
Looking beyond the Global Pharma Horizon

CPhI Annual Industry Report 2015

Industry Expert Panel Submissions

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

Contents

Part 1: Calling for change

My perspective for Pharmaceutical Manufacturing Technologies	4
--	---

GIRISH MALHOTRA

Part 2: Quality, metrics and continuous processing

Continuous Manufacturing: The "Missing Link" of QbD.....	8
--	---

EMIL W. CIURCZAK

Quality Metrics: Carrot & Stick.....	11
--------------------------------------	----

BRIAN CARLIN

The Impact of Process Validation and Harmonization	16
--	----

BIKASH CHATTERJEE

Part 3: Push-pull factors on growth

Mega Trade Pacts and Their Impact on the Pharmaceutical Markets.....	26
--	----

DILIP SHAH

The Fertile market of Sterile Injectables.....	30
--	----

VIVEK SHARMA

Can Pharma Manufacturing learn from lessons in the US?	35
--	----

PRABIR K. BASU

The real need for generic medicines	41
---	----

ALAN SHEPPARD

Part 4: The outsourcing perspective

CMO/CDMO Challenges and Opportunities.....	46
--	----

GIL Y. ROTH

What Does the Future Hold for Biopharmaceutical Outsourcing?	50
--	----

HEDLEY REES

Access and Affordability: Impact of Biosimilars	53
---	----

ARUN CHANDAVARKAR

Cold Chain Outsourcing: A Simple Answer to a Complex Question?	58
--	----

FIONA WITHEY

Part 1.

Calling for change



PANEL MEMBER

Girish Malhotra President, EPCOT International

My perspective for Pharmaceutical Manufacturing Technologies/Processes and Continuous Improvements

Introduction

Regulations are necessary for quality assurance of drugs. FDA established 21CFR314.70^(1,2) and it is a very important rule. It assures that there is no “by manufacturer’s choice” deviation from the manufacturing methods and practices that have been filed for the components involved in the manufacture of any salable drug – the active pharmaceutical ingredient (API) and their formulation – and labeling, packaging etc. Every change has to be reported. Drastic process changes are discouraged.

When there is a discussion about pharmaceutical manufacturing generally only formulations are

considered. API manufacturing is ignored and it should not be. Without API there is no drug.

21 CFR314.70 encourages “continuous improvements” in the processes that will create the best product for clinical trials and that’s the way it should be. However, in my estimation under the current rules all of this has to be done prior to going to clinical trials. QbD (quality by design) becomes a natural part of the process development before a process is commercialized. After the fact process change is difficult.

Batch processes

Generally, most APIs and their formulations are produced using batch processes. Existing approved products require annual reporting of improvements/changes. Most of the changes are minor. However, if the processes are to be revamped for process yield, operating parameters and manufacturing methods, they are going to be the biggest challenge as the efficacy of the API and its formulations,

especially prescription drugs could change. In my estimation re-approval would be needed. This can be a monumental task, even for over the counter drugs (OTC) not requiring prescriptions, because new monographs may have to be established. Money and time investment would be necessary. Such changes are major “continuous improvements” and deterrent for prescription drugs.

¹ Third World Network, 20 April 2015

Continuous Manufacturing

Continuous manufacturing for API and their formulations is pharma's new and least understood buzzword. In the annals of chemical engineering and for that matter in any industry "continuous manufacturing" means 24x7x50 hours of operation per year with pre-established down time. There are few selected APIs (OTC or prescription) that can be converted to continuous processes. (3, 4, 5) Totally different operational thinking/models would be required. The use of existing manufacturing equipment and technologies is very feasible.

Continuous processes for formulations should have been commercialized over sixty years ago. Manufacturing technologies and equipment along with knowledge base for such processes have existed since, but not incorporated. This is due to traditions of business and lack of application of chemical engineering knowledge base to commercialize such processes.

Benefits and Challenges of Continuous Improvement

Benefits of cost reduction, improved profits and larger customer base due to improved manufacturing technologies are huge and well documented. Best of the process technologies have to be created before clinical trials. As we know "after the fact" improvements, under the current regulatory environment, would not happen due to the financial and time elements discussed above.

Only a "maverick company or creative destructionist" can take on the task. Success would completely change the pharma landscape. I am not sure if pharma related components and that includes companies, legislature, vested interest groups, are ready for such an evolution. There will be microscopic examination and doubts raised, forcing many delays even if the companies do the "right" things based on excellent science and engineering.

Alternate Proposal

I would propose the following. I am sure there will be plenty of scrutiny and naysayers – unless we take bold steps not much changes. If there are alternate better ideas, let us discuss those also.

I propose that the pharmaceutical industry be allowed to commercialize process improvements (yield, process/operating conditions, operating parameters, cycle time) in the manufacture of approved APIs and their formulations. The manufacturing company will guarantee that the product efficacy and performance, along with impurities, will be better than the approved product produced by the company. There would be an added stipulation that if for any reason product performance, efficacy, labeling and impurities do not meet or are worse off from the approved product, company proposing improvements

will be barred from making the product using alternate process for the next e.g. two or three years. If they do decide to use the alternate process, they will have to go through the re-approval process. Minor changes that do not change the current filed processing methods etc. would be excluded. This would apply to OTC, brand and generic products also.

I propose that the pharmaceutical industry be allowed to commercialize process improvements in the manufacture of approved APIs and their formulations – without reapproval

Conclusion

I admit that my proposal is a bit bold but unless such bold steps are considered, very little will change in the current pharma's manufacturing methodologies or anywhere, for that matter. If incorporated in pharmaceutical manufacturing landscape, continuous improvements and innovation could become a routine and it could be extended to the whole healthcare industry. Wright Brothers did and so was the adventure of sending humans to moon and bringing them back. A successful trek to Pluto would also fit the category. It is time for the pharma industry to be bold. It has an opportunity to add as much as 20% of the global population (~1.4 billion)

to its customer base, an unprecedented opportunity for any industry on the planet. Profits will improve and healthcare costs can come down. It would be a win-win.

unless bold steps are considered, very little will change in the current pharma's manufacturing methodologies or anywhere, for that matter

References

1. CFR - Code of Federal Regulations Title 21 <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.70>
2. Malhotra, Girish: Impact of 21CFR 314.70 on The Life of a Pharmaceutical Manufacturing Process, Profitability through Simplicity, <http://pharmaceuticalscoatings.blogspot.com/2015/08/impact-of-21cfr-314670-on-life-of.html>
3. Malhotra, Girish: Why Fitting a Square Plug in a Round hole is Profitable for Pharma and Most Likely Will Stay? Profitability through Simplicity, <http://pharmaceuticalscoatings.blogspot.com/2014/08/why-fitting-square-plug-in-round-hole.html>
4. Malhotra, Girish: A Blueprint for Improved Pharma Competitiveness, Contract Pharma, Vol. 16, 7, Pg. 46-49, September 2014, http://www.contractpharma.com/issues/2014-09-01/view_features/a-blueprint-for-improved-pharma-competitiveness/
5. Malhotra, Girish: Continuous Process in Pharmaceutical Manufacturing: Considerations, Nuances and Challenges, Contract Pharma, June 2, 2015, http://www.contractpharma.com/issues/2015-06-01/view_features/continuous-process-in-pharmaceutical-manufacturing-considerations-nuances-and-challenges

Part 2.

Quality, metrics and continuous processing



PANEL MEMBER

Emil W. Ciurczak President, Doramaxx Consulting

Continuous Manufacturing: The “Missing Link” of QbD

Introduction

Since the idea of PAT was floated by the USFDA, almost all of our efforts have gone into the production process, per se. Yes, we have added NIR and Raman to aid in characterizing raw materials, both API and excipients. But most of our efforts have gone into (for example, for tablets) the blending, granulating, drying, lubricating and tableting, compressing and coating steps.

