pharmaceutical quality.

An excellent opportunity for continuous manufacturing of injectables exists and there is an urgent need for it so as to mitigate the risk of shortages. Although not prominent today, we should expect to see more progress for injectable manufacturing over the next three years.

The pharmaceutical education and training systems in the USA and Europe have been advancing anticipating this transition. It needs to do more to expand educational offerings and training opportunities. Efforts to support educational and training programs in India, China, and other regions should also be a high priority.

**Adherence to CGMP Regulations in the 21st Century: Summary**

Adherence to CGMP regulations provides ample flexibility to design and implement effective policies and procedures that are easy to comply with and can be improved when necessary. Such systems assure the identity, strength, quality, and purity of drug products. Regulatory requirements are minimal requirements. This means companies need to go beyond a regulatory check-the-box and ‘cut-paste’ exercise. Aiming high and taking ownership & responsibility for quality is essential.

To “get-it-right” in the 21st Century, let’s remember Einstein’s challenge that we will never solve the problems tomorrow with the same order of consciousness we are using to create the problems of today! When we chose to take off our blindfolds, and we commit to recognizing that pharmaceutical quality is like an elephant in the dark; Rumi’s centuries old strategy can still work for us - If each of us held a candle there, and if we went in together, we could see it.
## References


Manufacturing Processes Require Financial Justification

Introduction

Every business has a mission of making profit, satisfying return on investment expectation of its stakeholders while fulfilling needs of their customers with consistent quality products. In this effort company’s investment in product development, manufacturing technology and innovation has to be justified. In a competitive business world many a times process improvements are necessary to meet prevailing regulations and staying competitive. Related costs are either passed on to the customers or counterbalanced by productivity or technology improvements.

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

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

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

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

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

**Manufacturing Methods:**

Batch manufacturing methods for the active pharmaceutical ingredients (API) and their formulations have been the norm. Since dose can vary from e.g. from micrograms to as much as 500 milligrams or more low to high volume API might be needed to serve the same population number. Generally the needed APIs are produced using a batch process. Tables 1 and 2 illustrate examples of different process (batch and continuous) possibilities for API and formulations at two different doses. Broader review showing different process possibilities are discussed elsewhere (1,2).

### Table 1

<table>
<thead>
<tr>
<th>Milligrams = 0.112</th>
<th>Drug use days per yr. = 365</th>
<th>Population = 5,000,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milligrams/ year</td>
<td>API Kg per year</td>
<td>Tablets per year</td>
</tr>
<tr>
<td>204,000,000</td>
<td>204.4</td>
<td>1,825,000,000</td>
</tr>
</tbody>
</table>

API production batch

Tablets per hour = -255,000

Most likely batch but can be produced continuously at one plant

Continuous API manufacturing is limited to products that would exceed yearly production volume of about e.g. 400,000 pounds. There are very few APIs that would meet this volume criterion.

### Table 2

<table>
<thead>
<tr>
<th>Milligrams = 10</th>
<th>Drug use days per yr. = 365</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population = 50,000,000</td>
<td></td>
</tr>
<tr>
<td>API needed Kg per year = 91,250</td>
<td></td>
</tr>
</tbody>
</table>

Continuous process very possible but financial justification needed. Most likely batch due to many plants

### Formulations

| Tablet produced per year = 18,250,000,000 |
| Tablets per hour = -2,556,000 |

Most likely multiple batch operations; Can be produced in two continuous plants

Between batch and continuous processes there is another possibility where products can be campaigned for longer than batch times and less than continuously. Such processes generally would require that their API chemistries and formulations are very similar. Equipment utilization of as much as 80% would be necessary in such campaigns. Such product runs are feasible but will have to be evaluated by each operation. cGMP practices will have to be very carefully monitored.

Industries other than pharmaceutical industry generally use the dictionary definitions in their practice of continuous processes. Recently few pharma companies have claimed to use continuous processes. How they define continuous

**Continuous manufacturing needs a proper definition, and is very unlikely for nearly all APIs (as volumes are too low) and the business case is not justified**
is not known. USFDA has indicated that the operation at these are continuous but has not elaborated on details. USFDA has indicated that they would publish guidance for continuous processes in future (3). Based on my conjecture volume of drugs produced at these operations are not large enough to warrant continuous processes and could be easily produced using batch processes. It seems that these companies are labeling their processes to be continuous using a definition that is different from the dictionary and/or industry practiced acknowledged/established definitions.

Better reactor technologies are evolving for API production but they are expensive and at times are chemistry specific. Thus compared to the existing technologies they might not find widespread use. Their widespread use and financial justification most likely could come from contract manufacturing organizations specializing in similar chemistries. As a substitute much cheaper existing equipment could be used instead efficiently but significant creativity, finesse and imagination are needed.

Continuous formulation processes need their own financial justification. If the equipment is used to produce a single drug and has less than 80% or lower asset utilization, then the plants are no different from the current batch operations. There are unique tableting methods that can improve overall operations. As has been stated earlier drug dose and population dictate the asset utilization.

All said and done each company producing APIs or their formulations has to justify and use the most cost efficient technology (batch, campaigned batch or continuous) to produce products that are economic and deliver the same quality all the time. Regulators can only regulate and assure product quality. They can suggest the technologies and methods companies should consider for their products. However, companies have to justify use of such technologies. Excellence comes from within the companies rather than outsiders.

Contract Manufacturers, with similar chemistries, will be first with continuous manufacturing

References

3. Conversation with Dr. Sau Lee and Dr. Thomas O’Connor, CDER, USFDA July 6, 2016
Introduction

CGMP provides a discrete set of instructions that involve many actors and many independent systems. It is difficult to see the "big picture" without a proper systems approach. Issues where an action impacts (or is affected by) the environment surrounding the issue (including people involved in the issue), cannot be solved without a systems approach. Systems thinking allows people to make their understanding of systems explicit and improve them in a manner similar to how engineers use engineering principles to analyze and improve their understanding of mechanical systems. Systems thinking is fundamentally different from that of traditional forms of analysis. Without a systems approach, problems reoccur and are made worse by past attempts to fix them.

Deming's Plan-do-Check-Act was a keystone in design of CGMP in the 1960's.
Also called PDCA, or Shewhart Cycle, the plan-do-check-act cycle in the figure above is a four-step model for carrying out continuous improvement in a manufacturing facility to ensure compliance. CGMP always takes into account the current developments in technology, guidance or decisions or communications from the FDA or other industry practices that may be applicable. The pharmaceutical manufacturer is expected to have a continuous improvement program in place to continue to check its performance, detect issues and continuously correct itself. This is normally done through collection of data and statistical analysis of the data which is also an integral part of measurement of any performance. Over the past decade, the FDA has been working with the pharmaceutical industry to encourage the industry to adopt modern quality systems and risk management approaches to management of GMP compliance. The idea is that a system of management controls can serve to support and maintain a company’s CGMP compliance status. The establishment of management controls is a concept that is embodied in the FDA guidance documents that have been advanced by the FDA in recent years.

The Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations was issued in 2006 where the FDA explained that the Agency’s intent was “to integrate quality systems and risk management approaches into its existing programs with the goal of encouraging industry to adopt modern and innovative manufacturing technologies. … This guidance describes a comprehensive quality systems model, which, if implemented, will allow manufacturers to support and sustain robust, modern quality systems that are consistent with CGMP regulations. The guidance demonstrates how and where the elements of this comprehensive model can fit within the requirements of the CGMP regulations. The inherent flexibility of the CGMP regulations should enable manufacturers to implement a quality system in a form that is appropriate for their specific operations.”

So, the FDA realized that a robust, modern quality system would ensure that the management of a pharma company valued discipline and exhibited an understanding that in a properly designed system, examining the linkages and interactions between the components that comprise the entirety of the system would readily tell them whether CGMP principles were being followed or not. Systems are composed of several entities e.g. policies, processes, practices and people and may be broken down into further sub-systems. These are the fundamental pillars of CGMP. A robust quality system would also distinguish between a management philosophy which is based on PDCA principles from one which is content with firefighting as and when problems crop up.

Thus, FDA provides a clear definition of a Pharmaceutical Quality System (PQS) and how to measure the performance of the PQS while defining Quality Systems for drugs (the critical words have been underlined):

“The requirements of good manufacturing practice are underpinned by a central objective: to create a system of programs, policies, processes, and facilities that prevent errors and defects. Senior managers in the drug industry are responsible for the effectiveness of this system, which is known as the Pharmaceutical Quality System (PQS). A PQS is successful when it assures an ongoing state of control. In a healthy PQS, managers establish a vigilant quality culture in which timely action is taken to prevent risks to quality. Lifecycle adaptations are made to address manufacturing weaknesses and continually improve systems. An effective process performance and product quality monitoring program provides early warning of emerging quality issues. Systemic solutions are implemented rather than ineffective shortcuts. A firm will also habitually attend to the seemingly small problems that quality experts remind us later would accumulate into costly, complex problems. An effective PQS will ultimately support stable processes, and predictable quality and supply.”

Deming stated, “Management of a system … requires knowledge of the interrelationships between all the components within a system and of the people that work in it.” To manage quality of a pharmaceutical operations, one must adopt a systems approach.
Paradox of Measurements

One has to be careful in choice of metrics. In the article titled, “You are what you measure,” Ariely states, “Human beings adjust behavior based on the metrics they’re held against. Anything you measure will impel a person to optimize his score on that metric. What you measure is what you’ll get. Period.” …. CEO’s care about stock values because that’s how we measure them.” He adds, “If we want to change what the CEO’s care about, we should change what we measure.”

We also sometimes hear the phrase “What gets measured gets done.” It has been attributed to Peter Drucker, Tom Peters, Edwards Deming, Lord Kelvin and others. It sounds like If we can measure X, then X will get done and we will achieve the performance we want. But, simply measuring something does not ensure that some action will then take place. Just because we measure something does not mean it leads to improvement. If continuous improvement is the goal, then measurements must be linked to processes and must reflect process performance. There has to be a feedback loop where an action is attached to the measurement result such that depending on the measurement, some actions are taken to adjust, correct or improve the processes.

So, in order for the metrics or the scoreboard to be effective, it must be tied to specific processes that are in turn derived from and aligned with the overall operations or quality management system. There needs to be a process that demonstrates this link and management must prove that adequate actions are being taken based on this set of metrics. Simply measuring something will never ensure corrective actions are being taken.

There also needs to be some goals or standards established to compare the measured values to the targets. Joseph Juran said “Without a standard, there is no logical basis for making a decision or taking action.” A standard or goal to attain must be established first before one decides what to measure and then current performance must be measured compared to that standard so that actions may be taken to get closer to that standard. What is being measured must be important to both the operations and those who directly and indirectly impact what is being measured. If something that is being measured is considered not important to improving operations or the system, then it is likely that it won’t get measured properly.

Measurements should lead to Continuous Improvement of Systems

Potocki and Brocato recommends a system of management for organizational improvement which is very appropriate for pharmaceutical manufacturing. The system is depicted as follows:

In this system, metrics and benchmarking act as sensors in a feedback control loop which provides input to which the system should react. This allows an organization to objectively evaluate how the system is performing and whether changes are necessary. Measurements can also identify gaps between where the system currently is and where it should be. The input is then used to make incremental improvement of the system. Process improvement works best in an environment where a responsible leadership manages the system and there is employee involvement.
Measurement of Pharmaceutical Quality

It is a common understanding that quality of products, manufactured in a pharmaceutical manufacturing operation, is the ultimate performance indicator of that operation. But, a performance measurement system should also play a critical role by providing the information necessary for decision making and actions. Otherwise, it becomes a daily firefighting exercise, dealing with problems as they come up at the end of the production line when it is too late to correct the problem other than rejecting the product. Quality will then depend on the rigor of inspection or the probability or effectiveness of the inspection process and the quality control process for catching all defects. In situations where products are manufactured in faraway countries where perhaps there is low probability of the plant or the product being ever inspected by the FDA, our patient population is exposed to severe risks.

Effectively using metrics based on a robust quality system will allow management of companies or the FDA to monitor the company’s quality performance on an ongoing basis and will allow them to identify factors or issues and rectify them before they occur. Thus, the metrics, designed to measure quality in pharmaceutical manufacturing, must be a true measurement of the performance of its Pharmaceutical Quality System (PQS). There should be a manageable number of metrics that strike a balance among different criteria for measuring effectiveness of the PQS and are linked directly to whatever drives its values. “Essentially all deficiencies result from an ineffective PQS no matter what heading you give it.”

Quality metrics, as defined by the FDA as recently as 2013 states that it “is an objective measure of the effectiveness of systems associated with the manufacture of pharmaceutical products, including the pharmaceutical quality system.” This means that ideally a set of metrics used to measure the performance of a pharmaceutical operation should be systems oriented. Conventional metrics such as measuring the number of deviations, batch failure rate or number of Out-Of-Specification incidents are not true measures of the PQS systems. They are symptoms and lagging indicators. These types of metrics do not point out the systemic issues that are bound to crop up over and over again and they are not associated with a feedback system. A few important problems of conventional measurement are: The systems and measurements are not connected – the measurements are not true reflections of how to improve the overall systems such that similar errors or mistakes do not reoccur.

1. A biased focus on cost or financials – the focus is on how to improve the financials and not on how to improve quality.
2. Too many isolated and incompatible measures— the number and variety of metrics used in organizations tend to increase over time, and require more and more resources to produce. Because metrics once introduced are too seldom removed, they soon become obsolete as strategy and underlying activities continue to change measurement systems.
3. Therefore, the true purpose of a quality metrics should be to monitor quality control systems and processes. Many of the components of a systems oriented quality metrics (e.g., data on process capability output or statistical process control) are already collected and maintained as part of a properly executed OPEX program. Metrics for the OPEX systems have been accepted, and are already being measured, reviewed and implemented by many of these plants. Developing synergistic quality metrics that will have wide-ranging acceptance by the industry makes tremendous sense.
Operational Excellence (OPEX) and Quality Metrics

As discussed earlier, traditional quality measurement systems and quality metrics are usually based on result-oriented measures as opposed to long-term and process-oriented measures. Thus, these traditional way of quality measurement is unsuitable for the fact that they do not reflect true manufacturing performances, do not cover all necessary performance dimensions and, are not integrated with the quality systems approach. In other words, these metrics are not tied to specific processes nor do they directly lead to improving the system. This type of metrics is considered to work against continuous improvement and the overall philosophy of systems thinking, espoused by PQS or other systems such as ICH, to modernize pharmaceutical manufacturing.

Therefore, an attempt to suggest performance measures for pharmaceutical manufacturing that do not incorporate a systems approach is perhaps an attempt to divert attention from measuring true quality. We live in an environment where we find that even clinical studies data is being falsified. How do we ensure that the metrics will truly reflect the quality of the operations? Basing metrics on systems performance ensures that integrity of measurements can be preserved.

Below is the OPEX framework developed by the University of St.Gallen, Switzerland which incorporates many of the key criteria for an effective PQS system as defined by the FDA. This is a representation of the system to measure performance of manufacturing operations of pharmaceutical companies and is widely being used by more than 300 manufacturing plants around the world. Several Key Performance Indicators (KPI's) have been developed and widely tested to measure whether the plant system “assures an ongoing state of control” through stable equipment systems and stable processes, whether there is a vigilant quality culture established by management and if there are risks not to deliver quality and operational excellence. The KPIs provide warning and an assessment of variation in operations and risk to quality as well as productivity.