To monitor, understand, control and eventually improve these steps was the goal of “pure” PAT. In PAT, it was assumed that we had already designed the “proper” mixture and all that was needed was control of the process. However, when the idea of QbD was floated, the paradigm included more latitude and discretion for the operators. Instead of strict ratios of ingredients and strict parameters for production of the product, the concept of “design space” (DS) replaced unwavering and strict SOPs. The DS meant that, within certain boundaries, an operator could adjust the formulation and/or operating conditions to make a product with (predetermined) properties, considered as “correct.” The idea that the “enshrined” Master Manufacturing Formula (MMF) was, in reality, only a suggestion, threw Quality Assurance people into fits. Nonetheless, the cost savings and quality increases have convinced a number

of companies to invest in PAT monitors and software (and training). While the gains seen were both real and substantial, one major hurdle stood in the way of ubiquitous acceptance an implementation of PT/QbD: we use a 1950’s manufacturing system.

That is, the VAST majority of pharmaceutical manufacturers use a discreet step-by-step process:

1. Incoming raw materials are placed in quarantine, sampled, labeled “hold,” samples are sent to QC, wait for results, get results, either green “passed” label or red “failed” labels affixed, moved to “destroy” or “use” areas. This can take over 30 days per lot. (PAT solution: check with NIR or Raman in loading dock; immediately pass or fail.)
2. Blending has not changed in decades. The blender is charged, started, and rotated/mixed for the time listed on the MMF. If being performed by a generic company (in US), samples must be taken and sent to QC to assure well-blended bulk. If actually followed, this procedure could delay granulation for up to a week. Most companies opt for “risk continuation,” where samples are sent, but the process continues on the assumption that they will be fine. (PAT solution: NIR, Raman, or LIF monitor to blend to endpoint.)

¹ Third World Network, 20 April 2015

3. Granulation is where a solvent is added to the powder blend, the blend mixed, and dried, in some fashion (pan drying, fluid bed) for a pre-set time. Unfortunately, if samples are actually taken and measured, the method used is an archaic wet method, such as Karl Fischer (which may give total water, but does not show its location in the blend or on the API). (PAT solution is NIR, for real-time monitoring and shut-down; information about API crystallinity and hydration state is gleaned.)

After each step, the contents of the equipment is dumped, possibly stored, and moved on to the next step, until the final product is made. Between lots, the equipment used must be cleaned and inspected (cleaning validation, including lab work) before the next product is made. At this point, it should be apparent that step-by-step processing, even with a PAT measurement and control system in place.

A number of larger companies have turned to continuous manufacturing (CM) to obviate these time-consuming problems. In CM, the (pre-approved) ingredients are metered into a screw-blender, compacted into a ribbon (or left a powder mix for direct compression), chopped and lubricated, then tableted. In this case, the process is integral, with no manual movement of material from step to step.

Thus, CM has immediately solved several problems:

1. The lot can be as large as needed. Without multiple lots, we have dispensed with
 - a. Cleaning and validation; equipment down until CV results received
 - b. Intermediate storage, awaiting lab results
 - c. Multiple lab tests, including sampling, notation, delivery, lab work, etc.
 - d. TIME! A multi-day batch has just been shrunk to hours
2. Since the ingredients are constantly monitored, there is no worry of OOS materials. In addition, real-time release (RTR) is quite easily performed, obviating final QC testing with its quarantine and storage time, not to mention the savings in lab effort and materials.

There is one glaring difficulty with CM that tends to keep it from being used, especially by smaller companies:

The effort needed to determine Design Space. The DS is not something easily gleaned by “normal” product development. While some pre-formulation studies may have been performed, seldom does a company invest in a full Design of Experiment (DoE) to build a DS. Why? Well, since all companies have to perform scale-up studies from development-level studies, often taking up to 18 months, it is apparent that any DoE should be run on production-level equipment.

The cost and time involved in performing a full-scale DoE study can be daunting, even to major Pharma companies. To smaller proprietary and generic companies, the cost of the API, excipients, and labor is a killer. Using CM immediately does several (good) things: [Assume that we are checking six possible changes (disintegrant, binder proportion, ratios of excipients) in order to design the correct dissolution profile and assay. We will examine six parameters at three levels, each.]

1. Using a “normal” DoE (from pre-software days), we could have to run 2N experiments. In this case, 64 full-size production batches. Even assuming multiple sets of equipment (although that adds another unknown factor), the cost (same as 64 regular batches) and time (weeks, at best), shows this is clearly not the way to approach DS building.
2. Using a DoE software program to cull the number (e.g. Plackett-Burman), we could glean quite a bit of information out of eleven (11) experiments.
3. Bad news is that we still need to make 11 production sized batches, still taking weeks and still expensive.

Using a CM set-up for development, in addition to production, accomplishes a number of things:

1. The immediate benefit is the size of DoE batches, often savings of up to 90%. This is especially important when the API is expensive, a controlled substance, or a limited amount of orphan drug (with a small profit margin).
2. The time of experimentation immediately drops from weeks to day(s). As lab results are obtained, the spectral data from the CM may be used to generate equations for RTR (down the road).
3. There will be no cleaning, with its accompanying

²William New, ip-watch.org on 05/06/2015

³Frederick Abbott, Bloomberg, 10/07/2015

⁴Wikipedia, the free encyclopedia

⁵World Economic Outlook Database October 2013

⁶TTIP – A Civil Society Response to the Big Pharma Wish List. Joint Position by commonsnetwork.eu

validation, between experiments, further lowering costs and speeding the data generation.

4. And, best of all (from my perspective), there is no scale-up. I'll wait while you consider that... No scale-up! That part alone can add up to 18 months to a patent or get a product into the market before another generic company.

So, in my humble point of view, the "Missing Link" in PAT and QbD is continuous manufacturing, especially in the formulation stage. More food for thought: how much

help to the eventual product would having the final formulation available at the clinical trial stage be? CM answers a multitude of questions, many of which haven't even been asked yet.

The "Missing Link" in PAT and QbD is continuous manufacturing, especially in the formulation stage

Some observations, Comments, and Predictions (not necessarily in that order)

1. While the first "buy-ins" will be large proprietary firms, I would think the cost savings would really appeal to generics firms and those investigating orphan drugs, if for no other reason than the cost savings for low-margin products.
2. As for "when," I would say the leaders will continue at the 1-2 products per year pace for the next several years, then move on to only submitting NDA's with CM at the heart. After that, at first, we will see one or two of the larger generic firms (Sandoz, Teva?) dip their toes in the pool. With success (and having purchased the equipment already), I see more and more getting into the act. Within 10 years, the question will be 1) why the @#\$% did we ever do batch production? And 2) what ever happened to those that didn't switch?
3. When Janet Woodcock stated to a Congressional committee that we should be "moving away from batch processing," it kind of sounded the death knell for the "good old way" of producing drugs.
4. As for how much may be saved by implementing CM, it depends on the extent of immersion. If they "only" use CM for production, I would estimate a 25-35% savings, to be conservative. When you expand to formulation (and clinical trials) to obviate the pain of scale-up, the combined production savings and non-existent OOS problems could easily top 50%.
5. Despite drug shortages becoming an increasingly common phenomena and regulations changing (to accommodate CM), some still see a switch to continuous processing as a risk. What is stopping more widespread implementation? Well, the same thing that held up HPLC in 1970 and NIRS in 1985 and PAT in 2003: inertia. And the fact that companies (in the US) can charge anything they wish for drugs, why change?
6. Enough has been achieved on continuous processing in the last year, but I believe industry should be changing faster. It works and the industry, if it wants to survive, will endorse it or go the way of the village blacksmith.
7. The idea of CM can be merged with 3-D printing and making variable dosage forms, so that is another plus. The "process signature" of a single production stream will also help identify counterfeits and tighten the Supply Chain a touch more.
8. Many API's are being shifted to CM, although, in most cases, large amounts of API are not always needed. In cases such as vaccines for outbreaks, there are exceptions. As far as excipients, the producers have two problems: 1) they are marginal (profit) producers of pure materials, so many of the cost savings won't apply, and 2) most of their product goes to non-Pharma industries (lactose to food producers, for example), so the pressure isn't there.



PANEL MEMBER

Brian Carlin Director Open Innovation, FMC

Quality Metrics: Carrot & Stick

Introduction

The FDA quality metrics initiative¹ has elements of carrot and stick: compliance with baseline metrics (stick?) and optional metrics to demonstrate quality culture (a do-it-

yourself carrot?). Increased attention to finished product quality metrics will drive greater scrutiny of the impact of excipient variability, a rich source of special cause variation.

What happened to QbD?

Quality by Design (QbD) assumed that if all critical sources of variability are identified, and controlled by the process, then product quality can be reliably and accurately predicted.² In practice, not all critical sources of variability will be identified and explained at time of filing.

“The number of post-approval supplements received for review has increased over the past decade, in part owing to our current practice of “locking in” an applicant’s manufacturing process before it is fully optimized. A burdensome regulatory framework requires manufacturers to submit supplements as they strive for process optimization.”³

This may explain why the desired state of “a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight”³ has yet to be realized. Despite QbD, quality risk management, pharmaceutical quality systems, process analytical technologies and other initiatives:-

“we have not fully realized our 21st century vision for manufacturing and quality – there continue to be indicators of serious product quality defects.”¹

As a result, FDA intends to use industry quality metrics data to develop risk-based inspection, reduce risk of drug supply disruption, and improve their evaluation of drug manufacturing and control operations.¹

“Establishments that have highly controlled manufacturing processes have the potential to be inspected less often (as a lower priority for inspection) than similar establishments that demonstrate uncontrolled processes (as a higher priority for inspection). In addition, FDA intends to consider whether these metrics may provide a basis for FDA to use improved risk based principles to determine the appropriate reporting category for post-approval manufacturing changes.”¹

The choice of a universal set of baseline metrics is controversial. Simple metrics such as “right first time” are

¹ Third World Network, 20 April 2015

lagging indicators and may not be comparable for products with differing degrees of complexity or frequency of manufacturing. However, in addition to baseline metrics, the FDA is also considering the option of submitting additional, optional metrics as evidence of manufacturing robustness and a commitment to quality.¹ A demonstrated quality culture, however quantified, is a better leading indicator than compliance with minimum standards. Villax⁴ has emphasized the need for FDA to recognize and reward best practices, as well as enforcing minimum standards. In addition to manufacturing track record, and the degree of QbD/PAT implementation, Villax suggests that high performing sites should allow the FDA direct IT access to quality data, and support inspector training on site. Therefore, the potential exists for companies to use their metrics and quality systems to promote themselves in terms of a favorable risk ranking. They might not only have fewer inspections, but, more importantly, they could gain favorable reporting categories for post-approval manufacturing changes.

With increased focus on quality metrics, there will be greater scrutiny of excipient variability, a source of special cause variation. At time of filing the product history will have limited excipient experience, and the process may still be subject to scale-up. Excipients generally receive less attention than APIs and the assignment of criticality for an individual excipient may be subjective. Design of Experiments (DOE) usually involves screening down to a simple model with a few dominant variables. Most

excipients are categorized as “non-critical”. However, their presence in experimental batches without incident does not prove non-criticality.

Absence of evidence of a problem is not evidence of absence of that problem!

The product is then subject to cumulative, multivariate changes in its lifecycle, usually with univariate change control. Prediction of quality (i.e. Design Space) becomes uncertain. The process cannot be uncoupled from the raw materials.

“Surely every medicine is an innovation; and he that will not apply new remedies, must expect new evils; for time is the greatest innovator; and if time of course alters things for the worse, and wisdom and counsel shall not alter them for the better, what shall be the end?”⁵

Good design minimizes, but cannot totally eliminate raw material impact. Excipient risk must be managed but this requires understanding the complexity of both the excipients, and the finished drug products into which the excipients are formulated. The variability of all excipient attributes, not just the ones on the Certificate of Analysis (CoA), must be understood. Pharmacopoeial compliance does not guarantee the fitness for purpose of an excipient in a particular application. Compliance & supply chain security alone are insufficient to manage excipient risk.

It ain't so simple

Complexity arises from the repeated application of simple rules in systems with many degrees of freedom, giving rise to emergent behaviour not encoded in the rules themselves.⁶ Reliance on pharmacopoeial compliance and fixed formulae are simple rules, but are not predictive of undesirable emergent behaviours impacting upon product quality.

Excipients themselves are complex and differ from reagents or engineered components. Add the right amount of reagent in solution and the chemistry follows. This does not apply to mixtures of excipients in solid dose forms, where

there are inadequate powder mixing rules. The composition and manufacturing tolerances of an engineered component are controlled to deliver performance, but excipient particles are mass produced with a very wide tolerance (span).

Excipient composition may be variable and ill defined, which is why the International Pharmaceutical Excipient Council (IPEC) has published an Excipient Composition Guide.⁷ If the excipient is a polymer, there will be polydispersity in terms of molecular weight. Some of the feedstocks may be natural and subject to

multiphase reaction. If the excipient is manufactured by high volume continuous production there could be additional variability behind the CoA figures, which may be composite or average results. Continuous manufacture over years or decades represents a very high degree of process understanding and control: in effect, QbD. However, supplier QbD may not always be congruent with pharmaceutical product QbD, especially if the pharmaceutical usage is only a small proportion of the market. Excipients are often produced for other industrial applications and it is the responsibility of the user to qualify the excipient. Applicants may receive questions if they rely solely on pharmacopoeial or supplier specifications without justification.

“For an excipient, conformance to compendial specifications alone can be inadequate for performing its intended function in a drug product, and/or for its suitability for use in commercial scale manufacturing (of the drug product), if the critical attributes of the excipient are not similar, when obtained from multiple sources”⁸

Excipients are a source of unknowns.⁹ Unknowns confound design and risk assessment. Unknowns will cumulatively degrade model validity and therefore continuous monitoring throughout the product lifecycle is necessary in order to understand the system limitations in the real world. Unknowns lead to rare and unpredictable “Black Swan” events with disproportionate impact, subject to post hoc rationalization.¹⁰ Having regularly used the Black Swan metaphor someone asked me that if Black Swans are so rare how come there are so many in the pharmaceutical industry? They then asked if I could simplify things. However, that poses the question: could oversimplification be the reason for so many Black Swans in the pharmaceutical industry?

Simplification facilitates compliance but given the earlier definition of complexity,⁶ where simple rules are not predictive of the emergent behaviours, simplification may be detrimental to quality. Common pharmaceutical simplifications include over-reliance on pharmacopoeial specifications, underestimation of variability, discounting improbable (Black Swans), and an over-reliance on fixed processes and formulae. Many people fail to understand that fixing everything under their control only makes them

more sensitive to raw material variability. The incoming variability will feed forward to finished product quality in the absence of any compensatory mechanisms. By building variability and flexibility into your system it can be used to offset raw material variability.

Finished product complexity is often discounted: “it’s only a simple immediate release tablet”. However there is no pharmaceutical product simple enough to never fail. There may be criticalities or latent conditions within the product, which, by definition (“latent”) are not apparent at time of design or filing. They may remain dormant for months or years until a triggering event reveals their existence. The triggering event could be an excipient variability, possibly a known attribute within its norms of variability, hitherto without impact. ‘Criticality’, in this context refers to a transition of the system from one state to another.