Normally manufacturing operations metrics comprise of four types of performance: time, quality, performance of service, and cost. However, all the different measures are interdependent. For example, time can be measured from the time an operations take to complete a batch of a product from start to finish. Longer times could indicate not only inefficiencies in manufacturing, but also perhaps a large number of process interruptions such as deviations or errors, etc. Quality thus could also be a reflection of the measure of on-time delivery, the accuracy of the company’s delivery forecasts.

The important components of a true operational excellence program (OPEX) are continuous improvement, management commitment, and employee involvement. In principle, there is an excellent match of the key components of OPEX and those of an ideal quality system. Therefore, it makes tremendous sense to develop and integrate the metrics for OPEX implementation with an appropriate metrics for “Quality” for pharmaceutical manufacturing operations. Many pharmaceutical plants are keen on implementing an OPEX program to improve their operating efficiencies.

The important components of a true operational excellence program (OPEX) are continuous improvement, management commitment, and employee involvement. In principle, there is an excellent match of the key components of OPEX and those of an ideal quality system. Therefore, it makes tremendous sense to develop and integrate the metrics for OPEX implementation with an appropriate metrics for “Quality” for pharmaceutical manufacturing operations.
OPEX is Synergistic with ICH Q10

The Medicine and Healthcare products Regulatory Agency (MHRA) stated, “Deficiencies relating to ‘Quality Systems’ are by far the most prevalent observed during inspections.” More than 10 years ago, it is probable that neither the industry nor the regulators really appreciated the importance of a PQS or indeed what it looked like and what system elements made up the QMS. There was a huge reliance on just GMP compliance.

Now with the introduction of ICH Q10 we all have a much better understanding of what a PQS is. So why do inspectors still find so many inspection deficiencies relating to the PQS?

“ICH Q10 aims to promote a paradigm shift from discrete GMP compliance procedures at each stage of the product lifecycle to a comprehensive quality systems approach over the lifecycle of the product.” ICH Q10 in fact provides us with the foundation to set up an effective systems oriented quality metrics.

As per ICH Q10, the key criteria for effective PQS are:

*Achieve Product Realization* - To establish, implement, and maintain a system that allows the delivery of products with the quality attributes. The TPM and TQM components of the St. Gallen OPEX system essentially represent the effectiveness of product realization. TPM and TQM consists of preventive maintenance, cleaning, housekeeping processes, reliability, effectiveness and robustness of equipment, with the aim to stabilize the plant and equipment as a first step to stabilizing performance and minimizing variations.
Establish and Maintain a State of Control - To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes. TQM essentially is a measurement of the stability of the processes being run in the plant. Once equipment reliability is established, only then can one effectively measure and control process variability.

Facilitate Continual Improvement - to identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations, and pharmaceutical quality system enhancements, thereby increasing the ability to fulfill a pharmaceutical manufacturer’s own quality needs consistently. Continuous Improvement, often referred to by the Japanese word ‘Kaizen’, is an integral part of a systems approach. Kaizen means ‘change for the better’ and covers all processes and systems. Continuous Improvement starts with management and under their leadership works down through the organization. The key to success in systems approach and continuous improvement is that everyone is responsible and has a part to play in making improvements. All employees must work together to identify the steps needed to improve work practices. Successful and sustainable Quality and OPEX programs require systems thinking, and an effective continuous management program. The EMS component of the OPEX system represents amongst others continuous improvement.

The enablers for implementing an effective quality system according to ICH-Q10 are:

Knowledge Management - Knowledge that is proactively managed to facilitate continuous improvement.

Quality Risk Management - A structured, scientific decision-making process about risks to product quality. Thus, risk management can be defined as the identification, assessment, and prioritization of risks to minimize uncertainty in processes and operations. Project prioritization activity should be both “cost” and “risk” driven – both are really the same – in fact, “risk” should have a priority over “cost” to prevent quality deterioration. In order to implement a risk-informed decision making approach, risk management activities should be embedded into organizational structures and processes at both the operational and strategic levels.

Management Commitment - CGMPs are unfortunately often seen as an impediment to business. Defending the business value of CGMPs can only be successful if management actually believes it is true.

Figure 4: ICH Q10 and OPEX are Synergistic
Conclusion

In collaboration with the FDA and the pharmaceutical industry and based on St. Gallen’s extensive global OPEX database (consisting of data from more than 300 pharmaceutical manufacturing sites around the world) and nearly fifteen years of experience of research and collaboration with the pharmaceutical industry, the St. Gallen OPEX research team, in collaboration with Prabir Basu, USA and Nuala Calan of Dublin Institute of Technology, will propose a meaningful, measurable and reportable quality metric including quantitative and qualitative cultural related indicators and evaluate these potential candidates of quality metrics. The proposed set of metrics will help the FDA to establish a clear standard for review and inspection and in that regard use metrics to inspect facilities operating at risk. These metrics will ultimately increase the ability for FDA to adopt a risk-based regulatory approach that will increase the efficiency and effectiveness of the inspection activities and will transform quality oversight from a qualitative to a quantitative risk-based process. An understandable algorithm will also be developed to allow conclusion from data analysis of pharmaceutical production sites.

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A Critical Look at Excipient Criticality

Introduction

O’Keeffe et al (2016) are critical (disapproving) of the current binary approach to classifying process parameters and quality attributes as being critical or non-critical. It is too simplistic to adequately reflect current science and risk-based approaches to product quality. The authors note how embedded the term “critical” has become in GMPs and guidances, but question the difference between criticality and importance. They advocate a more realistic “spectrum of importance” with respect to process parameters and material attributes. This is of particular relevance for excipients, which in Europe are subject to formalized excipient risk assessment, as of March 2016 (European Commission, 2015).

Criticality

In English the term "critical" has several meanings, which may cause confusion, even before translation into other languages. Merriam Webster (2016) lists several relevant definitions:

• Crucial, decisive, a critical test
• Indispensable, vital, a component critical to the operation of a machine
• Being in or approaching a state of crisis, a critical shortage, a critical situation
• Of, relating to, or being a turning point or specially important juncture, a critical phase.
  – a state in which or a measurement or point at which some quality, property, or phenomenon suffers a definite change, a critical temperature

All excipients are critical (indispensable, to the formulation) but not all are critical (crucial, to the design, or finished product performance). The ICH (2009) requirement that “at a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified,” begs the question, how important to be decisive? Inappropriate selection and control of excipients will lead to a critical situation (state of crisis).

MIL-STD-1629A (US Dept Defense, 1980) uses the word ‘critical’ as a severity classification, one stop short of catastrophic, and defines criticality as a relative measure of the consequences of a failure mode and its frequency of occurrence. A similar approach was adopted by ICH (2009) together with the additional criterion of
detectability. Mcfarland & Waldron (2015) criticise reliance on detectability because, “in the absence of knowledge management and a science- and risk-based rationale supporting monitoring programs, undue emphasis may be placed on implementing detection controls rather than directing resources towards preventing failure in the first place”. The authors concern was to avoid Quality by Inspection, but it could be argued that Process Analytical Technologies (PAT) enable process control and even Real Time Release (RTR) because of increased detectability.

ICH (2009) did not include the last definition of critical, as relating to, or denoting, a point of transition from one state to another. The criticality (importance) of an excipient may suddenly change if a finished product criticality (critical transition) is encountered during the lifecycle.

“Excipients are often divided into critical and non-critical categories, the latter receiving less attention. Such arbitrary classification runs the risk of surprises if subsequent experience invalidates the assumption of non-criticality.” (Carlin, 2012)

If the choice of materials is critical (of the essence) for product safety, how may excipients be successfully factored into product design. Determination of the criticality (importance) of an excipient is critical (essential) but, as suggested by O’Keeffe et al (2016) this will be a continuum rather than a binary classification. If every excipient is treated as critical then there is the potential for Quality Risk Management (QRM) to degenerate into a non-value added exercise of identifying noncritical, improbable, low risk scenarios indefinitely. (Orloff, 2011)

How Critical?

Kano analysis (Matzler & Hinterhuber, 1998) can be applied to provide a more structured approach to excipient incorporation in formulation design:

- **Must-be requirements**
- **Performance requirements**
- **Surprises**

**Must-be requirements**

Compliance with Pharmacopoeial specification, manufacture under GMP and a secure supply chain are all examples of basic or must-have requirements, critical (essential) to excipient selection, regardless of the finished product design. Such requirements are also known as “entry tickets”, or minimum standards, to operate in the Pharmaceutical market. Unfortunately, compliance with specification by itself ensures neither GMP nor supply chain security, hence the European guidelines on formalized risk assessment for ascertaining the appropriate GMP for excipients (European Commission, 2015), and corresponding US requirements under FDASIA (FDA, 2012). Reliance on specification alone opens the door to economically motivated adulteration. Non-compliant materials should be rejected by the quality system. Compliant materials are actually a greater and more insidious threat. Melamine was added to pet foods and infant formulae to bolster the apparent protein content, as specified by a test for nitrogen content in lieu of an actual protein determination (FDA, 2009).

There may be additional basic requirements dependent on route of administration, such as absence of endotoxins for injection use, which in turn imposes additional excipient GMP requirements. Chemical compatibility with the API is another basic requirement, regardless of the finished product design. If an incompatibility is dependent on the source of the excipient, it is likely that the reactants may be trace components, which are not always specified.

In terms of these basic requirements all excipients are critical because non-compliance, contamination, or incompatibility can render the finished product unacceptable. Such requirements tend to be taken for granted by users, with extreme dissatisfaction if not met, but with little reward for quality beyond compliance with specification.

**Performance requirements**

Performance requirements are those excipient attributes, which govern finished product quality in terms of performance. Patient-centric product performance is
specified by the Critical Quality Attributes (CQAs), as formalized in the Quality Target Product Profile (QTPP). Rather than arbitrarily classifying the excipients in a formulation as critical or “non-critical,” a better approach is to ask to what extent are they design critical?

Design-critical implies a direct cause-effect on finished product performance where the level of the excipient is titrated above a minimum, or to an optimal level, for specific performance in the finished product. Examples of design-critical excipients include modified release polymers and suspending agents, which control the CQAs of release and content uniformity respectively. At the other end of the spectrum a filler-diluent should have no impact on the CQAs, and therefore is not design- or performance critical. In practice the distinction is not absolute. Between the two extremes of a dominant functionality and no impact, other excipients in the formulation may interact and modulate finished product performance. Their design criticality will vary along a spectrum of importance.

A filler-diluent in a tablet formulation, affecting compactability and release, is more performance-critical than the same filler used to stop mini-tablets rattling inside a hard gelatin shell. Magnesium Stearate in tablets is more performance-critical because of side effects on dissolution rather than its function as a lubricant. (As a process aid it has no function in the finished product).

If design-critical excipients are titrated into the formulation to deliver specific performance it follows that excipient variability could impact performance. Two questions must be answered:

1. What is the concentration-response relationship for that excipient in that formulation?
2. What attribute(s) of the excipient govern performance, and how variable are they?

If the excipient use level corresponds to a steep part of the concentration (x)-response (y) curve, then performance is sensitive (dy/dx) to precision of dosing and content uniformity of that excipient. Performance is also likely to be sensitive to variability in that excipient. Similarly, if there is a minimum effective level for that excipient, operating close to that minimum has a higher risk of impact from excipient variability. Near the minimum effective level the concentration-response curve may be a step function (dy/dx → ∞), characteristic of percolation, or threshold, effects.

For example, if a matrix sustained release polymer gives a desired release profile close to the minimum feasible level of usage it is better to look for a “faster” grade which can be used at a level higher than the minimum feasible but still give the desired release profile. For a given release profile, using the smaller amount of the “slower” polymer (with minimum feasibility) is likely to make the formulation more sensitive to variability in that polymer than using a higher amount of the “faster” grade.

Having selected an excipient to deliver a functionality, what attributes of the excipient govern its performance. What are the Critical Material Attributes (CMAs)? There may not be a CMA on the official specification, usually Pharmacopeial. For example Avicel® RC591 is a structured vehicle former used in pharmaceutical suspensions to ensure content uniformity, a CQA for suspensions. As implied by its British Pharmacopeial title (“Dispersible Cellulose”) the particle size is not a CMA. The specified viscosity also cannot be a CMA for two reasons. Firstly viscosity is a liquid property and therefore never a CQA in terms of suspending power. Secondly the specified (apparent) viscosity is measured on a de-structured sample and is therefore not predictive of structured vehicle performance. In the absence of a CMA an alternative design approach is to consider the Critical Formulation Attribute (CFA), in this case Rheology, and assess the extent to which variation in the CFA can impact on the quality of the drug product (FDA, 2009). In this case the CFA is both formulation and process dependent.

Excipient viscosities are often apparent dilute-solution viscosities of no relevance to applications beyond low level use as thickeners. Fu et al (2010) found viscoelastic properties of sodium alginate at higher concentrations to be more predictive of performance as a controlled release matrix former than the specified dilute solution viscosities, noting that “polymeric excipients are often the least well-characterized components of pharmaceutical formulations.” Performance requirements of an excipient for a particular application should be explicitly specified, both to
avoid regulatory requests to justify reliance on official specifications, and to avoid surprises if the suppliers are unaware of the requirements. If possible the design should also utilize design-critical excipients at levels where the sensitivity of performance to concentration is minimized.

**Surprises**

Surprises, also called exciters, are those product criteria which have the greatest influence on customer satisfaction and are neither explicitly expressed nor expected by the customer. When eventually specified they become performance requirements. Surprises can be beneficial where increasing raw material experience and insight drives process efficiency, higher yields or enhanced finished product performance. Unfortunately most excipient-related surprises are negative, reflecting design uncertainty due to the complexity of the raw materials and the products into which they are formulated (Carlin, 2016). Risk applies when the odds can be calculated, but with uncertainty there is no information to set the odds in the first place (Knight, 1921).

Often, it is variability in a so-called “non-critical” excipient, which causes a surprise when it suddenly correlates with an out-of-specification (OOS) or out-of-trend (OOT) excursion, a special cause variation. The variability may be within norms for a known attribute. The excipient variability may not have caused the problem but is now controlling the transition in and out of acceptable finished product quality. Two preconditions for such indirect excipient impact are a finished product criticality and product or process drift. Criticalities, a point of transition between two states, should always be anticipated in complex products such as pharmaceuticals. Such product weaknesses or latent defects may not be seen during development and come to light as a result of cumulative changes during the product lifecycle. Individual changes, usually subject to univariate change control, do not affect the CQAs but may allow system drift. Eventually, one change too many reveals the interaction of an excipient variability with a criticality. What was previously “non-critical” is now critical in controlling the critical transition between states.

Surprises are inevitable in complex systems with too many degrees of freedom. For excipients the answer is to anticipate application-specific failure modes and design the Control Strategy accordingly. Designing for failure will make the product more robust, especially when compensatory mechanisms are built in to address raw material variability. The fixed processes and formulae so common in pharmaceutical products are rigid systems through which raw material variability can feed forward to impact CQAs.

**Manufacturability**

Manufacturability should always be taken into account in product design (FDA, 2009) but treated separately from the CQAs in the QTPP. Critical (one step short of catastrophic) manufacturing problems are self-limiting. Only manufacturing with zero, minor or marginal severity defects will yield commercial product. If manufacturability is included as a CQA then the number of potential CPPs and CMAs increases and focus is lost on what is critical for performance in the hands of the patient.

The distinction is exemplified in the QbD Sampling Guide (IPEC Americas, 2016) where bracketing with multiple grades can be used to widen the range of material attributes in order to gain a higher degree of understanding of raw material impact. The criterion is not absence of impact but more specifically "no unanticipated effects of bracketing with readily available grades on the performance of the process or finished product". For example if you substitute Avicel® PH102 with Avicel® PH101 in a high speed direct compression it should come as no surprise that you have to slow the tablet machine down. If it does not affect the CQAs, such as content uniformity and...
release rate, then the particle size distribution is not critical to the QTPP, even if critical to the flow of the compression mix (by design).

The quality of manufacturing, as opposed to the manufacturing of quality products, is better controlled through the Quality Metrics initiative (FDA, 2015). This is currently specified in terms of lot rejection rate (FDA, 2016) but a quality culture will seek to control excipient-related special cause variation before an out of specification excursion. Most excipient-related impact on manufacturability will not be known at time of filing.

**A Critical Look at Excipient Criticality**

Applying the simple binary logic of critical vs non-critical to excipients can lead to inconsistencies. Can a "non-critical" excipient have a CMA? Logically a CMA governing finished product performance would make that excipient critical, but, as illustrated by the earlier discussion on excipient surprises, CMAs can arise during the product lifecycle due to drift and interactions. If what was originally considered non-critical suddenly becomes critical the question is a dynamic lifecycle-management issue, rather than an initial static assessment. Continuous monitoring of impact from all excipients throughout the lifecycle is more important than a one-off arbitrary binary classification during development.

Must a critical excipient have a CMA? The question assumes a linear one-to-one relationship between an excipient attribute and finished product performance which is not always the case given the multi-functional nature of many excipients and the number of interactions in complex systems. As originally envisaged by ICH (2009) would a CFA be a more appropriate level of control where there is not a simple correlation of product performance with an excipient CMA? The biggest problem in assigning a CMA is the tendency to pick an attribute on the official specification, without critically (careful judgement) assessing how relevant that attribute (and associated measurement methods) is to finished product performance (fitness-for-purpose). Failure to specify the material attribute actually controlling a CQA is akin to a skater using the coefficient of friction to measure the thickness of the ice (Consistency and compliance, up to point of failure without warning).

The development of a spectrum of importance advocated by O’Keeffe et al (2016) is a better way to handle quality attributes (including raw material attributes), instead of classifying the excipients as critical or non-critical. If the relative importance of the excipients (to both CQAs and manufacturability) is understood then qualification and validation efforts can be prioritized accordingly to reduce variation and to control the risks of producing a product that is not of the required quality. The authors note that this approach is consistent with the FDA Process Validation Guidance for Industry (2011), which saw criticality as a continuum rather than a binary state. The importance of all attributes and parameters should be evaluated for impact, and re-evaluated as new information becomes available.

All excipients are potentially critical, especially when subject to cumulative changes throughout the product lifecycle.
References

Part 2.

Outsourcing Strategies and Growth Opportunities in Biosimilars
What does the future hold for the CMO and CDMO sector?

Introduction

Last year, I started off by setting up a broad perspective on the size of the global CMO/CDMO sector, carefully curating figures from PharmSource, ICON, and others to illustrate the growth rate of the business. That was a lot of work, and the scene hasn’t changed appreciably, so this time around, we’re going to dive right into trends, drivers and some predictions, if my crystal ball doesn’t fail me.

Consolidation

The number one trend from last year’s edition demands a repeat. The CMO/CDMO sector remains fragmented, and business logic dictates that the sector needs to consolidate (or rationalize, if that’s your term of choice). It’s been this way for years, so if we keep calling for it, it’s bound to happen, right?

Consolidation doesn’t just mean big CDMOs will be devouring smaller ones to shrink the food chain. In fact, the big rumor to crop up last year was Lonza Group’s interest in acquiring Catalent, one of the largest CDMOs in the world. According to a Reuters report, the two sides failed to agree on a price, but “Lonza, which is keen on an acquisition, may decide to pursue other targets.” You might recall that in 2009, Lonza launched a bid for Patheon, long before the latter merged with DSM.

So will we see CDMO mega-mergers, combining API-heavy firms with formulation-oriented ones, or mid-tier mergers of equals, or the aforementioned big fish eating the little ones in bolt-on, accretive deals? I think there will be plenty of the latter, but I also think we’ll see a significant attempt at building a soup-to-nuts drug substance through drug product company in the next year or so. Mind you I don’t think such a structure -- going from APIs to dosage forms -- will necessarily work, but I think some companies will try.

Of course, that’s only the intra-CDMO sector we’re talking about. It doesn’t cover pharmas buying pharmas that own CDMO units, like Pfizer’s acquisition of Hospira (and the One 2 One CDMO business), or one of the more interesting acquisitions in the past year: Mylan’s purchase of (most of) DPT/Confab. The press release announcing that move.
focused on DPT/Confab’s ANDAs, not their manufacturing facilities and CDMO operations, and it remains to be seen how Mylan integrates the CDMO business, but the acquisition is a sign that CDMOs can be valued for more than their service businesses.

A few years ago, Metrics Contract Services was another example of this, when the firm was acquired by Mayne Pharma as part of Mayne’s entry into the US generic space. The good news is that the parent company has remained committed to Metrics as a CDMO business. I think we’ll see other CDMOs get snapped up because of non-CDMO assets.

### Buy in

On the flipside, some CDMO opportunities may arise from large pharma companies trying to rationalize their own manufacturing networks. A CDMO buying a pharma site in exchange for a trailing supply agreement is still a risky proposition -- if you don't build up enough new business by the time the supply agreement ends, you could be stuck with a lot of overhead costs -- but there can be good fits.

In the last few years, Teva has been working on a $2 billion/year restructuring plan that has put many of its facilities in play; a few of them have already been sold off to CDMOs and other generic firms. Teva also recently closed a $40 billion deal for Actavis’ generic portfolio, in which it had to divest significant generic holdings to receive government approval for the deal; presumably, more facilities in its network will lead to more spinout possibilities. Look for more of those facility-deals to happen across the spectrum.

But I’m guessing we’ll see plenty of intra-CDMO mergers or sell-offs of specific sites. Recipharm got into the US by acquiring a site from Indian CDMO Kemwell, after a series of non-US deals. CMOs with no US footprint will keep looking for avenues to enter the world’s biggest pharmaceutical market, especially with the uncertainty facing the EU in the wake of the Brexit.

### Cash out

One of the biggest players in the industry, Patheon, recently went public. Like the other top-rank CDMO, Catalent, proceeds from the IPO were used to pay down debt. There are upsides and downsides to having these companies on the stock market. As Jim Miller put it in the July, 2016 issue of PharmSource’s Bio/Pharmaceutical Outsourcing Report:

> “Adding another public company to the CMO industry is good . . . because it makes it more transparent and helps customers and investors appreciate the industry’s development. For instance, the equity analysts who follow the CMO industry still try to shoehorn it into models developed from 15 years of following the CRO industry. Perhaps with another significant public CMO they will refine their understanding of the industry.”

That said, I was around the last time Patheon was public (and Catalent was the Pharmaceutical Technologies and Services division of Cardinal Health), and the quarter-to-quarter earnings pressure was fierce. Still, the company has completely different management that it had in those days. Also, I like to think we’re in a slightly more enlightened age when it comes to expectations about the CDMO sector’s revenues – that is, that they’re not a smooth curve – but as Jim Miller pointed out, the market’s not exactly well-informed about the CDMO space, and that could lead to some incorrect assessments of its health.

Patheon’s in a unique position, and I doubt any other pure-play CDMO could manage a public offering, so I predict a one-off here, not a trend. (I know Therapure announced plans an IPO early this year, but that company’s a hybrid bio-CDMO with a pipeline of its own biologics.) I think it’s a good sign that Patheon’s IPO did well, because it signals a positive trend for funding “biopharma” companies. And if more small companies get investors, that’ll keep drug development programs going and feed CDMOs’ business pipelines.
Quick hits

Continuous manufacturing: CDMOs will advance this and other new manufacturing technologies faster than in-house pharma will (provided pharma clients are on board with it).

Biosimilars: Some CDMOs will benefit now that the US regulatory system is growing clearer (and some US payers are signaling that they’ll favor biosimilars over innovator biologics).

Rare Diseases: CDMOs will become a missing link in facilitating R&D into less profitable areas of the rare disease space, as well as in tropical diseases.

Complex Generics: As more complex drugs arc toward the end of patent protection, CDMOs with novel formulation technologies will benefit from helping clients develop generic competitors.

Harmonization/Harmonisation: FDA, EMA, Health Canada and other regulatory bodies will advance mutual recognition of inspections, but it’ll take a while; first, they have to settle on a spelling of harmonization.

My last prediction for the CDMO sector is, I admit, self-aggrandizing. For the past year, our trade association has been working closely with FDA on reauthorizing the Generic Drug User Fee Amendment (GDUFA), and as a result, we’ve built relationships with many levels of the agency, including a high-level presentation with CDER about the CDMO sector. We’ve demonstrated that CDMOs are an important part of the healthcare ecosystem, and have given a professional face to our industry.

So I’m predicting that CDMOs are on the cusp of a transformation, in terms of the FDA, CDER, and other stakeholders seeing us as partners, not just service providers. In the years to come, the CDMO sector will be recognized for its role in bringing safe and effective medicines to patients.

All predictions null-and-void if Trump wins the US Presidential election.

Gil Y. Roth is the President of the Pharma & Biopharma Outsourcing Association (www.pharma-bio.org), a US-based trade association representing CMO/CDMOs in the regulatory, legislative and general business spheres. From 1999 to 2014, he was the Founding Editor of Contract Pharma magazine. He can be reached at gil.roth@pharma-bio.org.

So will we see CDMO mega-mergers, combining API-heavy firms with formulation-oriented ones, or mid-tier mergers of equals, or the aforementioned big fish eating the little ones in bolt-on, accretive deals?
High Potency API growth trajectory

Introduction

Oncology continues to grow as a disease area of focus at almost all innovator firms, with investments in both drug discovery and development, predominantly driven by the unmet needs of patients. The principal need for most cancers is the availability of safe and effective targeted drugs that treat the advanced stages of the disease, when patients often stop responding to chemotherapy. Interest in high potent drugs that can treat cancers have followed suit, as they can play an important role in achieving those objectives. The percentage of drugs classified as “highly potent” with occupational exposure limits (OELs) ≤ 10µg/m³, has been progressively increasing, and is currently estimated to be 25% of the global pharmaceutical development pipeline.

Market size and drivers for growth

New Chemical Entities (NCE’s), particularly those intended for use in oncology, are now designed to be highly selective in their interaction with biological targets, with pharmacological activity often being achieved with very small amounts of the active ingredient. These high potent NCE’s also are active for a longer duration in the body, thereby reducing the dosing frequency required, while potentially increasing patient compliance and minimizing discomfort. Finally, since these compounds are much more selective towards the target of interest, they can reduce side effects, and minimize damage to the tissues surrounding the diseased area. Due to these reasons, targeted, potent therapies offer significant benefits over their lower potency counterparts. In addition, within the oncology market, a niche market segment is Antibody Drug Conjugates (ADC), which are cytotoxic small molecules linked to monoclonal antibodies. ADCs, certain oncology drugs, and other high-potency compounds (such as hormones) require high-containment manufacturing.

The anti-cancer market with its unprecedented growth is the engine that fuels the High Potency Active Pharmaceutical Ingredients (HPAPI’s) market, since 60% of highly potent APIs are targeted towards oncology. The global HPAPI market, which was $12.6 billion in 2014, is projected to reach $25.1 billion by 2023, at an estimated CAGR of 7.8%. 
This growing demand and explosive growth has in turn led to an increased demand for HPAPI production. Firms with existing HPAPI capabilities have been busy expanding their facilities, while many without, have sought to acquire existing businesses or add HPAPI capacity. In this article, we provide the various classifications under which high potency compounds are categorized, review regulatory requirements that govern manufacture, discuss the HPAPI manufacturing landscape, and finally, review the recent market activity in this area.

**Categorizing compounds based on potency:**

A compound is generally defined as highly potent if it has:

1. an occupational exposure limit (OEL) of ≤10 μg/m³,
2. a daily therapeutic dose of ≤10 mg/day or
3. a 1 mg/kg/day dose produces serious toxicity in laboratory animals.

OEL is the maximum permissible concentration of a hazardous substance in the workplace air so as to ensure health and safety of the people engaged in work. OEL levels define the threshold that a physically fit individual can be exposed to in an 8 hour work time. However, there is a high level of uncertainty associated with each compound.

Most new developmental products do not have the toxicity information available. Often companies work on products where it may be difficult to determine the potential risk of exposure. At present, there is no official guidance for the safe handling of highly potent compounds.

Most companies have a banding system that categorizes compounds based on their toxicity and this dictates the handling containment required to work with the compound. Often companies can determine an exposure limit of a known compound based on the lowest therapeutic dose, but many other factors have to be considered, including the form of the API (liquid or powder), the formulation process and the frequency of contact.

To add some structure, in recent years, several systems have been proposed for categorizing drug substances according to their potency, based on the use of occupational exposure limits (OELs) or occupational exposure bands (OEBs). There are currently two commonly used programs—a five-tiered system such as the one used by Merck & Co., and a more frequently used four-tiered system devised by the industrial hygiene consultancy - SafeBridge. A description of both these systems is given in the tables below.

**Table 1: OEB System by Merck:**

<table>
<thead>
<tr>
<th>Occupational Exposure Limit (OEL)</th>
<th>Band</th>
<th>Production Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1-10 mg/m³</td>
<td>1</td>
<td>Good manufacturing practices</td>
</tr>
<tr>
<td>&gt;0.1-1 mg/m³</td>
<td>2</td>
<td>Good manufacturing practices (with local exhaust ventilation)</td>
</tr>
<tr>
<td>&gt;0.01-0.1 mg/m³</td>
<td>3</td>
<td>Essentially no open handling (ventilated enclosures required)</td>
</tr>
<tr>
<td>&gt;0.001-0.01 mg/m³</td>
<td>3+</td>
<td>Virtually no open handling (containment systems required)</td>
</tr>
<tr>
<td>&lt;/=0.001 mg/m³</td>
<td>4</td>
<td>No opening handling (closed systems required)</td>
</tr>
<tr>
<td>&lt;/=0.001 mg/m³</td>
<td>5</td>
<td>No manual operations/human intervention (robotics or remote operations required)</td>
</tr>
</tbody>
</table>

Source: http://cen.acs.org/articles/86/i24/Contained-Chemistry.html
Table 2: SafeBridge Classification System

<table>
<thead>
<tr>
<th>Property</th>
<th>Category I</th>
<th>Category II</th>
<th>Category III</th>
<th>Category IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupational exposure limit (µg/m³)</td>
<td>&gt;500</td>
<td>10-500</td>
<td>0.03-10</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Toxicity and potency</td>
<td>Low</td>
<td>Moderate</td>
<td>Potent</td>
<td>Highly Potent</td>
</tr>
<tr>
<td>Genic effects</td>
<td>No</td>
<td>No</td>
<td>Suspected or known</td>
<td>Known</td>
</tr>
<tr>
<td>Sensitiser property</td>
<td>No</td>
<td>Weak</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
<tr>
<td>Medical intervention required on exposure</td>
<td>No</td>
<td>May require</td>
<td>Moderate to intermediate</td>
<td>Higher degree</td>
</tr>
<tr>
<td>Absorption rate</td>
<td>Slow</td>
<td>Moderate</td>
<td>Quick</td>
<td>Quick</td>
</tr>
<tr>
<td>Reversibility of health effects</td>
<td>Minimal reversible</td>
<td>Reversible</td>
<td>May not be reversible</td>
<td>Irreversible</td>
</tr>
<tr>
<td>Examples of drugs in this category</td>
<td>Naproxen, Acetaminophen</td>
<td>Atorvastatin, Niacardipine</td>
<td>Gancyclovir, Thalidomide</td>
<td>Leuprolide, Ethinyl Estradiol</td>
</tr>
</tbody>
</table>

SafeBridge system is now widely accepted among CMOs. SafeBridge’s system involves ranking a compound for potential potency and toxicity on a scale of I to IV. Category I covers low-irritant drugs, while Category II, currently the largest, includes drugs that can cause organ toxicity. Category III is the first tier of potent drugs that cause genetic effects plus organ toxicity, and finally, a tier Category IV, of the most potent compounds.