At a phase transition many microscopic parts give rise to macroscopic phenomena that cannot be understood by considering the laws obeyed by a single part alone.⁶

Percolation¹¹ effects and conflicting technological objectives are the most common source of criticalities in pharmaceutical systems, especially in tablet design. Both powder mixing and tablet compaction physics are very prone to percolation effects.¹¹

Design of Experiments (DOE) is another source of oversimplification and misinterpretation. Screening experiments to establish the critical parameters will tend to be dominated by design-critical raw material attributes. For example, it would be unusual for a “simple” immediate release tablet of a poorly soluble drug not to exhibit strong dependence on the API particle size, and the presence or absence of a disintegrant. A controlled release matrix will be dominated by the level and properties of the rate controlling polymer.

Design of Experiments (DOE) is another source of oversimplification and misinterpretation

Subsequent experiments narrow the focus onto fewer parameters to give the simplest model accounting for the variability encountered. Whether by experiment or committee the excipients are divided into critical and “non-critical”, the latter receiving less attention. Critical, or more specifically design-critical excipients will generally have a direct causal effect on product performance and quality. If the impact of variability in the design-critical excipients cannot be fully controlled by the process then controls

on Critical Material Attributes (CMAs) may be required. An application-specific CMA may not always be on the supplier or pharmacopoeial specification.

A DOE for filing must be complemented with multivariate monitoring throughout shelf-life. Under QbD, production itself is an ongoing DOE and the relevance of the original assumptions and models from the initial DOE should be continuously verified.

Why has my “non-critical” excipient gone critical?

If the so-called “non-critical” excipients are present in DOE and production batches, without incident, this may be misinterpreted as proof of non-criticality. This is the White Swan argument (All of the swans I have ever seen have been white, therefore, all swans are white). I’ve never seen a failure associated with this (“non-critical”) excipient, therefore it cannot affect my product. Hence when a product failure is associated with a “non-critical” excipient it is a Black Swan event. Control strategy should include contingencies against all application-specific failure modes associated with all the excipients, including those initially deemed “non-critical”.

For “non-critical” excipients the impact of their variability is a function of both the variability and the distance from the product criticality. If the finished product drifts toward

a criticality then what was previously “non-critical” may become critical. An excipient variability could now govern the transition between one state and another. A simple analogy is the decrease in process capability index (Cpk) when drifting towards a specification limit. When Cpk drops below 1 the excipient can no longer be considered “non-critical”. The interaction of an excipient variability with a product criticality is correlation rather than causation. It may be what is called in the safety literature a proximate cause, but what predisposed it to be now critical? The regulatory authorities are well aware of the concept of product drift:-

“The root cause of root causes is often the failure of management to focus on minimizing unwanted variability, differences, and discrepancies throughout the product life cycle.”¹²

Who are you going to call?

Unfortunately in real life the “limit” associated with a criticality is not known in advance. Product criticalities and verification of excipient non-criticality are not experimentally verifiable during development. Most product failures are complex and multivariate. To factor excipient complexity into Design and Control strategy it will be necessary to access supplier data beyond the CoAs from purchased batches. At a minimum, historical CoA data over several years is required to evaluate supplier process capability and realistically model the excipient variability. If there is a higher frequency of in-process testing behind the CoA data this may be more relevant for QbD purposes, especially if it is noisier than the CoA data.

Access to supplier data will facilitate modelling or simulation of excipient impact, particularly if there is uncertainty as to the critical attributes, or more likely attribute combinations in the finished product. An example from the food industry,¹³ with multivariate control of nine ingredients from multiple vendors shows the inadequacy of univariate specifications. Quality may require the right balance of properties, not just each property separately. Lots of which are acceptable in terms of individual properties (i.e. in spec) still have to be rejected. However, relying on rejection by a multivariate model could pose problems for suppliers and is akin to lot selection. Building in some latitude in formula levels

during development (DIY SUPAC?), should the desired attribute combinations prove elusive, will buy time until the process can be adjusted. Ranging studies where a level of excipient is titrated are a good measure of robustness. If performance is very sensitive to titration then you can expect a higher risk of susceptibility to excipient variability. Never formulate close to a margin (criticality).

Suppliers can reduce the risk from complexity, both from their product and from the use of their excipient in a particular application. However, they can identify potential failure modes associated with their materials only if they know and understand the application. If you are unfortunate enough to run into a criticality correlating with an excipient variability, a good question to ask of your suppliers is whether there is anything under their control

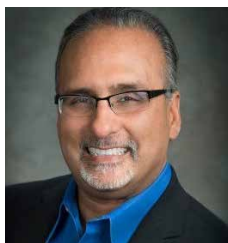
that can be used to back you off the criticality. As we move towards a more metrics-driven regime perhaps some measure of the degree of user-supplier joint due-diligence should be included.

“So it is in contemplation: If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts he shall end in certainties.”¹⁴

Suppliers can identify potential failure modes associated with their materials only if they know and understand the application

References

1. Request for Quality Metrics; Notice of Draft Guidance Availability and Public Meeting; Request for Comments: Docket No. FDA-2014-D-2537, Federal Register Vol. 80, No. 144 July 28, 2015
2. D Christopher Watts 2004 http://www.google.com/url?url=http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm089031.ppt&rct=j&frm=1&q=&esrc=s&sa=U&ei=HXLrVJz9LIGNNu3kgqAL&ved=0CBQQFjAA&sig2=oY4RmfK9-ZLNxgbm36bIAA&usq=AFQjCNEbHd27U0GWaFL9n8T0o_ul517g5Q
3. FDA Pharmaceutical Quality Oversight <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM442666.pdf>.
4. Villax G, Pharm Tech September 2014 www.pharmtech.com/case-fda-deans-list
5. Francis Bacon, Essays: Of Innovation 1625
6. Christensen K Moloney NR “Complexity and Criticality” Imperial College Press 2005
7. IPEC Excipient Composition Guide 2009
8. Rajendra Uppoor, FDA, “Multisource Excipient Equivalence –FDAs Current Views”. 2004 USP Annual Scientific Meeting
9. Carlin BA, “Quality Risk Management of Compliant Excipients.” J. Excipients and Food Chem. 3 (4) (2012), 143-153
10. Taleb NN. The Black Swan: The Impact of the Highly Improbable, 2nd Ed, Random House Publishing Group, NY, 2010
11. Percolation theory - a novel approach to solid dosage form design Leuenberger H et al Int J P'ceutics 38 (1987) 109-115
12. R Friedman FDA, Process Drift: When Do We Detect it? PQRI Process Drift Workshop December 1, 2010 <http://www.pqri.org/workshops/ProcDrift/imagespdfs/Friedman.pdf>
13. Z. Liu, M-J. Bruwer, J.F. MacGregor (ProSensus), B. Polsky, G. Visscher (Mondelez International), “Setting up simultaneous specifications on multiple raw materials to ensure product quality and minimize risk,” IFPAC-2013 <http://www.prosensus.com/multivariate-case-studies/100-mondelez-multivariate-specification>
14. Francis Bacon, The Advancement of Learning, Book 1 v8 1605



PANEL MEMBER

Bikash Chatterjee President and CSO, Pharmatech Associates

The Impact of Process Validation and Harmonization on Drug Development and QbD

Introduction

The movement toward scientific understanding as a basis for quality determination has been quietly gaining traction for over a decade. In the US, the FDA first issued its landmark guidance in 2004 titled Pharmaceutical cGMPs for the 21st century - A Risk Based Approach, which proposed a new definition for evaluating product quality based upon scientific understanding of the product and process, rather than inspection and testing. In parallel, the International Committee for Harmonization has been issuing its best practices guidances specific to product and process development (ICH Q8), risk management (ICHQ9) and quality management systems (ICHQ10) since 2005. If adoption of these best practices concepts was slow, perhaps it is because the principles represent such a significant paradigm shift in product and process development, or it may be that the indigenous skill set to support scientific understanding was typically found only in pockets of most drug development organizations.

In January 2011 the FDA issued a new Process Validation Guidance, representing the first formal incorporation of the principles of ICH Q8, 9 and 10 by the agency, this was the first guidance pertaining to process validation since the original guidance was issued in 1987. This

new guidance shifted the concepts behind process validation from a development activity that represented the final step in product and process development, to a product lifecycle model. As with many FDA guidances, the new approach included few details regarding agency expectations and implementation requirements. However, understanding the activities within the three stages of this new lifecycle is the key to satisfying the FDA's modern vision for product quality and process predictability.

The EMA quickly followed with two guidances: *Guideline on process validation for finished products - information and data to be provided in regulatory submissions* which was formally issued in 2014; and *Annex 15: Qualification and Validation*, formally adopted in March 2015 and most recently adopted by the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) as their standard. Understanding the concepts behind the Annex 15 guidance and the FDA guidance reveals a great deal in terms of the direction these two major market regulatory bodies are moving, and the implications for the industry and the potential for the adoption of Quality by Design (QbD).

The QbD Paradigm

The adoption of QbD as a framework for product development has also been slow. The biotechnology sector was one of the first to adopt many of the key tenets of QbD. This may be in part because of the inherent complexity of the biotech manufacturing process that required a greater level of characterization and process understanding to establish a commercially viable product and process. Some call QbD a patient-driven development philosophy because it utilizes a product's performance metrics, called **critical quality attributes** (CQAs), as the primary criteria for evaluation importance. That is, a process parameter or material attribute is considered critical if it impacts the product's performance as measured by its predefined CQAs. But the notion of QbD is not new. Dr. Juran first introduced the concept of QbD in 1985 in his seminal book "Quality by Design". In it, he reasons that most quality problems are designed into the product and process and should be eliminated at the design level rather than at the execution level. Further, ICH Q8 defines QbD as:

"A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management."

Taking this basic concept to the implementation level, I have developed my own version of this definition:

"Understand what factors have an impact on variation in your process and your product's performance; then establish a control plan to monitor and maintain product quality."

This definition encompasses and reveals the crux of the issue in the slow adoption of QbD. Over the last decade in which we have seen the global market grow and ultimately begin to stabilize and mature, many companies turned to in-licensing and acquisition as a strategy for growth. In such an environment it is difficult for an organization to sink additional time and money into understanding the key sources of variation that drive product performance, for a product that has been on the market for years.

The following are the key elements of a QbD development program:

- Defining the quality target product profile (QTPP) as it relates to quality, safety and efficacy, considering e.g., the route of administration, dosage form, bioavailability, dosage and stability
- Identifying critical quality attributes (CQAs) of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled
- Determining the quality attributes of the drug substance, excipients etc., and selecting the type and amount of excipients to deliver drug product of the desired quality
- Selecting an appropriate manufacturing process
- Establishing a control strategy

These core tenets comprise the foundation of the new process validation guidances, even if they are not explicitly identified in all documents.

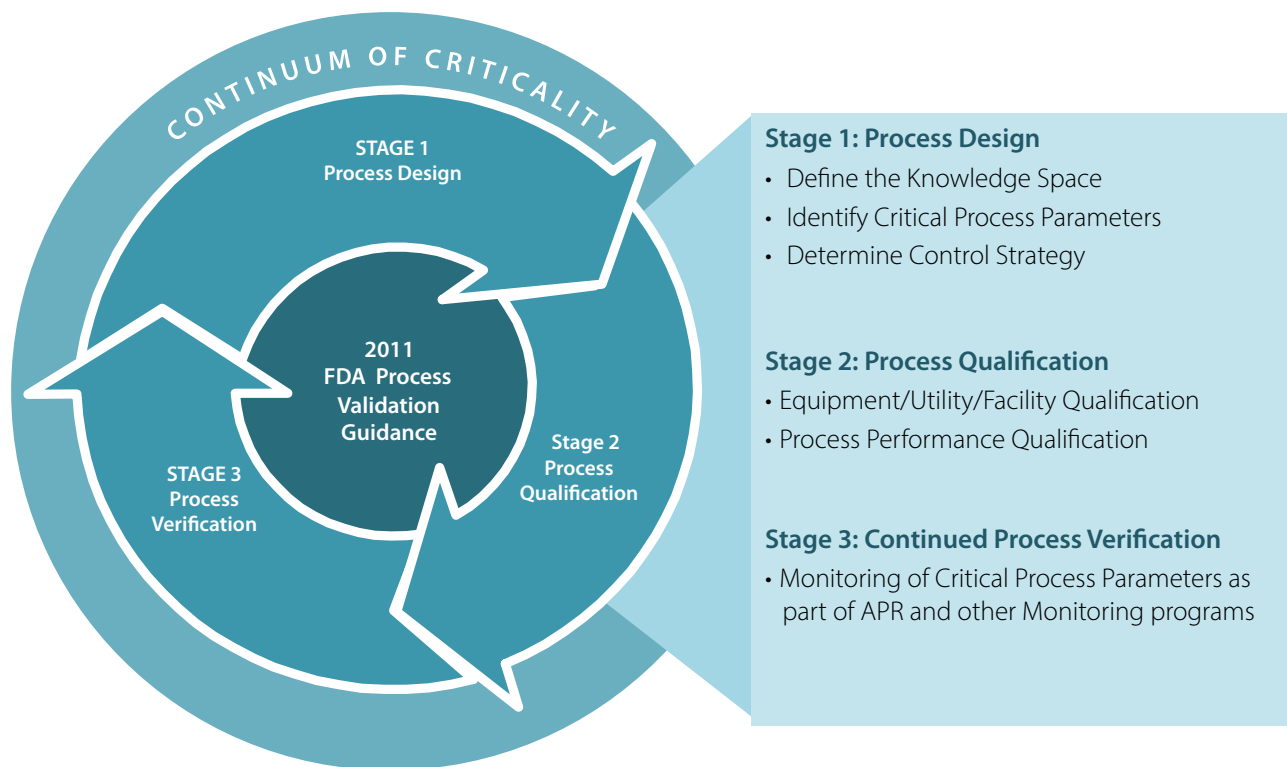
Components of the 2011 FDA Process Validation Guidance

In the lifecycle concept for Process Validation the new guidance has redefined Process Validation as consisting of three stages. Stage 1: Process Design, Stage 2: Process Qualification and Stage 3: Continued Process Verification. The underlying premise here is understanding what is important in the manufacturing process, either as a critical material attribute (CMA) or as a critical process parameter, that impacts the product performance as defined by its critical quality

attributes (CQAs). By controlling what matters, the premise is that the overall product performance will be more predictable. This is the rationale behind utilizing a measurement metric.

The new FDA guidance, its stages, key deliverables and activities are shown below in Figure 1; the stages are enveloped within what we call the "**continuum of criticality**" which is central to the new process validation

Figure 1. 2011 FDA Process Validation Lifecycle



Stage 1: Process Design

Process Design picks up after product development. Historically these two steps in the development process have been largely independent endeavors. Once the formulation and the basic unit operations were defined, it was up to the downstream organizational functions to translate these requirements into a commercially viable and sustainable process. In the new vision for Stage 1, the process design activity begins with the product design. The premise being that by understanding the **components function** in the product’s performance, and its **potential impact** to the patient’s safety, it is possible

to steer the process development and characterization activity to focus on addressing the components with the greatest potential to impact performance.

Both QbD and the FDA guidance advocate using risk assessment tools to focus development activity where it is likely to have the greatest impact on the product’s performance. Through the use of simple risk assessment tools such as “Cause and Effects Matrix” (CE matrix) it is possible to identify focus areas. Figure 2 is a simple example of a CE matrix for oral solid dose (OSD) formulation.