It is essential that there exist a well-defined framework for HPAPI classification as any confusion or mistakes while classifying compounds could have a significantly detrimental effect on safety.

Regulatory and Manufacturing guidelines:

Handling, containment, manufacturing, facility design, machinery and regulatory requirements of these compounds are more stringent and different from conventional APIs.

In general, good manufacturing practices (GMP) apply to the production of highly potent and cytotoxic compounds. The only regulatory body to have flagged up the importance of bringing in updated guidance for safely dealing with HPAPIs is the European Medicines Agency (EMA). In 2005, EMA (European Medicines Agency) published a concept paper on HPAPIs, though it was mainly focused on high potent product segregation rather than classification. The concept paper primarily addressed the need to update GMPs and have better clarity on classification systems in order to determine requirements for working with specific compounds. In 2011, EMA introduced another concept paper mentioning the requirement for a toxicological tool and a risk-based scientific approach to establish exposure limits. Then, in January 2013, EMA published a draft guideline on setting health based exposure limits. The primary purpose of this guideline was to advocate the assessment of pharmacological and toxicological data of individual active substances, which would allow establishment of safe threshold levels as mentioned in the GMP guideline. Around the same time, the EU came up with proposed amended text for managing the concern of cross-contamination in chapters 3 and 5 of GMPs.6

There are cGMP guidelines from other regulatory bodies such as FDA and others for Japan, Switzerland, India and China but they do not address the issue of occupational health hazards.

FDA also recommends risk based assessments in this field. However, the guidelines issued by the organization only deals with cross contamination issues associated with the production and not on worker protection.
Manufacturing HPAPI’s: Captive and Contract

Manufacturing HPAPI is a complex process, and involves manufacturing and processing in clean room operations with containment facilities. In most instances, special safety considerations for employee protection and facility design are required when dealing with highly potent APIs. These processes are generally carried out at negative pressure to prevent materials from entering the environment, with workers wearing full protective gear. This differs from the containment requirements at manufacturing units of traditional APIs.

HPAPI manufacturing requires significant investments (in millions of dollars) over and above that of conventional API manufacturing. These include appropriately designed facilities, with the necessary engineering and containment controls in place to handle potent compounds, as well as requiring highly trained and experienced staff to ensure safe and contained operations.

Innovator firms have developed strategies that suit their needs best. Larger pharmaceutical firms, that have several clinical programs ongoing in high potents, may choose to invest in captive capacity to address their needs. Mid-size and smaller firms on the other hand have focused on utilizing Contract Development and Manufacturing Organizations (CDMO’s) and Contract Manufacturing Organizations (CMO’s) to drive their programs forward. Lack of an in-house manufacturing facility and absence of internal expertise are the primary drivers that encourage these firms to outsource to (CDMOs). Irrespective, we expect all innovators to eventually utilize CDMO’s/CMO’s to fulfill some aspect of their HPAPI needs due to the flexibility, and cost efficiency that these providers offer.

Furthermore, CDMOs/CMOs providing contract HPAPI manufacturing services must be prepared to adopt, improve, and/or implement new protocols, equipment, training, and technologies to meet the ever-rising bar for risk reduction and regulatory compliance in HPAPI manufacturing. Continuous improvement is essential to sustaining safe operations, mitigating risk, and attracting client opportunities.

CDMOs come in different shapes and sizes with respect to the services they offer, from integrated providers that offer a suite of services, to those with expertise focused exclusively in a single area. For example, some CDMO’s can offer both HPAPI and also the ability to formulate the drug product at scale. Other CDMO’s prefer to build a deeper vertical around a single offering- for example, the ability to go to significantly low OEL levels. The industry has also witnessed multiple strategic collaborations between client firms and CMOs wherein a few chosen/preferred suppliers service most of the development and manufacturing requirements of the client.

Chart 2- HPAPI Contract Manufacturing Market (USD Billion) Forecast

Source: 2014 - 2024 HPAPIs and Manufacturing Market report – Roots Analysis
With HPAPI manufacture, there are certain key factors that innovators need to consider as they evaluate the build vs outsource decision.

1. Large capital investment.
2. Absence of an official guidance on safe handling of highly potent substances by pharmaceutical regulatory bodies.
3. Stringent need for specialized equipment and facility design with containment controls.
4. High investment required prior to NDA approval – coupled with the difficulty to predict commercial success.
5. OEL/Toxicity not confirmed until very late in development, it is a late phase decision.
6. Assumption of highest level of containment in early clinical development due to absence of data.

There are the preferred features for CMOs having HPAPI capabilities:

1. Exemplary track record of safety and regulatory compliance.
2. Robust Environment, Health & Safety (EH&S) practices.
3. Ability to provide both development & manufacturing services to avoid tech transfers.
4. Proper engineering controls and cleaning procedures to prevent cross-contamination.

Many life science firms developing potent small-molecule drugs prefer to use a HPAPI manufacturer in the U.S. or Europe that has a sustained and exemplary track record for safety, regulatory compliance, and a successful audit history when working with HPAPIs. The ability to support both the development and commercial manufacture of highly potent compounds in order to avoid any need for process transfers is also often preferred. The demanding nature of HPAPI manufacturing requires careful scrutiny of the potential CMO/CDMO partner’s chemical hygiene and environmental, health, and safety (EH&S) programs as well as an understanding of their commitment to HPAPI manufacturing, and continuous improvement. When it comes to HPAPI manufacturing, there is no middle ground – it is “all in” or nothing.

**HPAPI deals and investments:**

An expanding list of contract businesses are strengthening their offering by investing in or acquiring high potent drug substance/drug product capabilities.

Strategy is a combination of either

(a) Entering/expanding HPAPI footprint (higher potency, getting into Hormones etc., expanding capacity etc.)
(b) Adding capabilities to become more integrated (drug product addition for an API firm and vice versa)

Some recent activities are summarized below.
### Table 3: Recent HPAPI Investments

<table>
<thead>
<tr>
<th>Companies</th>
<th>Deals/Investment</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fermion</td>
<td>Plans to invest $33M to expand its API facility in Hanko, Finland to build its HPAPI business. Will increase reactor capacity to around 400m3 and introduce isolators and containment technologies.</td>
<td>2016</td>
</tr>
<tr>
<td>Aesica</td>
<td>Added capabilities to conduct formulation development work on highly potent active pharmaceutical ingredients (APIs) and controlled drugs</td>
<td>2016</td>
</tr>
<tr>
<td>Cerbios</td>
<td>Opened a new R&amp;D center for high-potency active pharmaceutical ingredients (HPAPIs)</td>
<td>2016</td>
</tr>
<tr>
<td>Corden Pharma</td>
<td>Completed expansion of development capabilities for mid-scale (up to 20 kg) contained capacity of highly potent and oncology oral dosage forms</td>
<td>2016</td>
</tr>
<tr>
<td>Patheon &amp; IRIX</td>
<td>Patheon’s acquisition of IRIX Pharmaceuticals in March 2015, providing expanded HPAPI capacity for late-phase development customers</td>
<td>2015</td>
</tr>
<tr>
<td>Johnson Matthey</td>
<td>Completed and commissioned new high containment facilities for potent product manufacture at its Edinburgh, UK site (Macfarlan Smith)</td>
<td>2015</td>
</tr>
<tr>
<td>Regis Technologies</td>
<td>Opened a new suite for manufacturing highly potent APIs</td>
<td>2015</td>
</tr>
<tr>
<td>Hovione</td>
<td>Installed commercial spray-dryer specifically designed to handle potent drug substances (APIs) at NJ facility</td>
<td>2015</td>
</tr>
<tr>
<td>Catalent</td>
<td>Expanded its potent handling and manufacturing capabilities at its facility in Somerset, New Jersey</td>
<td>2015</td>
</tr>
<tr>
<td>Carbogen Amcis</td>
<td>Agreed to take over the operations of a high-containment facility located in Vionnaz, Switzerland, previously managed by Bachem. Plans to introduce additional capability for highly potent drugs at its site in Neuland (Hunzenschwil), Switzerland</td>
<td>2014</td>
</tr>
<tr>
<td>Wuxi PharmaTech</td>
<td>Invested in new HPAPI facility in Shanghai</td>
<td>2014</td>
</tr>
<tr>
<td>Novasep</td>
<td>Completed $5.5M investment to expand its highly potent API manufacturing capabilities at its facility in Le Mans, France</td>
<td>2014</td>
</tr>
</tbody>
</table>

These activities indicate that HPAPI facilities are predominantly located in the West, mainly in the US followed by countries like UK, Germany, Switzerland, Italy etc. This is due to the fact that most clients prefer to outsource HPAPIs to suppliers in the West due to perceived superior quality and safety track records. Proximity to the CMO is an additional factor while deciding to outsource HPAPI since they will seek better control over development and manufacturing activities.
Conclusion:

HPAPI manufacturing is a capital intensive process that requires technical expertise and state of the art manufacturing facilities. Although there are guidelines for segregation of high potent products, it is vital that there exist an industry wide approved framework for HPAPI classification. This eliminates ambiguity related to compound potency, especially when a pharmaceutical company is planning to outsource the manufacture of HPAPIs to a CMO. Additionally, regulatory bodies need to address the issue of occupational health hazards and worker protection for the manufacture of high potent APIs.

High potency needs are expected to grow due to growth in oncology and the need for selective targeted therapies. Despite innovator’s captive capacity, outsourcing in this segment is expected to grow at close to double digits driven by mid-size, small-size, and virtual firms. CDMO partners with a track record of HPAPI development and manufacture, a clean safety and compliance record, proximity to innovators and a long term commitment to service business can expect to benefit from the growing market.

At Piramal, we are focused on building an integrated platform with leadership capabilities in each element. With our state-of-the-art ADC facilities, our fill finish/aseptic capabilities, we are now focused on adding HPAPI manufacturing capabilities, to offer clients an integrated solution that includes both drug substance and drug product. We expect to continue to invest in those areas that address our clients’ future needs.

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2, 6. 2014 - 2024 HPAPIs and Cytotoxic drugs Manufacturing Market – Roots Analysis report
3. DCAT Value Chain Insights (VCI) Newsletter
5. Developments in high potency API manufacturing – Article by Thomson Reuters
6. American Pharmaceutical Review article - Growing Demand for Small-Molecule CDMO Services

Q&A

Q) Do we envisage much of this work being outsourced to Asia in the next 5-years?
For now the preference is clearly to work in the West (for HPAPI). We expect medium/virtual firms to continue to principally utilize the Western CMO’s in the immediate future.

Q) what percentage of outsourced work do they feel will come from big pharma verses mid-size, small-size, and virtual firms.?
Some of the big pharmas do have some captive capacity, which they could utilize as needed. The mid size to virtual firms on the other hand outsource almost all their development and commercial requirements.

Q) Is there any particular reason/trend there are more oncology products being made by smaller companies now? (will CDMOs invest in risk sharing)
As CDMO’s evolve several models are coming into play:
- Some CDMO’s have investment arms where they take equity position in a firm or in a venture fund; Some CDMO’s have their own venture fund. In these cases, the portfolio firms tend to work with the CDMO for their outsourcing needs
- For late stage development projects, risk sharing approaches may be utilized based on need of the client and the comfort level of the CDMO. In exchange of exclusivity of supply, or a committed larger share of the commercial volume, CDMO’s may consider risk share at late stage development
• For early development, some CDMO’s may consider receiving lower compensation upfront, in lieu of future payments tied to a fund raising event.

Q) What is Piramal’s perspective on the growth potential for non-oncology HPAPI products (things like opiates etc)
About 80% of the controlled substances market is generic with the patented products mainly in the ever growing ADHD segment. Due to higher scrutiny and internal controls required to manufacture controlled substances, not many CMOs are entering this segment. It is a highly regulated and closed market growing at a CAGR of 6%, dominated by players who have been manufacturing controlled substances historically. The overall market size of DEA Schedule II APIs was ~ $ 500-600 M in 2015.

Q) Is there a drive amongst CDMOs to move from just HPAPI producers into finished product production – is this what the market requires. (the article alludes to this)
Integration is a key sell for CDMO’s but only if it is done right. Clients will not just go a CDMO that has integrated capabilities- they will select an integrated offering only if the CDMO can show case excellence in each of those components. If the CDMO can demonstrate that, the client management of the project becomes seamless. Nevertheless, clients typically would like to have more than one source to ensure security of supply.

Q) Do they have a feel for how much growth is made up of synthetic versus biological HPAPIs- how do they see this evolving
On the basis of synthesis route, the HPAPIs can be synthetic or biotech. While synthetic HPAPIs hold a dominating share of 85 percent in the global market, the use of biotech HPAPIs is gradually increasing as there is a focus on research and development work on the use of biological molecules for many therapies.

Q) What are the medium term growth prospects for generic HPAPIs – or is demand coming from patented products ?
At the moment an estimated 80% of HPAPIs in the market are still under patent.

Q) Do they envisage new formulation technologies being needed for some of these compounds – what are the technology challenges that will need to be addressed in medium term (e.g. single use facilities)
The current formulation technologies available in the market can handle these high potency compounds. Most of them will be in the Sterile Injectable Dose form filled in either Vials or Unit Doses like Pre-Filled Syringes. On the oral solids front, there are only a handful of manufacturers who can handle high or very highly potent drugs as the safety standards required to handle the processes of manufacturing of tablets or capsules are extremely high. Piramal’s site in Lexington, US, dedicated to manufacturing of Sterile Injectable Dose Forms, can handle highly potent oncology products and nicely compliments Piramal’s API strategy going in that direction. Apart from the Oncology products, the site can handle other drug classes like the Hormones, Steroids, etc. Piramal’s site in Morpeth, UK can handle Oral Solids products in the hormonal category, which needs containment to handle.