CQA	Microcrystalline cellulose	Povidone	Mg. Stearate	API
Appearance	Low	Low	Low	Low
Assay	Low	Low	Low	High
Content Uniformity	Low	Low	Medium	High
Dissolution	Low	Medium	Medium	High
Hardness	Medium	Low	Low	Low

Figure 2. Product Design C&E Matrix

PSD critical to solubility of drug. Low loaded dose can affect CU

Similarly, this can be extended to the process' unit operations by comparing the potential impact of a unit operation on a product's CQAs

and in-process control strategy. An example of a simple C&E matrix for an OSD process is shown in Figure 3.

Figure 3. OSD Process C&E Matrix Risk Assessment

CQA	Unit Operations						
	Granulation	Drying	Sieving	Enteric Coating and Drying	Sieving	Blending	Capsule Filling
Appearance	Low	No	No	Low	No	Low	Medium
Assay	High	No	No	Low	No	Medium	No
Content Uniformity	Low	No	No	No	No	High	Medium
Dissolution	High	No	Low	High	Low	Low	Low
Impurity	Medium	Medium	No	Medium	No	No	No
Residual Solvent	No	No	No	Medium	No	No	No
In-process controls							
Particle size	High	No	Medium	Medium	Medium	No	No
Water content	Medium	Medium	No	Low	No	No	No
Fill weight check	No	No	No	No	No	No	High
Visual Inspection	No	No	No	No	No	Low	High

In these approaches anything with a **High** ranking requires a scientific justification and should be a key component of the characterization activity during the process development.

In evaluating the basic principles of QbD, the primary characteristics defined above represent a minimum in terms of process understanding. However, some may choose to enhance these minimum requirements through a more extensive understanding of the relationship between the process and the products performance. Often termed "Enhanced Process Development," this approach strives to achieve a systematic evaluation, understanding, and refining of the formulation and manufacturing process by:

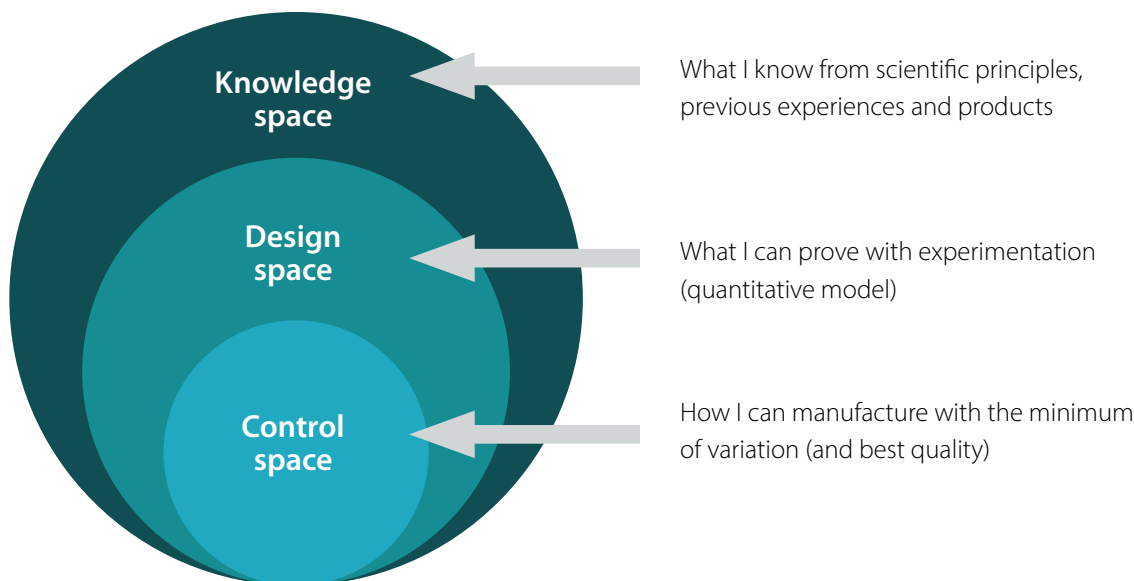
- Identifying, through the application of prior knowledge, experimentation; risk assessment, the material attributes

and process parameters critical to the product's functionality as defined by its CQAs

- Determining and defining the functional relationships between these critical material attributes and critical process parameters to the product CQAs
- Using the enhanced process understanding in combination with quality risk management to establish a defensible control strategy

Historically, process design has been largely based upon trial and error, or upon One-Factor-at-a-Time (OFAT) type experimentation. In an **Enhanced Process Development approach**, the goal is to determine the relationship between the potential process **Knowledge Space**, **Design Space** and **Control Space**. Figure 4 illustrates the relationship between these three concepts:

Figure 4. QbD Relationship between Spaces



In practical terms, these translate into the following stepwise activities:

- Eliminate parameters which do not matter from a product performance perspective, (i.e. CQAs)
- Define the proven operating range (POR) for each of the Critical Process Parameters identified based upon their relationship to each other
- Establish a recommended normal operating range for routine production (NOR)

The culmination of Stage 1 is the establishment of a defensible control strategy. Traditionally, all process development exercises established some manner of control strategy. However, the expectation today is that the data supporting this control strategy be scientifically defensible, not just generally supportive. This translates to statistically justified sampling plans, raw material specifications to demonstrate adequate resolution and capability, supportive data to determine criticality either from the process or material attribute perspective, in-process controls and defensible POR limits for critical process parameters and, finally, meaningful CQAs.

Stage 2 Process Qualification

Of the three stages, Stage 2 of the new PV lifecycle most closely resembles what we used to commonly think of as process validation, i.e., demonstrating that the process is consistent and capable of manufacturing product that meets specification. The prerequisites to demonstrating process capability still apply. The equipment, facility,

analytical methods, and cleaning methods still need to be qualified before proceeding. However, the new approach is less prescriptive than the original 1987 guidance and leaves the rationale of demonstrating readiness up to the drug sponsor. In other words, the agency is open to alternative models to the classical commissioning and qualification steps, to qualify manufacturing equipment and facilities such as ASTM E2500. This is another example of the movement away from a documentation centric approach to establishing equipment predictability and stability, which was the hallmark of the 1987 guidance, to one which is based on scientific understanding and insight as it pertains to its contribution to the variation of the product's performance.

What were once called process validation lots are now called **Process Performance Qualification (PPQ)** lots. Unlike classical process validation lots that tested product to specification, PPQ lots must establish acceptance criteria that demonstrate both within-batch and between-batch variability, and that utilize predictive statistical measures to calculate the certainty of the process. In addition, the default number of three lots has also been eliminated. Now it is up to the drug sponsor to defend the number of lots required to demonstrate process predictability. A variety of approaches can be used to arrive at the proposed number of batches, with the industry typically utilizing a risk-based justification based upon process capability as a foundation for the number of lots required. Anyone interested in a detailed discussion of the alternative approaches to use

should refer to the PDA's Technical Report #60 on Process Validation.¹

Stage 3: Process Verification

This last stage is completely new to the process validation framework and is the primary element driving the lifecycle concept. This part may be defined as **continued process verification** (CPV). In the past, once a process was validated there was very little motivation to optimize or adjust the process when a manufacturer encountered greater material variability or equipment duty cycle variability.

The concept of CPV is to create a system to capture, monitor and measure the variability of the critical process parameters and materials identified in Stage 1,

and demonstrated to be in control in Stage 2, with the intent of being able to make process adjustments, within design space defined in Stage 1. This would typically be addressed within the organization's change management system. For legacy products that are unlikely to have development data to meet the expectations of Stage 1 process understanding, the first step is demonstrating that the process is in control. If, after evaluating the process and product performance, the process is deemed to be out of control, then some corrective action will be required. This does not mean conducting a full Stage 1 exercise, but rather using prior knowledge to make process improvements that bring the overall process back into control, then demonstrating process predictability via PPQ lots.