Q) What are the trends looking ahead, what will Piramal respond with?
• Globally the API market is growing at mid to high single digits. Within this sector, certain segments- for example, HPAPI- are growing faster per estimates.
• At Piramal, our API facilities in North America, UK, and India, we have seen a significant uptick in demand and utilization. And the future pipeline for all sites looks promising.
• To meet demand, we have invested some capital, and have also undertaken a focused effort on capacity debottlenecking/improving operational efficiency to meet demand.
• Piramal management is now evaluating the next steps we need to take to address the future demands of our API customers.
• The definition of what is ‘core’ and hence held ‘captive’ by the innovator is constantly evolving. As you know, synthetic chemistry and routine biology were considered ‘core’ 10 years ago. Now they are routinely outsourced. Similarly, it is fair to expect that as API suppliers invest in infrastructure and expertise, innovator firms that have retained ‘internal, captive capacity’ will take a hard look at their future strategy: the flexibility, efficiency, and cost benefits that CMO’s provide can be significant. There have been several news releases on innovator firms consolidating their manufacturing operations and partnering with CMO’s instead.
• We believe that the market is growing and firms with (a) good quality and compliance records (b) a strong balance sheet and a demonstrated commitment to invest and meet longer term client needs (c) a strong focus on customer centricity will continue to do well.
A Global Chinese perspective on outsourcing and growth

Q&A

Q 1) Are you looking to bring continuous processing at the new site in Shanghai – we note that Minzhang is formally of Vertex Pharma…. If yes, how do you see continuous processing changing pharma supply over the next 5 or 10 years

WuXi’s STA has established a comprehensive continuous processing platform in Shanghai for producing small molecule APIs from laboratory to commercial scale under cGMP environment. This platform was built through the strategic partnership with one of our major pharma clients.

The technology for continuous manufacturing of bulk chemicals and APIs has been relatively established. In the past, the prevailing thoughts by pharmaceutical companies are only adopting the continuous manufacturing technology when there is a very compelling justification to do so, primarily due to the lack of material regulatory guidelines for approving a continued process. Companies are even more reluctant to change their API manufacturing for the existing products since they have to reconfirm the drug performance due to the change in API manufacturing process. However, today the environment is changing. We see that more and more clients are willing to embrace continuous processing concepts starting from the very early development stage – and whenever it makes sense; the goal is to adopt continuous processing of certain steps of chemical reactions from the start. Such collaboration requires higher degree of commitment, trust from our customers and closer communication between the two parties. We’ve seen an increasing demand of our continuous processing platform and I expect this trend to continue in the next few years.

Q 2) What do you feel the API market will look like in 5-years time? (both in terms of clinical development and commercial scale)

The custom API manufacturing sector has been and will continue to grow rapidly in the next 5 years as a result of the increased innovation in the life science sector. Our customers are paying more attention to data integrity issues after a higher number of warning letters issued to drug manufactures by FDA. We see that business is shifting more and more to companies who are free of regulatory issues and can offer a wide range of solutions to customers. On the other hand, companies who are less qualified experience overcapacity.

A number of prominent CMOs are currently investing in plant expansions including STA. In 2016, STA opened a 39-acre integrated process R&D and manufacturing site in Changzhou, where we plan to eventually run 9 large plants. Many of the programs that we’re running are entering process validation stage, requiring us to add production capacity to support our customers’ product portfolios.

Current global API market is highly fragmented. There are 1600 API producers in China and India alone (source: Thomas Reuters
The appearance of new product classes such as ADCs, oligonucleotides and other complex combination products post the new challenges and opportunities to the CDMO industry. It’s not good enough to be an expert in small molecule or large molecule alone any more, global leading CDMO players shall be equipped with an integrated technology platform and talents pool to master more and more complex pharmaceutical products.

Q 5) What should CROs and CDMOs be investing in now to meet changes in the market?

New technologies - See answers to Q4

Bridging the gap – Large drug manufacturers have been routinely acquiring small biotech firms as part of their innovation strategy. On the other hand, small biotech firms which may only focus in one therapeutic area have also been actively seeking to acquire drug candidates from large pharma. Good CDMOs shall understand the different requirements from these two very different customer segments and be able to seamlessly bridge the need between large pharma and small biotech companies. With shorter drug development timeline and higher pressure to optimize the drug cost, good CDMO partners shall not only cover the actual development phase, but also support the entire process as well, from approval and subsequent commercial manufacturing.

Sustainability: Global leading CDMO players must set the industry model for sustainability as well – that means being innovative in reducing waste generated, applying more green solvents and chemicals, investing in biocatalysis and continuous processing technologies.

Q 6) WuXi (STA Pharma) is the standard-bearer for the Chinese industry, but do you feel other CMOs or MNCs will emerge from China over the next 5-years? Please comment.

Yes.

WuXi is proud to serve as a catalyst to stimulate the growth of China’s biomedical innovation ecosystem. Several key factors are the key drivers of China’s biomedical innovation: the Chinese government’s pro-innovation policies and investment, the strengths and scale of the country’s scientific talent pool including rapidly growing number of western trained professionals, and “mass entrepreneurship and innovation” as first proposed by Premier Li Keqiang in 2014.

It has been well recognized that the biomedical innovation in China can only be sustainable by integrating itself with the international community, and adopting global quality standards and state-of-the-art technologies.

A number of emerging China based biotech companies such as Hutchinson Medi Pharma, Hua Medicine and Nasdaq-listed BeiGene, just to name a few, will start to commercialize their innovations in China and in global markets over the next 2-5 years.
In the CMO world, WuXi is among a handful of emerging reputable China based CMOs, some are focused on branded drugs and some are focused on generic drugs. These companies will continue to evolve and rise in the global stage, while playing a significant role to support the Chinese biomedical innovation.

Q 7) What major threats or difficulties do you foresee for the industry over the next 2-5-years?

Speed and Flexibility: Today, new drug molecules are becoming more and more complex while development timelines are becoming shorter and shorter, emerging biotechs who heavily focus on addressing a specific therapeutic area are rising in every corner of the world. One may assume that the production schedule with the CMO can be modified, shifted, decreased or increased whereas the reality of the experience could be the total opposite. On the other hand partnering with a CDMO who can provide both “upstream” development services and “downstream” manufacturing services are becoming more and more essential.

Maintain global regulatory compliance: A growing list of regulatory requirements and expectations from agencies in different parts of the world are imposing new challenges to our industry. We hear more stories about companies failing US FDA inspections than ever before, making global CMO business shifting toward those highly qualified suppliers.

Higher pricing pressure: As governments and other payers are imposing price controls and increasing their use of generics and biosimilars to contain drug costs, the supply chain managers in pharma companies are facing higher pressures to control the COGS of their products.

Q 8) How do you foresee the regulatory environment changing in the USA, EU and China over the next 5-years?

I expect a more harmonized international regulatory environment over the next 5 years. Regulations and guidelines from China FDA will be more aligned with those from the USA and EU.

Q 9) Prospects for Chinese R&D industry and how a company like STA with sites in both the USA and China fit into this picture?

The USA and China are the world’s top two largest pharmaceutical consumer markets, as well as the hubs of biomedical innovations. STA’s newest facility in San Diego brings our comprehensive R&D services closer to our North American customers and partners. Having the operations in both the USA and China positions companies like STA as a unique bridge, which will enable companies outside China to bring their products to China, or Chinese biomedical research companies to bring their products to global markets faster and more efficiently.

Q 10) How far away is the industry from patented drugs emerging from China?

It won’t be long before we see patented drugs emerging from China for global patients. Icacinib from Zhejiang Beta Pharma, a new patented class 1 anti-cancer drug, has been made available to Chinese patients. Meanwhile a handful of China based biotech companies such as Hutchinson and BeiGene are running mid- to late-stage global clinical trials.
Realizing the Promise of Biosimilars in 2020

Introduction

The ability of biologics to target specific proteins makes them more effective treatments than small molecule therapies for a variety of medical illnesses and conditions. Biologic therapies such as insulin, erythropoietin and growth hormones have played an invaluable role in treating serious illnesses such as diabetes, anemia and renal diseases. More complex biologics like monoclonal antibodies (MAbs), cytokines and therapeutic vaccines, are now transforming the standard of treatment for cancer, autoimmune disorders and other chronic diseases. It is expected that by 2020 new biologic treatment options will be available for conditions like severe asthma, chronic eczema, atopic dermatitis, and familial hypercholesterolemia across developed markets.

Cancer immunotherapies, which harness the power of the immune system to target and fight malignant tumors, are expected to revolutionize cancer treatment by sparing patients toxic effects of chemotherapy.

Biologics Landscape: 2020

The global biologic drug market will top USD 390 billion by 2020, accounting for nearly a third of the global pharmaceutical market by value. The increasing penetration of biologics will in turn lead to higher demand for biosimilars, or follow-on versions of original biologics, in the global pharmaceutical market. Since the first biosimilar approval in the European Union (EU) in 2006, there are now a few hundred biosimilars approved globally. By 2020, biosimilars have the potential to enter markets for a number of key biologics that have current sales of more than USD 50 billion annually. With the approval of the first biosimilar in the US in 2015 and the expected patent expiration of 12 biologics by 2020, estimates suggest that the global biosimilars market could reach USD 25-35 billion by 2020.
Access and Affordability

Globally, we are witnessing the rapid spread of a pandemic of non-communicable diseases (NCDs). It is estimated that 38 million people succumb to NCDs like cancer, diabetes, cardiovascular diseases and chronic respiratory disease annually. Today, cancer is the cause of ‘one in seven’ deaths worldwide\(^5\), while diabetes now affects nearly ‘one in 11’ adults globally\(^6\).

Biologics like insulins and monoclonal antibodies have emerged as a class of highly effective transformational life-saving drugs targeted at chronic diseases like diabetes and cancer. The high cost of biologic therapies, however, pushes them out of the reach of many patients, especially those in low- and middle-income countries (LMICs) like India where drug regimens can cost several months’ wages making the treatment of chronic disease simply unaffordable.

This large unmet need can only be addressed through high quality, affordable biosimilars that provide cost-effective alternatives to expensive reference biologics. Biosimilars offer patients, physicians and payers a wider option of treatment choices as they compete with original biologic medicines across a growing range of therapy areas.

The imperative to improve health care access and reduce the cost of care present growth opportunities for biosimilars manufacturers in both emerging and developed markets. According to investment research organization Sanford C. Bernstein & Co, 70 programs are now in clinical trial stage or later, with 11 approvals in EU, three in US and 44 programs in pivotal trials\(^7\). This is likely to result in a highly competitive marketplace over the next five years. The cumulative potential savings to health systems in the five major EU markets and the US, as a result of the use of biosimilars, could exceed EUR50 billion in aggregate over the next five years and reach as much as EUR100 billion\(^8\).

The experience of the European medical community has been positive in the 10 years since the approval of the first biosimilar in EU. The use of erythropoietin, granulocyte-colony stimulating factors and human growth hormone have all increased in this period driven by the availability of biosimilars as well as factors such as expanded indications\(^9\).

Going forward, insulins and monoclonal antibodies are also expected to experience similar uptake as biosimilar versions become widely available. Infliximab, the first biosimilar MAb to be approved by the EMA in 2013, was offered to patients in Europe at a deep discount of nearly two-thirds the price of the innovator product. Since then, Norway, Denmark and Finland have achieved a near total switch to biosimilar versions of Infliximab\(^12\).

Biosimilars and Developed Markets

Developed markets such as the US, EU and Japan, offer strong growth opportunities for biosimilars manufacturers. As governments in developed markets like EU and Japan strive to rationalize healthcare spends, they are encouraging the entry of high quality yet affordable biosimilars through dedicated regulatory pathways and stringent, abbreviated approval processes.

Biocon, through its partner FUJIFILM Pharma, recently launched Insulin Glargine in Japan. This product is the first biosimilar from India and second biosimilar Glargine to be approved in Japan. Industry guidance on biosimilars was released by Japan’s Ministry for Health, Labour and Welfare (MHLW) back in 2009. Nine biosimilars have been approved in Japan between 2009 and 2016, according to Generics and Biosimilars Initiative (GaBI).

In fact, developed markets continue to have the highest number of biosimilar molecules in development – estimated at 29 in Europe, 19 in the US and seven in Japan\(^8\).
Biosimilars and Emerging Markets

High out-of-pocket costs for medicines in emerging markets means physicians are more open to prescribe low-cost alternative therapies. In India, a Deloitte survey found that physicians were willing to prescribe a first-line critical therapy if it was offered at a 60-70% discount. In China, getting on the essential drugs list means mandatory usage by many hospitals; however, it also comes with price cuts of 25-50%. This offers a huge potential opportunity for biosimilar manufacturers committed to develop high quality, yet affordable, world-class biosimilars. Emerging markets, such as the BRICS (Brazil, Russia, India, China and South Africa) and MIST (Mexico, Indonesia, South Korea and Turkey) provide the best future opportunity for manufacturers of biosimilars.

India saw the launch of its first biosimilar way back in 2003, when Dr Reddy’s Laboratories launched biosimilar Rituximab at half the price of the innovator product that is used to treat certain kinds of cancer and autoimmune diseases such as rheumatoid arthritis. A year later, Biocon introduced an affordable recombinant human insulin product developed through an innovative proprietary technology, which enhanced patient access to insulin across India, resulting in improved diabetes management. Since 2008, the Indian biosimilar industry has been growing at a compounded annual growth rate of 30%.

There are around 25 Indian companies operating in the biosimilar space, marketing close to 50 products in the Indian market. Today, Indian patients have access to some of the biosimilars like insulins, insulin analogs, Filgrastim, Trastuzumab, Rituximab, Adalimumab etc.

This early experience with developing biosimilars is paving the way for Indian players to capitalize on the unfolding global opportunity. While, Biocon has its core focus on biologics and biosimilars there are other Indian pharma companies who have expanded their pipeline to include biosimilars, as top-selling biologics go off patent worldwide. Biocon, in partnership with Mylan, is developing a high-value portfolio of six biosimilars for oncology and autoimmune indications - Trastuzumab, Pegfilgrastim, Adalimumab, Epioxalam, and three generic insulin analogs - Glargine, Lispro and Aspart. The two companies are well-positioned to be among the first wave of entrants to address the biosimilars opportunity globally. They recently moved a step closer to enabling affordable access to these life-saving drugs in developed markets after the European Medicines Agency (EMA) accepted for review the Marketing Authorization Applications (MAAs) for two of their biosimilars, Pegfilgrastim and Trastuzumab.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>2015 Sales* (US$ bn)</th>
<th>Biosimilar Development Pipeline@</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegfilgrastim</td>
<td>4.7</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biocon, Sandoz, Apotex, Coherus, Richter</td>
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<tr>
<td>Trastuzumab</td>
<td>6.8</td>
<td>Oncobiologics, Dr. Reddy’s/Genor</td>
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<tr>
<td>Insulin Glargine</td>
<td>7.1</td>
<td>Phase I</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>14.0</td>
<td>Epirus, Oncobiologics, Dr. Reddy’s</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>6.9</td>
<td>Celltrion</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>1.0</td>
<td>Biocon, Pfizer</td>
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<td>Etaencept</td>
<td>8.7</td>
<td>Biocon, Celltrion</td>
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<tr>
<td>Insulin Aspart</td>
<td>4.7</td>
<td>Biocon</td>
</tr>
<tr>
<td>Insulin Lispro</td>
<td>2.8</td>
<td>Biocon</td>
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<tr>
<td>RH-Insulin</td>
<td>3.1</td>
<td>Biocon - US</td>
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*Reported sales of Innovator Companies, conversion from reported currency into USD.
@Approved and launched in Japan.
**Approved in Japan, EU and US. Launched in Japan & EU.
**Launched in EU & US.
*Biosimilar Development Pipeline details may not be exhaustive; Source: Company disclosures, various reports.
India, which first issued biosimilar guidelines in 2012, recently announced updated draft guidelines for biosimilars. The 2016 Guidelines for Similar Biologics incorporates high-end analytics and clinical science to abbreviate the development pathway. However, whilst the timelines may be compressed for Marketing Authorization, the emphasis is on a science-led regulatory pathway that delivers safe and efficacious biosimilars with comparable clinical and immunogenic profiles. Additionally, there is a post-marketing pharmacovigilance plan to monitor safety, efficacy and immunogenicity in a real use setting which truly differentiates these guidelines.

In addition to India, many other emerging market countries have either defined biosimilar approval pathways or are finalizing guidelines. South Korea has published biosimilars guidance back in 2009, while China unveiled them in 2015. In Latin America, several regulatory authorities such as ANVISA in Brazil, COFEPRIS in Mexico or ANMAT in Argentina, have developed their own biosimilar regulatory abbreviated pathways.

**Evolution of Global Biosimilar Regulations**

Global regulations and guidelines need to evolve if biosimilars are to make as much of an impact as small molecule generics have in the past 25 years.

‘Interchangeability’ is an important issue globally that regulators will need to address if patients are to be offered the choice of taking the original biologic drug or substitute a biosimilar drug, just as they currently do with generic versions of chemically synthesized small molecule drugs. US biosimilar regulations have not addressed the issue, while in Europe there are country-specific rules on biosimilar interchangeability.

The lack of clear guidelines on interchangeability with reference biologics is likely to be a cause for concern among physicians until they gain confidence with the usage, experience and outcomes of biosimilars. However, payers are influencing biosimilar decisions in the US even as the government thrashes out guidelines for interchangeability. Leading US pharmacy benefit management (PBM) company, CVS Health, recently left out Sanofi’s blockbuster Insulin Glargine product Lantus from its 2017 formulary, replacing it with Eli Lilly and Boehringer Ingelheim’s biosimilar version of Lantus. Such exclusive arrangements could mean deemed interchangeability for the patient subset covered by the PBM.

The naming convention for biosimilars is an issue that needs to be sorted out to ensure that it does not complicate their uptake. The US FDA has proposed a four-letter suffix to distinguish between a biosimilar and its reference product, similar to the ‘biological qualifier’ proposed by the WHO. The first approved biosimilar in the US filgrastim-sndz (Zarxio) had a common United States Adopted Name (USAN) and a suffix (sndz) that reflected the manufacturer (Sandoz). But the second FDA approved biosimilar, infliximab-dyyb (Inflectra), manufactured by Celltrion, was named using a common USAN with an apparently random suffix devoid of meaning. However, the requirement to add a suffix at the end of a biosimilar’s non-proprietary name could lead to confusion among prescribers and patients.

Biosimilars uptake could also see a boost as more regulators back data extrapolation, which will allow a biosimilar to be approved for multiple indications without undergoing clinical testing in those conditions as long as the reference product itself was approved in those conditions.

**Stakeholder Education: Need of the Hour**

Concerns among health care providers and patients over biosimilars acceptance can only be addressed through stakeholder education. Physicians, patients and payers require balanced and adequate education on the role that biosimilar medicines can play. Physicians need to be provided data and evidence that biosimilar medicines offer a safe and efficacious alternative to original biologics. Moreover, they also need to be helped to understand the broader clinical and health system benefits of prescribing biosimilar products. Patients need to be reassured that biosimilar products are safe and efficacious. Payers need to be educated about the potential offered by biosimilar
medicines in ensuring affordable healthcare. Educating these stakeholders about their safety and efficacy will likely require cultivating knowledgeable market and opinion leaders. Biosimilar manufacturers have a key role to play in building trust with these key stakeholders.

Biocon’s strategy of combining products, patients and physician support programs have enabled it to achieve market leadership in the therapeutic areas of diabetology, oncology, immunology and critical care in India. The company is now extending its physician education programs to address the credibility hurdle that needs to be crossed in the minds of biosimilars prescribers.

Biocon organizes an annual breast cancer summit ‘Converge’, which is attended by oncologists from India, Nepal, Sri Lanka and the Gulf countries, where Key Opinion Leaders share clinical data gathered in a real-world setting in order to bust certain myths associated with the use of biosimilars.

To enhance scientific capability and credibility in the immuno-oncology area, Biocon recently organized an Immuno-Oncology symposium with eminent scientists such as Prof. Vijay Kuchroo (Harvard), Prof. Gordon Freeman (Harvard) and Prof. Varsha Gandhi (MD Anderson Cancer Center) as key speakers. This was followed by a round table discussion where Indian Key Opinion Leaders (KOLs) in the field presented their perspectives.

Conclusion

These are exciting times for the life sciences sector as it builds on its understanding of the disease at the cellular and genetic level to usher in new and differentiated therapies into the market. Furthermore, biomedical advances are likely to transform global health with early diagnosis and therapeutic intervention for chronic and killer diseases like autoimmune and cancer. The forthcoming generation of biosimilar products is going to provide affordable access to complex biologics with a promise to enhance the quality of patients’ lives.

Governments in major markets like the EU have recognized the potential financial benefit of biosimilars and are driving their uptake. Besides the developed markets like the US and EU, the developing world can also gain from easier accessibility to these cutting-edge treatments that will lead to better health outcomes in these geographies. It is hoped that in the coming years prudent policymaking will result in expansion of biosimilar volumes with governments providing patients with greater access to these drugs.

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Part 3.
The future - generics, big data and 3D formulations
3-D Printing: Next Step or Parallel Technique to Continuous Manufacturing?

Introduction

Unless you have been on an interplanetary voyage for the past decade or so, you should be aware of all the major changes in the production of pharmaceutical dosage forms and medical components. Many of the changes were inspired by the very Agencies that have been accused of blocking progress over the years. The USFDA, EMA, and ICH issued a series of guidances and Guidelines on Process Analytical Technologies (PAT), Quality by Design (QbD), Risk Management (RM), and Continuous Manufacturing (CM).

The USFDA, especially, has encouraged the on-line monitoring and control of processes, including “real-time release,” based on the data generated by the monitors controlling the process. Simply put, the Agencies (both FDA and EMA) are stating that a well-controlled and documented lot need not have after-production analyses run before releasing the product. Numerous (large) Pharma companies began applying PAT, successfully, but not always in large numbers. Unfortunately, the institutional inertia within a government-regulated industry has slowed the adoption of PAT and QbD as “the Gold Standard” for production.

Nonetheless, the spate of smaller, faster, and even sometimes, less expensive instruments developed for monitoring each step of the process line has enabled companies to enjoy the speed and cost-savings of PAT/QbD (for those who may not know the difference, PAT is the measure-control arm or the QbD program). Basically, it is a modern process: QbD-based, allowing “designed” variations in a product whilst raw materials vary. It needs the PAT portion of the program to implement the Design Space portion of a “designed” process.

With the process-monitoring/control experience and the newly-minted instrumentation (near-infrared, Raman, light-induced fluorescence, etc.), plant engineers and product development scientists were able to move to the next logical step: continuous processing (CM). Basically, CM consists of an apparatus where the (normally) discreet process units are attached and work in a unified manner, where the powders (API and excipients) enter one end of
the unit and finished product emerges from the other. Each step is monitored, controlled, and released by PAT tools.

Several products have been approved under New Drug Applications (NDAs), such as Vertex’s cystic fibrosis drug (Orkambi [lumacaftor/ivacaftor]) in July 2015. Also, several have been “retro-submitted” the processing of dosage forms under Amended New Drug Applications (ANDA’s), such as Janssen’s HIV-1 treatment Prezista (darunavir). The success of Janssen prompted Janet Woodcock (USFDA) to suggest CM is the future and batch processing might be well phased out over time.

The idea of CM was a giant leap in manufacturing efficiency for several reason. The immediate benefit was the ability to develop a dosage form (via Design of Experiments, or DoE) in a faster and more economical manner. How? Well, a “traditional” DoE is carried out on a full-sized batch size. That means, for example, that a DoE with 25-30 experimental batches might take weeks or months to accomplish. The reason is that data from a lab-level batch is seldom scalable to production levels. That means that many, many kilos of API and raw materials need to be blended into products that may or may not represent the final product and might have to be destroyed.

Using CM technology, an experimental batch might only be 2-3 kilos, greatly saving on time (might take 1-2 days, at most to run) and materials (especially when there is a limited amount of an experimental API available). When the Design Space is calculated, there is no “scale-up,” because the experimental batch size is the production batch size.

The process hardware takes up a fraction of the floor space of conventional units. The savings on “brick and mortar,” electricity, HVAC, and land, itself, are almost too good to be true. In addition, the traditional batch mode of production, counting analyses, storage, and transportation of the batch from blending to granulation to compressing to coating could mean a single batch can take weeks to complete.

With CM, the first tablets come off a CM rig within an hour of start-up. The batch size depends only on how long the unit is run. One, two, three million tablets? No problem. 100,000 tablets? Also no problem. So anything from clinical batches to major lots of a best seller take the same effort of set-up and cleaning.

What comes after CM?

The next great step would be in fabrication of specialty drugs and medical devices. Clearly, even a CM set-up cannot do unusual dosage forms of mechanical device. Something was needed and it came in the form of 3-D printing. While prototype units were around since the late 1990’s, the computer power and miniaturized components have only recently been available.

Loosely based on the technology used for document printing (desk-jets, LASER-jets), where droplet size and chemistry were controlled by a computer, the 3-D printers are step-wise systems. Figures 1-4 show how the layers of powder, then liquid, then powder, and so on, are laid down on a moving belt to generate a “dosage form.” But is it “allowed” by the Agency? Well…

“FDA has developed this draft guidance to provide FDA’s initial thinking on technical considerations specific to devices using additive manufacturing, the broad category of manufacturing encompassing 3-dimensional (3D) printing. Additive manufacturing (AM) is a process that builds an object by iteratively building 2-dimensional (2D) layers and joining each to the layer below, allowing device manufacturers to rapidly alter designs without the need for retooling and to create complex devices built as a single piece. Rapid technological advancements and increased availability of AM fabrication equipment are encouraging increased investment in the technology and its increased use in medical devices. The purpose of this guidance is to outline technical considerations associated with AM processes, and recommendations for testing and characterization for devices that include at least one AM fabrication step.

This draft guidance is a leap-frog guidance; leap frog guidelines are intended to serve as a mechanism by
which the Agency can share initial thoughts regarding emerging technologies that are likely to be of public health importance early in product development. This leap-frog guidance represents the Agency’s initial thinking, and our recommendations may change as more information becomes available. The Agency encourages manufacturers to engage with the Center for Devices and Radiological Health (CDRH) and/or CBER through the Pre-Submission process to obtain more detailed feedback for additively manufactured medical devices.”

Does that answer that question? So, what types of “things” can be done with 3-D printing?

1. Personalizing dosage forms
3D printing adds a new dimension to personalized medicine. Simply stated the idea is to produce personalized 3D printed oral tablets. Personalized, 3D-printed medications could be helpful for patients who respond to the same drugs in different ways. A doctor or a pharmacist would be able to consider a patient’s individual information (age, race, and gender), producing an optimal medication dose, in lieu of stock, commercial medicines. 3D printing should allow tablets to be printed in complex layers, using a combination of drugs to treat multiple ailments at once. The concept is to give the full spectrum of what a patient needs in a single dose. This is critical for the elderly (who could confuse multiple tablets each day), people with trouble swallowing tablets, and very young patients, who might also have trouble swallowing many drugs.

2. Unique dosage forms
3D printing may be used to create unique dosage forms. The idea would be to use inkjet-based 3D printing technology to create limitless dosage forms. This would challenge conventional drug fabrication. The process to create novel dosage forms has already been tested for many drugs, making “osmotic pumps,” multilayered doses, where each layer dispenses API at a different rate, and other such novel technologies.

3. More complex drug release profiles
Drug release profiles explain how a drug is broken down when taken by the patient. 3-D printing makes it possible to construct personalized drugs that facilitate targeted and controlled drug release by printing a binder onto a matrix powder bed in layers. This barrier between the APIs, allows researchers to study the variations of the release more closely. As drug manufacturers understand the opportunities in 3-D which will allow them to make more effective drugs, there will likely be more research and investment into this area, making future equipment better and better.

4. Printing living tissue
While not currently possible on a large scale yet, it is projected that the technology is less than 20 years away from a fully functioning 3-D printed heart. For now, 3-D is challenged by the intricate nature of vascular networks. According to the director of the Wake Forest Institute for Regenerative Medicine, each organ presents a different level of complexity. So while some tissue would be much easier to print (e.g., flat structures, like human skin), the most difficult and ultimately most important areas in organ printing are the heart, liver and kidneys.

3-D printing is being applied in areas of healthcare such as dental, medical, and implants. The materials used for these vary. Dental implants mostly use metals and ceramics to print dental crowns, the medical industry has an array of bio-materials. One estimate has the 3DP in healthcare market with a revenue of $284.7 million as of 2014, and potential to grow at a CAGR of 19.1% over the next 6 years.
Comments

The price of 3-D printers in healthcare should become lower due to increased demand, and government subsidies (research grants). The materials for 3DP healthcare are plastics, metals, ceramics, donor cells, bone cement, biomaterials, etc. Metal powders and biomaterials are expensive and numerous biomaterials are being researched and expected to be important in the 3DP in healthcare. The high growth rate in healthcare is because of the increased adaptation of 3DP technologies by their producers. The market will be driven by the increasing demand for patient-specific tailored products in orthopedics and maxillofacial surgery. Advances in tissue engineering for 3D bio-printing is gaining importance (the tissues generated by 3-D bio-printing should be available in the near future. For the foreseeable future, however, high costs and regulatory barriers are likely to hinder the market growth. North America is the currently the largest consumer of 3DP in healthcare industry, closely followed by Europe. Factors affecting the growth of the market include technology innovation, efficiency and flexibility of printers and availability of good quality materials.

While mass production of dosage forms will probably remain the mainstay of the industry, with CM taking more and more of the workspace, 3D printing will also expand, due to the growth of personalized medicines and medical devices. A synergy between 3D and CM is also a potential, where formulations are developed on CM units and produced on 3D units, as needed.

The limits of 3D printing are merely the needs and imagination of the researchers modelling the products of 3DP.

Trends in 3D Printing

As interesting as the application above might be, there are some specific near-term as well as long-term products that the technology would be perfect as the preferred technology.

1. Orphan Drugs. The actual reason that these older, less volume-driven products are “orphans” is that the effort to formulate and produce a product that a. is (most likely) already off patent and b. has too a small market to justify the production costs. This is a case for “on-demand” production that would, in a best case scenario, only involve cleaning two spray heads (one powder, one liquid) and the moving belt. This would be a case of minimizing the cost of goods sold (COGS), while keeping the retail costs within the reach of most patients. (A “win-win?”)

2. Tester Tablets. The USP (United States Pharmacopoeia) sells tablets to companies that do release testing of solid dosage forms. The tablets are used to “calibrate” their dissolution testers for both immediate release and continuous release products. The current USP tablets are produced once every few years, under what can nicely be called “older” manufacturing conditions. The batch-to-batch differences are often enough to force Pharma companies to make major changes in their procedures. If these tablets were made in smaller lots, as needed, instead of every several years, there could be a consistency that would be welcome to the industry. 3D printing would assure a higher degree of reproducibility than making them in the “traditional,” batch-wise manner.

3. Special Cases. As far back as 1999, the company (for which I was working) was experimenting with 3DP for controlled substances. Aside from the danger of too rapid release when taken as instructed, there was the abuse potential. A 12 or 24-hour dose, chewed or ground and extracted could easily be abused. One approach was to encapsulate Naloxone (sold under the brand name Narcan® among others, a medication used to block the effects of opioids) and press it with the “normal” oxycodone granulation, making (theoretically) abuse-proof tablets.