Components of the EMA Annex 15

In contrast to the FDA 2011 guidance, Annex 15 is a much broader document that addresses process validation and many of the supportive systems required to manufacture a commercial product. Specifically, the document describes EMA's expectations for:

- Qualification
- Process Validation
- Transportation Verification
- Packaging Validation
- Utility Qualification
- Test Method Validation
- Cleaning Validation
- Change Control

It is more prescriptive than the FDA guidance and still contains many of the classical components of equipment and facility qualification. Deliverables cited in the guidance specific to qualification include developing a:

- Validation Master Plan (VMP)
- User Requirements Specification
- Design Qualification
- Factory Acceptance testing/Site Acceptance testing
- Installation, Operational and Performance Qualification

The EMA defines three approaches to process validation: Traditional, Continuous Processing and a Hybrid Approach.

Traditional

Traditional process validation is similar to the classical 1987 guidance approach in that three lots are the minimum required to demonstrate process reproducibility. But it does say that all manufacturers must justify the number of lots necessary to demonstrate a high level of assurance that the process is capable. It further states that additional lots may be required, based upon the risk profile for the development activity. Finally, it states that the rationale for sampling plans and acceptance criteria must be clearly defined in terms of demonstrating process reproducibility.

Continuous Processing

The guidance states that for products developed by a QbD approach, where it has been scientifically established during development that the established control strategy keeps a high degree of assurance of product quality, continuous process verification can be used as an alternative to traditional process validation. This requires a robust science-based control strategy for the required attributes for incoming materials, critical quality attributes, and critical process parameters to ensure product performance. In addition, manufacturing control approaches should also include regular evaluation of the control strategy. Process Analytical technology and multivariate statistical process control are tools to use to ascertain final product performance.

Hybrid Approach

The hybrid approach is unique to this guidance. It allows a combination of traditional process validation and continuous processing to be applied. This is particularly useful in cases where there is extensive prior knowledge of the process, or in cases where adjustments may be made to a process that was originally validated using a traditional approach.

Ongoing Process Verification

This last part of the new process validation framework applies to all three approaches to process validation. This activity requires that process trends be evaluated to ensure product quality, just as Stage 3 CPV does in the FDA guidance.

CDMO and CMO Impact

In today's market it is rare to find any product development program that doesn't include some element of outsourcing. In biotech, the prevalence of virtual companies has become more the norm than the exception. The challenge with this commitment to outsourcing is the drug sponsor's reliance on the contract service provider (CSP) to be capable of developing and executing the necessary studies required to comply with these new guidances. The challenge for CSPs is their need to establish a QMS that can handle legacy products and new products that does not penalize either group. In the interim, over the next decade, drug developers and CSPs will have grapple with escalating expectations for what defines a successful drug development program. Practically, Contract Development and Manufacturing Organizations (CDMOs) whose business model is geared toward partnering with virtual drug development companies are likely to be the first to embrace the core tenets of QbD. In particular those CDMOs which support biologic and cellular therapy drug therapies are most likely to have recognized that the core principles

of QbD are essential to moving a program forward that will satisfy the expectations of the FDA and EMA. The focus on personalized medicine and the promise of CAR Technology space in oncology space will require CSPs to be facile with the core concepts of QbD, and more than likely require an even more advanced application of these principles to be successful.

By contrast conventional Contract Manufacturing Organizations (CMOs) and Contract Packagers whose primary business model is commercial manufacturing support will be more resistant to the principles of QbD. The reality is these entities will have the learning curve to overcome, including building in-house expertise in statistics, experimental design and risk management before they can be as effective as CDMOs in this regard. In the meantime, this means both CMOs and drug development sponsors are at risk of blindly moving forward without establishing the necessary supportive data to support a successful BLA, MAA or NDA filing and a PAI inspection.

The Potential Impact of PIC/S

Perhaps the greatest impact on a global basis will be as a result the adoption of PIC/S. Started in 1995 as an agreement between 10 member countries PIC/S currently has 46 member authorities and is steadily growing². It has been forecasted that PIC/S could have 55 member authorities by 2020³. PIC/S differs from the FDA and EMA in that it is not a legal treaty between countries. Rather, it is an informal cooperation scheme that describes itself

as a forum for networking and confidence building, exchange of information and experience on GMP, focus on Quality Systems for Inspectorates, focus on training of GMP inspectors and strive for international harmonization of GMPs. There is no obligation for member authorities to accept inspection reports of other members as is required for countries that participate in a Mutual Recognition Agreement (MRA), so countries are more inclined to

collaborate regarding new regulatory and compliance standards.

The challenge with PIC/S' decision to adopt Annex 15 is the paradigm shift. Many of these drug manufacturers have been selling into markets where there is practically no non-conforming material generated. By that I mean, if a lot fails its release criteria, it is simply reprocessed and tested again. This will not be allowed in this new quality

paradigm so there will be a tangible impact to a drug manufacturer's bottom line. As a result the role of QA within the manufacturing culture will have to change dramatically. Complicating this will be the education and training of regulatory authorities to be able to inspect and evaluate manufacturers to the new standard. In the absence of consistent application of the regulatory expectations, adoption will be uneven, akin to what China has struggled with since the issuance of its GMP 10 guidance.

Conclusion

The 2011 FDA Process Validation guidance and the EMA Annex 15 guidance, define a new lifecycle concept for process validation that reflects industry best practice principles first put forth in ICH Q8, 9 and 10. The adoption of the Annex 15 guidance by countries subscribing to the PIC/S compliance philosophy means that this new approach to process validation will become the standard for a majority of the world markets. The rate of adoption is difficult to predict, but the rapid escalation of PIC/S member authorities since its inception, point to a desire and commitment to elevate the quality philosophy in these markets. It is likely larger drug manufacturers in the emerging markets which have the financial bandwidth to absorb the required increase in infrastructure and non-conforming product, will be the first to move significantly in the direction of QbD. Those that do will reap the benefits of access to the US and European markets which still constitute nearly 60% of the world pharmaceutical market.⁴ If the adoption of QbD as a framework for product development has been poorly embraced, the integration of QbD principles as a main and recommended approach to satisfy these new guidances is unmistakable. Both the FDA and EMA guidances have taken a significant step in

advocating the principles of QbD, and while not completely aligned the expectation is that as the industry evolves its best practices, approaches and solutions to both guidances will converge. The US has seen a marked increase in FDA 483 citations relating to Process Validation as the FDA has stepped up enforcement in this area. Those that have been through Pre-Approval inspections since 2011 have experienced the new greater emphasis on QbD principles, and this trend is not likely to go away. CMOs and CDMOs will find themselves at a significant disadvantage if they are not able to articulate and provide the necessary support to bring new products through a development program which will meet these new expectations. The hope is that the long-term benefit will be greater process predictability that translates to fewer non-conforming losses and, ultimately, more consistent product quality.

It is likely larger drug manufacturers in the emerging markets will be the first to move significantly in the direction of QbD

References

1. PDA Technical Report No. 60- Process Validation: A Lifecycle Approach, www.pda.org
2. Pharmaceutical Inspection Co-operation Scheme, <http://www.picscheme.org>
3. Tribe, Robert, PIC/S and International Regulations Update, 2013 ISPE Australasian Conference, September 9-10, 2013
4. Deloitte, 2015 Global life sciences outlook-Adapting in an era of transformation, <http://www2.deloitte.com>

Part 3.