Unfortunately, pressing tablets, even gently, can cause some of the Naloxone nonpareils to break, potentially causing the (legitimate) patient to undergo “withdrawal” symptoms. The gentler nature of 3DP could well overcome the potential dangers of including an “antidote” to the drug being administered (legally).
Polymer being sprayed as a part for a medical device. Unlike linear printers used in Pharma, device printers have freedom along the X-Y axes, allowing almost any shape to be constructed.

Figure 1. A fine mist of powder (excipient or API or mixture) is sprayed on the moving belt.

Figure 2. Liquid is then dropped onto sprayed powder in a controlled manner.

Figure 3. This liquid selectively binds the particles together in a layer that is still porous.

Figure 4. The process is repeated a pre-determined number of times to produce the dosage form of specified potency (weight).

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Generic medicines, the opportunity for growth

Introduction

For several years now the generic medicines market place has grown at a faster rate than the total pharmaceutical market. This growth was driven in recent history by what we all know as the ‘patent cliff’, whereby many blockbuster molecules lost protection, generating a huge opportunity for the generic medicine industry. This peaked in 2012 and since then there have been fewer major patent expiries with several of them being respiratory products associated with a device and of course the loss of exclusivity for biological molecules which has driven the biosimilar market. This has meant that companies required a much broader number of development candidates in order to push forward with the refreshing of product portfolios and maintenance of revenue growth. For some this has meant partnering with CROs and CMOs to meet the breadth and complexity required for the development of the new product pipeline. Procurement of external APIs rather than vertically integrated programmes has added to the challenge, at a time when cost controls are of paramount importance. Despite this the generic medicines industry has adapted its capabilities across formulation and innovative skills in delivery technology to open up new avenues of opportunities. At the same time, we have seen the introduction of several new molecules from R&D which has rejuvenated the pipeline of many major pharmaceutical companies; the return of the blockbusters as it has been said. Thus, the future development programmes for the generic industry look positive with significant opportunities across a wide range of therapies. Specialisation and technology will be required in certain areas in order to successfully deliver generic alternatives in the fields of oncology and hepatitis, but to date this has not presented an insurmountable barrier for the industry. For those companies where the focus has been on small chemical molecules the pharmerging markets continue to offer growth opportunities. In these markets, it is the legacy products for the treatment of infection, pain, cardiovascular disease and a host of other chronic primary care indications that are the foundation of a generic portfolio. This is in contrast to the developed markets where the focus is on speciality areas such as oncology, autoimmune disease and most recently hepatitis therapies. In these markets, the legacy products are under increasing competition surrounding pricing and new clinical alternatives. For the pharmerging markets affordability and access to medicines are key influencers and with the expansion of the availability of clinical support and insurance schemes we have seen new market opportunities open up for these older medicines. The future forecasts reflect a continuing trend as shown in the table below.
Legacy generic medicines continue to offer growth opportunities in pharmerging markets

From the table it can be seen that in the developed market forecasts there is little or no growth in the therapy areas of pain, respiratory, anticoagulants and mental health, whereas oncology, diabetes and autoimmune therapies show a continued focus and expenditure on specialty medicines. It should be noted that the viral hepatitis market has sprung from a low base to a major contributor in a very short space of time and is expected to continue to grow. On a separate note, the importance of anti-diabetic therapy is relevant to all markets and the availability of generic medicines across the spectrum of alternative therapies will play a vital role in the cost effective management of this chronic indication.

Focussing down to specific market trends and therapy usage can give an indication of future needs for generic medicines.

Japan for instance, mirrors other developed markets with significant usage of both sofosbuvir and the combination of sofosbuvir/ledipasvir. Following these exceptional items comes the increase in usage of bevacizumab, but it is the use of primary care products rosuvastatin, clopidogrel and esomeprazole that are driving expenditure. Completing the top ten products are pregabalin, olmesartan/medoxomil, infliximab and ketoprofen. The generic market is forecasted to be worth $12.5 billion by 2020. Interestingly of the top ten corporations in Japan, Japanese companies take just four places, with Pfizer topping the table followed by Takeda and Daiichi Sankyo.

In Europe the position is quite different, with a dominance of biological therapies in the top ten products. This reflects the importance of the biosimilar industry in contributing to cost savings across the range of specialty therapies that currently take 8 of the top ten places. The recent introduction of biosimilars for monoclonal antibody products has ignited a flurry of interest and changes to the positioning of these products, to the benefit of payers and patients. Although biosimilars remain a major area of interest at the moment, there has been a number of successful launches of small chemical molecules, heralding the return of the blockbuster status for some of these products. Although many are specialty

![Spending by Therapy area, 2019](image_url)
products including fingolimod, rivaroxaban, palperidone and abiraterone, longer term these will be the subject of development programmes and significant generic medicine launches.

China remains an area of interest for many international companies, but with mixed fortunes. Although market growth rates have fallen (down from double digit growth to around 6-8% CAGR for the next 5 years) the sheer size and future potential for this market means that it will feature in strategic growth planning for many years to come. Holding the rank of the second largest market come 2020 (even excluding traditional Chinese medicines sector) it cannot be ignored. The success of the government reform plans and access to medicines will of course be the deciding factor. New products are expected to come to market earlier and cost control, with pricing as a major feature, will continue. This environment favours generic medicines with a pool of new patients gaining access to medicines for the first time across a wide range of therapies. Generic medicines for the treatment of cardiovascular and respiratory disease alongside diabetes treatment (it is estimated that China accounts for 25% of the world’s diabetic population) will feature strongly. Local generic companies dominate and compete aggressively on pricing.

North America is dominated by the USA market, which in 2016 is forecasted to reach $472.9 billion in sales. Growth is forecast at a CAGR of 7.6% for the next 5 years (as compared to 4.5% for Canada) with new product launches fuelling the growth. Interestingly, small molecule patent expiries will have a larger impact in 2016-2020 than in the prior five years (on an absolute US dollar basis). The impact of this in the next five years is equal to $105.9 billion, compared with $87.2 billion in the five year period 2011-2015. The annual impact will be $17.5 billion in 2016, rising to $23.2 billion in 2017 and $30.6 billion in 2018 as a range of major brands lose exclusivity. Thereafter, the impact moderates somewhat, falling to $20.1 billion and $13.9 billion in 2019 and 2020, respectively. The generic market is forecast to reach $112 billion by 2020 (excluding discounts and rebates). With almost 90% of the products used being generic medicines, the market is competitive, very crowded and comprised of manufacturers from across the globe.

Opportunities for generic medicines therefore exist across the globe with an increasing demand for affordable safe and effective medicines. Each region has specific needs and opportunities that reflect the particular and sometimes peculiar requirements at a country level. North America remains the most lucrative region with Europe probably being the most competitive of the developed markets. The highest volume consumption is in the Asia/Australasia region, but this is also where the lowest revenue per unit is achieved, alongside Africa and the Middle East. Japan is now finally becoming a significant user of generic medicines and the government’s objective of targeting 80% generic utilisation of multi-sourced drugs by 2021 (up from just over 40% in 2015) could well be achieved ahead of time. Latin America remains a growth market but with local companies dominating market shares.

**The highest volume consumption is in the Asia/Australasia region, but this is also where the lowest revenue per unit is achieved**
As for the future outlook then generic medicine growth is forecast by IMS Health to grow at a CAGR of 6.9% with the USA leading the way in the selected group of markets. Europe is still beset by economic issues with price controls and increasing competition continuing to adversely affect the market. As mentioned earlier, Japan is making good progress with its programme to increase generic usage and Brazil is still an attractive market for generic medicines.

Interestingly of the top ten corporations in Japan just four places are taken by Japanese companies with Pfizer topping the table followed by Takeda and Daiichi Sankyo.

Conclusion

In conclusion, the growth opportunities for generic medicines remain strong and positive. The need for controlling healthcare costs remains a challenge for healthcare providers around the world. The availability of cost effective, safe generic alternatives offers a tool that can be used to balance access to and affordability of many of the major therapies required to maintain a healthy population of patients across multiple disease areas.
Future growth forecasted at a CAGR of 6.9%
Licensing of Generic: Needs and Expectations of Industry

Introduction

The generics face multiple challenges: ever increasing scrutiny by the regulators across the world; growing barriers of protection by innovators; and the government pressures for price reduction. All these tend to push up the costs of generics or make the business unviable. This is unlikely to change. If at all, it may become worse. The clamour for product quality; the impact of longer periods of exclusivity; push for liberal patentability standards; and need to contain health care expenditure in the major markets will continue to exert pressures on the cost and price of the generics. The product and process innovations that have helped generics in the past may no longer be enough for the future. The generics will have to look for something more to remain relevant and protect their growth. They need to work with the drug regulators to eliminate or reduce inefficiencies in the system. This article makes an attempt to identify and list potential areas that can be explored by the generics to remain viable and emerge stronger.

1. Cost Containment

The foremost among them is cost containment through regulatory approval process. It is difficult, but is doable. The five key areas are:

a. A Single Reference Product:
Regulators in several markets approve a new product based on a global multi-country clinical trial. The innovators use one product in all countries for its trials and subsequent registration. However, on expiry of patents and other exclusivity periods, when an approval is sought for generic version, many countries insist that the applicant must use a “local” product as reference product. This results in testing of multiple reference products for a company seeking regulatory approvals in more than one market.

Is it possible to convince the drug regulators to accept one “reference” product as was accepted by them during the global clinical trial? As the safety and efficacy of the product is already established by the innovator, irrespective of geography, a generic manufacturer operating in many countries should not be required to
prove equivalence multiple times with reference to a product in each country. It should suffice to establish equivalence with a product from the country of origin. This would save considerable costs in product registrations. This is particularly important for the follow on biologics or biosimilars.

**b. Uniform Product Standards:**
Some product monographs vary according to the pharmacopeia; e.g. USP, BP, JP, etc. All of these variations are not necessarily based on science alone. The variations reflect mindsets of different markets. The monographs usually incorporate the originator’s standards.

If only the regulators were to agree to a common standard for a product, instead of multiple pharmacopeias, the convergence of standards will not only reduce variability but will also help cost containment, as a manufacturer of a generic does not have to produce a product with multiple standards.

**c. Common Packaging Specifications:**
Like product standards, the packaging specifications vary according to markets. The variations in different jurisdictions are mostly linked to the regulatory and/or marketing needs. However, if only common specifications were laid down for each type of container, say, bottle, foil, blister, etc., and a manufacturer had freedom to choose its own packaging, the resultant synergy could help reduce cost. It is recognized that a generic producer would like to match his product with the originator in each market for better acceptance. At the same time, common standards could help reduce variability and cost.

**d. Timely Product Approvals:**
Currently, the time taken for approval of generics varies from 4 months to 36 months in various jurisdictions. If this time was compressed and the waiting period was reduced to max 12 months, not only the manufacturers could commence production earlier, but also benefit patients by early on-set of competition.

**e. Establishment Inspection & Report (EIR):**
The time taken by the regulators for inspection of new manufacturing facilities and re-inspection of old facilities under warning letters/import alerts is a major cost. The waiting period for establishment inspection and, after the inspection, time taken for releasing the report is crucial for business. The regulators have their own constrains. In addition, their annual travel schedules, finalized well in advance do not allow flexibility. Nonetheless, it must be recognized as a major element of cost for generics and the generic manufacturers and the regulators need to find a solution to this vexed problem.

Thus, a coordinated approach to regulatory convergence could help cost containment for generics.

**2. Compliance**

After cost, the next important issue is compliance. The manufacturers have increasingly realized that the cost of non-compliance is far greater than the cost of compliance. However, to improve compliance, it is important to also address the role of regulators. How can they help? What should they do?

It needs to be recognized that the regulators’ role does not end with laying technical guidance and checking their compliance. They should also assume responsibility for dissemination, understanding and absorption of the guidance. The compliance can be better achieved by explaining the scientific rationale behind the guidance, not just by diktats. Secondly, they should ensure that these rules and guidance are science driven, simple and practical. Thirdly, they must avoid creating a perception of frequently shifting goal posts. Fourthly, they need to ensure that their inspectors have understood the guidance and are adequately trained for their uniform implementation. These expectations change the role of regulators form merely being an auditor to that of being a facilitator. As the compliance is a major cost-saver, the generic manufacturers need to find ways of working with the regulators for ensuring product quality and patient safety.
3. Inspection & Inspectors

The resource constraints have forced regulators to develop quality metrics to move to risk-based inspections. It is a welcome step. However, a lot more requires to be done to develop the metrics and the standards of measurement. The generic industry can help in these efforts. Concurrently, the regulators need to explore possibility of evolving a common check-list to avoid multiple inspections of a site.

Likewise, and as noted above, the need of training and retraining of inspectors cannot be overemphasized. It is very essential to avoid subjectivity of inspectors and variability in the implementation. The effective management of the inspection and the inspectors require that the regulators continuously monitor and measure performance of their inspectors. These actions would inspire greater confidence in inspectors and promote better compliance.

4. Quicker Resolution of Remedial Actions

The warning letters and import alerts suspend supplies from many manufacturers for prolonged periods. The timely resolution of remedial actions and a system of providing an opportunity to manufacturers to discuss remedial actions could go a long way in resolving the quality issues and early resumption of supplies from the affected sites. This would not only help reduce cost of generics, but also prevent shortages of medicines and avoid unwarranted price increases.

5. Capability Building

Many regulators have demonstrated that they are willing to help industry in the capability building, if only the manufacturers were willing to take responsibility for quality of their products and ensure patient safety. It is important that the senior management of companies also demonstrate their commitment. This could pave the way for capability enhancing workshops. These workshops can promote two-way learning for the industry and the regulators. The discussion of scientific rationale by the regulators would help better absorption of guidance. Likewise presentation of practical problems of the industry in implementation would help regulators to improve the guidance. This dialogue can provide a lasting solution to the problems of compliance and quality.

The generic industry should therefore explore possibilities of working with the regulators in their own country and across the world. It may help improving affordability and availability of medicines, which is what the most governments are looking for.
Q&A

Q) Do you have any perspectives on GDUFA ii – do you think it’s a good idea, too expensive etc? (will it speed up regulatory approvals)?

The GDUFA II will further reduce the number of applications and discourage marginal players who do not have deep pockets. On the other hand, there is commitment by the FDA to clear the backlog. Thus, fewer applications and extra efforts by the regulator may result in improving the disposal time.

Q) How can we achieve the goal of having one reference product for generics – does this need some kind of harmonisation across countries, how long do you think that this will take? (who might be a leader(s) in this regard?)

This needs convergence of standards, not harmonization. International Generic Drug Regulators Programme (IGDRP) is already working for convergence by the regulators. If not all, at least a few major markets aided by the WHO can initiate this process. It is not necessary that all should do it at the same time. A beginning can be made by a few and others may follow.

Q) How can generic approval be kept down to under 1-year?

At one time, the USFDA had achieved 17 months. Some jurisdictions have made it possible. The cost of creating an appropriate organization is insignificant compared to the potential savings from early approval of generics.

Q) Do you think any regulators are yet acting as facilitators rather than simple auditors – I know many people are encouraging the FDA be part of a two way dialogue with industry. How long before this shift occurs, do you think it will occur. Are certain regulators better than others at acting in this more two-way educating role?

Not yet, but how many industry associations have even asked for it? The IPA is actively pursuing this goal. We believe that the regulators can achieve better results and ensure greater patient safety by helping manufacturers to do the things in the right way. Inspection is a snapshot, whereas training is long lasting. Some regulators seem to understand the importance of capability building as an option and are supporting these efforts.

Q) Do you think the industry and regulators are likely to engage more now, or do you fear the generics model will come under increasing pricing pressure – what will be the end result of this?

The engagement between the industry and the regulators is growing rapidly. However, this engagement and the pricing pressure are two independent phenomena. They are not interlinked. The engagement with the regulators could help save costs to cope up with the pricing pressures.

Q) Can you make any prediction(s) about the outcome for the generics market in 3-years time – do you think any of the above will be achieved or to the solutions found?

We will see pockets of success in the next three years. The industry and the regulators will be working jointly for capability building. We may not achieve everything, but we will see a beginning.

Q) Lastly, and most importantly, what sort of cost savings or magnitudes do you think can be achieved by these types of changes? (how long will it take to implement this properly)

Consider only the cost of procuring originator’s biotech products at the current prices for 100 subjects each from five different countries for BA/BE studies. The cost and time involved of doing this study on 100 patients for each market is extra. Add the cost of delay in launching the product... it is significant. The generics need to rely on “science” to convince the regulators that “one reference product” will not compromise patient safety.
Intelligent Application and Management of Data Will Define Pharma for the Next Decade

Introduction

The pharma landscape is evolving as rapidly as the speed of technology. The industry that former FDA Commissioner Dr. McClellan admonished in 2003 with “You need to improve!” has taken those words to heart to embrace innovation and technology as never before. Whether driven by the FDA’s shift toward a scientific, data driven definition for quality or a need to innovate to survive and be competitive in the new world marketplace, there is no doubt the push for greater understanding has resulted in a renewed emphasis on the ability to acquire, verify, and leverage the power of data.

Three Drivers for Change

Every market sector needs a push sometimes to adapt and evolve. The regulated life sciences are one of the most conservative sectors when it comes to technology innovation. However, several developments have elevated the need for pharma to move the management and security of data to a primary strategy. First, vertical drug manufacturing in the U.S. is no longer a leading strategy. While some companies continue to build internal manufacturing capability this is largely the exception. The emerging markets have matured over the last decade and most large pharma and biotech have established a distributed supply chain leveraging regional contract manufacturing organizations for internal development and manufacturing capability.

Second, supply segmentation has become a core strategy for large complex supply chains, creating multiple virtual supply chains within the construct of a single physical supply chain. Achieving this has reemphasized the importance of visibility and access to key information within each virtual supply chain.
Third, the maturity of mobile clinical platforms has resulted in a significant reduction in clinical trial costs on a per-patient basis, allowing virtual startups to move further into the clinical development process. Today, the rise of virtual biotech organizations has become a major factor in driving and growing the outsourcing movement. Compounding this is the growth of combination products. For many biotech products the ability to utilize a pre-filled syringe or auto-injector dramatically broadens the potential patient market. However, the complexity of establishing and controlling the drug, device, and system supply chain is significant for many virtual organizations. Finally, some may argue that the true potential for the life sciences will hinge on the ability of Big Data to identify new and effective therapies for disease.

The common denominator of these market drivers is information and data. We will explore the technology, regulations, security strategies, industry solutions and challenges behind this elevated emphasis on information and data management.

The Impact Technologies

Several technologies will have a profound impact on how drug companies bring products to market.

**E-clinical Mobile Platforms**

The e-clinical solution software market, valued at $3 billion in 2014, is expected to grow at a CAGR of 13.8 percent from 2014 to 2020 to reach an estimated value of $6.52 billion in 2020. Technology platforms have evolved with the market, focusing on functional re-usability, standardization, and quality resulting in decreased cost and implementation timelines. These solutions allow clinicians to rapidly tailor clinical data gathering and protocol requirements as commercial off-the-shelf (COTS) applications that are configurable. These systems will allow many pharma companies, on a global basis, to more easily comply with GCP requirements and best-in-class data management requirements from the Clinical Data Interchange Standards Consortium (CDISC) and Clinical Data Acquisition Standards Harmonization (CDASH).

E-clinical platforms are showing significant growth with the Software as a Service (SaaS) business models. All pharma organizations are managing risks in the extended enterprise – suppliers, contractors, and vendors. The SaaS model supports third-party risk management by providing an application to external users outside of the company’s firewall.

**Challenges**

The two dominant mobile computing platforms are Google’s Android and Apple’s iOS operating systems (OS). The market share for these two platforms cannot be more different between the rest of the world and the U.S., which causes near-term and long-term management challenges. A recent study4 by Atredis Partners summarized the U.S. market share for iOS and Android, as 43 percent and 53 percent respectively. The rest of the world is far more one-sided with Android commanding 83 percent and IOS only 14 percent. The challenge for mobile platform software is the issue of fragmentation. Fragmentation describes a software solution provider’s ability to keep up with OS changes. Android launches incomplete OSs and then iteratively optimizes them while Apple launches complete operating systems to the market. The disparity between U.S. and the rest of the world (ROW) is the ability to keep pace with patches. In the U.S. the assumption is you will change your phone every two years while the ROW may be closer to four to five years. This makes the challenge of managing security and updates incredibly complex for any organization banking on a mobile solution as a core vehicle for product development.

**Cloud Based Electronic Data Capture (CloudEDC)**

Augmenting the positive opportunities created by mobile data collection is the expansion of CloudEDC. Clinical trials data management is the biggest opportunity for CloudEDC and is the fastest growing application within pharma. The advantages of traditional EDC are well understood. By moving away from human data recording the consistency of data acquisition and accuracy of data acquired has increased exponentially. Anyone who attempted clinical trials ten years ago in the emerging markets experienced the frustration and regulatory consequences of having to repeat clinical studies because of poorly acquired data that could not be verified.
These systems provided rapid search and query functions, the ability to make field edits, and the ability to establish rules and get early notification of anomalous data. The downside of these systems is that they were fairly inflexible, very expensive, and typically required an external software team with the specific system expertise, making training and startup potentially a rate limiting step.

Cloud EDC addresses many of these shortcomings. From an investment and scalability perspective deploying a cloud-based system is far more scalable than traditional EDC and avoids the heavy investment required up front. These systems do not require specialized programming but are configurable, to obviate the need for a large specialized software platform team. This also means the clinician or end-user can easily configure forms for a study without having to invest in custom programmers. Data-intake forms can be built to guarantee Title 21 CFR Part 11 compliance and can be validated as such. Data can be stored in a data warehouse.

**Challenges**
The challenges facing CloudEDC are the same as for any IT solution. A comprehensive Information Security (InfoSec) and governance plan is required to assure data integrity.

**Internet of Things (IoT)**
The Internet of Things (IoT) is a network of physical computing devices, sensors, mechanical and digital machines with the ability to transfer data over a network without human-to-human or human-to-computer interaction. IoT devices are being used in many industrial market sectors including the regulated life sciences, such as the case of a human with an intelligent pacemaker. Potentially the IoT allows objects to be controlled remotely across existing network infrastructure, creating opportunities for more direct integration of the physical world into computer-based systems that allow data to be collected for analysis.

**Challenges**
While there has been a tangible effort to standardize IoT interfaces, there are still no universally accepted standards for IoT. This is likely to change in the next few years as the creation of huge data sets force organizations to pump development dollars into IoT solutions. Intelligent devices will continue to gain a greater foothold in almost every market sector and concerns about integrity, data structure, privacy, and security will move to the forefront of the discussion.

**Big Data vs. Smart Data**

Few topics have been discussed as much as the promise behind Big Data. Big Data is used to describe data sets that are so large that conventional data analysis solutions are inadequate. It represents a voluminous amount of structured, semi-structured and unstructured data that has the potential to be mined for information. Pharma looks to Big Data analytics as a possible avenue for everything from looking for the next big blockbuster drug to identifying a competitive advantage by analyzing its customer relationship management (CRM) data. The big question facing all sectors is when is Big Data or Smart Data?

Big data can be broken down into five primary dimensions that describe the challenge: Volume, Variety, Velocity, Veracity, and Value. When any one of these characteristics is not controlled this constitutes a big data problem. Smart data focuses on Veracity and Value and argues more does not necessarily equate with better.
Evolving Collaboration Models

Drug discovery has also evolved from the classical vertical models of two decades ago. Today early drug discovery is outsourced to research organizations around the world, and competitors collaborate to manage early product risk and accelerate product delivery.

To be successful, the data management strategy must be able to address data integrity and data security among collaboration partners and contract research organizations that may have developed supportive data using different systems.

Go ask Alice

Complementing these challenges is the cybersecurity challenge associated with Big Data. These issues can be described as a Red Queen problem. The Red Queen principle was first proposed by the evolutionary biologist L. Van Valen (1973), and is based on the observation to Alice by the Red Queen in Lewis Carroll’s “Through the Looking Glass” that “in this place it takes all the running you can do, to keep in the same place.” Because of the evolving nature of the threat to cybersecurity, hackers and companies are improving their methods and maintaining a sort of balance. Adopting the right analytics as part of the data mining exercise or cybersecurity strategy is central to obtaining the right conclusion.

Complicating the entire discussion of Big Data and Smart Data is the emerging ethical issue of data gathering and analysis. Europe has taken the first serious step in this direction. The European Data Protection Act, set to go into effect in 2018 will do away with the current fragmentation and costly administrative burdens across the EU. It will ensure that the personal data of victims, witnesses, and suspects of crime are duly protected, and will facilitate cross-border cooperation in the fight against crime and terrorism.

Historically, regulators have approached rapidly evolving problems using outdated approaches to problem solving, sometimes called Darkroom solutions, where experts on a particular subject are locked in a dark room until they solve the problem. This approach rarely works as the problem will have changed by the time they will have identified a regulatory solution. More likely these problems can only be solved by orthogonal, outside-the-box thinking. As organizations move in this direction it is likely that ethics will become part of the conversation as Smart data becomes entrenched in the pharma development strategy.

Adopting the right analytics as part of the data mining exercise or cybersecurity strategy is central to obtaining the right conclusion.
Data Integrity, Data Transparency, Information Security

Data integrity has always been a primary component of GxP system design. The FDA’s recent emphasis on laboratory and manufacturing data integrity has resulted in high profile import restrictions. As the complexity of data acquisition, transmission, and analysis expands to include big data, smart data, mobile platforms, and the IoT, ensuring data integrity will require a cohesive strategy encompassing every facet of data management. This responsibility falls under the area of information Security (InfoSec).

InfoSec is concerned with the confidentiality, integrity, and availability of your data. Most modern business data resides electronically on servers, desktops, laptops, or somewhere on the Internet. However, InfoSec is concerned with making sure data in any form is kept secure. It subsumes cybersecurity, which is only interested in data in electronic form. The focus is on the value of information, which, in the end, is the primary consideration for those who create it, access it, and seek to protect it.

The U.S. healthcare industry has been under siege by ransomware attacks that seek to usurp access to critical data. The exact number of attacks is not known because ransomware places hospitals in a unique legal position when, technically, HIPAA-protected data has not been breached. Hospitals are less inclined to report such attacks as HIPAA violation breaches, because they can incur a hefty financial penalty for every compromised record. The challenge with many hospitals is their antiquated and vulnerable IT infrastructure. Rather than invest in their IT infrastructure the default has been to invest in insurance in the event of a breach.

Unlike hospitals, pharma does not fall under the same financial constraints, so as we expand to harness the capabilities of new and better data it is essential to consider vulnerabilities to these systems.

With the plethora of wireless protocols used in IoT devices (from Wi-Fi, Bluetooth, ZigBee, GPRS, NFC, 6LowPan, LoRaWAN, Sigfox, Neul), security becomes an issue and in the absence of security countermeasures it is a simple matter for hackers to launch and exploit Man in the Middle (MITM) data interventions.

So what do these security threats mean to data transparency advocates? The movement is not isolated to a few small markets: both the U.S. and Europe have legislation in place to address clinical data transparency. Yet, only 9 percent of most big pharma’s clinical data is made available to clinicians and regulators. Many believe that even the data from failed clinical studies and new molecular entities (NMEs) can provide valuable information to physicians and researchers in industry and academia. Issues raised by big pharma are the challenges associated with Intellectual Property control, and legal liability.

Beyond these uncertainties is the question of what liability exposure exists for third party entities analyzing incorrect data that has been tampered with or adulterated? This cannot be a secondary consideration, or left to departmental functional areas of responsibilities. The creation and aggregation of data spreads across an entire enterprise and requires a clear strategy to ensure data integrity is maintained.

Conclusion

The next decade of therapeutic drug development will be based upon new and more effective means of data mining and data analytics. Competitive business drivers and compliance requirements will converge as data acquisition and analysis move to the forefront to drive discovery and manufacturing of new and more complex drug molecules. Clinical data transparency is here to stay and establishing a structured framework, infrastructure, policies and practices will be central to being compliant and avoiding controversy or even litigation in the future. As the industry looks ahead and moves forward, its ability to manage these constantly evolving threats to data management and integrity will define how we develop new drug therapies in the future.
Q&A

Q) How is big data changing the clinical trial industry and or the patient experience (mobile health industry - ongoing monitoring)....

90% of the world’s electronic data has been created within the last two years and the rate of creation will continue to accelerate. For clinical research big data presents a way to access historical clinical trial data bringing the potential of safely designing more efficient clinical trials at reduced cost, and to speed discovery of important treatment.

Q) Will clinical trials all be running using only e-clinical trial platforms – will this be using bring-your-own devices?

The future for e-clinical platforms is just beginning to crystalize. Universal standards will become much easier to implement and enforce and patients’ ability to participate in the acquisition and measurement of data will change the way clinical programs are designed and managed.

Q) How will big data change pharmaceutical manufacturing, in 5 yrs, in 10 yrs?

Big data will become the underlying foundation behind all electronic control and governance strategy, from product development and supply change management to business continuity.

Q) What will be the effect of big data on the outsourcing industry?

The current outsourcing model will soon completely replace the old vertical manufacturing business model of having everything in-house. As organizations shift their approach and policies to leverage this resource, governance and communication will be influenced by the insights gleaned from big data, in devising new treatment and driving the forward edge of science.

Q) Will we have harmonised standards and regulations in 5-10 years time? – who will create these?

The global standards and harmonization will be driven by the consortium entities which we follow today: ISO, IEC, GS1 and corresponding national regulatory agencies.
About CPhI
CPhI drives growth and innovation at every step of the global pharmaceutical supply chain from drug discovery to finished dosage. Through exhibitions, conferences and online communities, CPhI brings together more than 100,000 pharmaceutical professionals each year to network, identify business opportunities and expand the global market. CPhI hosts events in Europe, China, India, Japan, Southeast Asia, Russia, Istanbul and Korea co-located with ICSE for contract services, P-MEC for machinery, equipment & technology, InnoPack for pharmaceutical packaging and BioPh for biopharma. CPhI provides an online buyer & supplier directory at CPhI-Online.com.

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CPhI Global Events

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<td>CPhI North America</td>
<td>16-18 May 2017</td>
</tr>
<tr>
<td>CPhI China</td>
<td>20-22 June 2017</td>
</tr>
<tr>
<td>CPhI Korea</td>
<td>22-24 August 2017</td>
</tr>
<tr>
<td>CPhI Conferences</td>
<td>year round</td>
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