Push-pull factors on growth



PANEL MEMBER

Dilip G Shah CEO, Vision Consulting Group

Mega Trade Pacts and Their Impact On the Pharmaceutical Markets

Introduction

The passage of the Trade Promotion Authority (TPA-2015) Bill by the US Congress gives powers to the President, for the first time after 2007, to fast track the mega trade deals: a trade deal among 12 pacific rim countries and a trade and investment agreement with the European Union. After the Bill was passed, the US Trade Representative (USTR) Michael Froman, in a statement, said that the Bipartisan Trade Priorities and Accountability Act (TPA-2015) represents “the most significant upgrade to our approach to trade in over four decades, including the requirement that labour and environmental protections be fully enforceable; new requirements for taking on unfairly subsidized foreign state owned enterprises; strong and balanced intellectual property protections; and new consultations and transparency requirements.” He further claimed that “TPA will move us one step closer to delivering trade agreements like the Trans-Pacific Partnership (TPP) and the Trans-Atlantic Trade and Investment Partnership (T-TIP) which will open growing markets to “Made in America” exports, protect our workers, and ensure that America, not our competitors, sets the rules of the road on trade.”¹ The pacific rim countries negotiating the trade deal are Australia, Brunei, Canada, Chile, Japan, Malaysia, Mexico, New Zealand, Peru, Singapore, U.S.A. and Vietnam. The “companion agreement”

to TPPA is TTIP. President Obama is aiming to conclude the trans pacific deal in 2015 and the trans atlantic deal in 2016.

As both these deals are being negotiated in secrecy, their draft texts are not in the public domain. Whatever is written and discussed about these deals is based mostly on “leaked” texts; the 11 May 2015 version of the intellectual property (IP) chapter of the TPPA, and the proposed draft text of the TTIP leaked in March 2014. The European Commission disclosed some clauses in January 2015 for public consultation.

The academia, civil society, media and political commentators have all raised concerns about the impact of the TPPA on the public health and the TTIP on the inability of the governments to regulate the big corporations. This article seeks to assess effects of these mega deals on the pharmaceutical market by 2020.

TPPA-Key IP Provisions

The US negotiators want:

- Patent Law changes to make it easier to obtain “secondary” patent
- Regulatory Harmonization to fast track drug registration

¹ Third World Network, 20 April 2015

- 12-year Data Exclusivity to prevent generic competition
- Patent Linkage to prevent drug regulators from approving generic versions
- Patent Term Extension to keep the competition at bay
- Weakening of the early working provision (Bolar Exception) to delay entry of generics
- Empowering customs authorities to decide on “confusingly similar” trademarks

The deal would favour big companies like Pfizer, Roche, and Novartis if the 11 nations were to concede these demands. It would slow down and delay entry of generics in their markets. It would also force these countries to bear the burden of U.S. drug prices and create lucrative markets for patented drugs. No wonder that the Pharmaceutical Research and Manufacturers of America (PhRMA) has been lobbying for the TPPA.²

It is a different matter that the US domestic laws do not have some of these provisions.³ It is of even lesser importance that the Obama Administration wants to reduce drug costs for its citizens. It does not matter that it wants to dilute the patent monopoly for the benefit of its public. The contradiction between the demands on the Pacific Rim countries and the US domestic law could lead to one or more of three potential outcomes.

1. It could increase the cost of healthcare for 11 Pacific Rim countries
2. It could deny the U.S. citizens benefits of reduction in data exclusivity period for follow on biologics and higher standards of patentability
3. It could result in 11 Pacific Rim countries paying more for the medicines and providing justification to reverse policies of Obama Administration

The third and the last is the most likely outcome of the TPPA.

TTIP – Five Key Provisions

The US and the EU represent 60% of world GDP. They share 33% of world trade in goods and 42% of world trade in services,⁴ and yet they are home to only 20% of world population. A free trade agreement between the two,

covering 46% of world GDP, will potentially be the largest regional free-trade agreement.⁵

The free-trade agreements generally focus on tariff barriers to improve trade flows. Impact assessment of such agreements is relatively easy. The TTIP, on the other hand, aims to remove non-tariff barriers. Its societal impact on labour, employment, public health, markets, financial stability and governance are very deep and widespread but difficult to assess. Nevertheless, many have tried to assess and caution the negotiators based on whatever little is in the public domain.

The TTIP could also lead to harmonisation of North American Free Trade Agreement (NAFTA) and European Free Trade Agreement (EFTA) with the TTIP. The first will affect Canada and Mexico; and the second will affect Iceland, Norway, Switzerland and Leichtenstein in Europe and Canada and Mexico in North America.

The impact of the TTIP on the pharmaceutical sector has to be seen in the larger context and with reference to five key provisions being negotiated by the U.S. and the EU. They are:⁶

- Changes in intellectual property regulations
- Limits on pricing and reimbursement policies
- Attempts to limit transparency of clinical trials
- Increased corporate involvement in policy making + Dispute resolution mechanisms
- Setting a global standard

As is obvious, the intention is to push the EU to adopt the US standards and in return, the U.S. to raise its own barriers in the domestic market – “America sets the rules of the road on trade.” The most likely outcome of this trade deal is promotion of interests of the brand-name industry by delaying generic competition. The impact will not be limited to the U.S. and 28 Member States of the EU. It will extend not only to Canada, Iceland, Leichtenstein, Mexico, Norway and Switzerland but also to the developing countries and their generic industry. The new “standards” of IP, Drug Registration, Protection and Enforcement will hit the generic industry across the world.

²William New, ip-watch.org on 05/06/2015

³Frederick Abbott, Bloomberg, 10/07/2015

⁴Wikipedia, the free encyclopedia

⁵World Economic Outlook Database October 2013

⁶TTIP – A Civil Society Response to the Big Pharma Wish List. Joint Position by commonsnetwork.eu

Future of the Pharmaceutical Market

The chronology of events indicates that the U.S. will first conclude the TPPA and use it as a benchmark to negotiate the TTIP. The 11 Pacific Rim countries, looking for access to the US market, are more vulnerable and prone to giving in to the USTR pressure than the EU. Among them, only three countries namely, Australia, Canada and New Zealand are known to evaluate trade-offs between the public health and other sectors. Japan has been a moot supporter of the US for pharmaceuticals in various trade forums. It is already practising most of what is being negotiated. This leaves seven countries. They may be lured by the preferential treatment in sectors like textiles, minerals, leather footwear, coffee, rice, rubber, wood and wood products, palm oil, fruits, fish and fish products, paper and pulp, etc. Consequently, the pharmaceutical industry will face disruptions across all major markets.

The brand name industry will be a major beneficiary of the trade pacts. It will be able to improve its price realization in the low-priced markets. It will be able to delay generic competition in all markets, including the US. and the EU. This would however be not without a certain cost. Its consumers (the patients) will be unhappy. Its customers (the doctors) will complain of unwarranted high prices of medicines, as they did for Novartis' Glivec.⁷ Businesses and corporations will be concerned for rapid rises in the healthcare cost of their employees. The law makers (parliamentarians), feeling cheated by the trade negotiators, will target the brand name industry for rise in medicine prices. The civil society and health activists will raise their banners for denying access to affordable medicines. The net outcome would be a poorer image of the brand-name industry.

The generic industry will suffer on several counts slowing down its growth and earnings.

- A major driver of growth for generics is new product introductions. As data exclusivity period and patent protection get longer, the new product introductions will suffer
- As the new product launches become scarce, generic companies will focus on a slice of the pie of older products. The resultant competition will lead to price

- erosion of even mature products, affecting their earnings
- Thus, two major drivers of growth, viz. new introductions and value, could have negative impact
- The remaining two drivers of growth, viz. new markets and volume, could provide opportunity to efficient manufacturers as they would drive volume and enter “new markets”, but it would be at the cost of existing players, as they will eat into their share
- As the patent linkage kicks-in in EU and other trading partners, the generics will face delays in obtaining marketing approvals
- Dilution of the early working provision (Bolar Exception) for marketing approval in other countries would require a generic company to manufacture the medicine locally in every country where it wishes to seek early marketing approval
- Not only patents, data exclusivity, and patent linkage, the TRIPs-Plus provisions related to protection of trademarks could question prominent display of international non-proprietary name (INN) or generic name of a product. It could prevent generics from using colours or shapes identical or similar to those of the original products⁸
- The fear of costly and lengthy infringement proceedings will keep generic companies at bay and limit them challenging even poor quality patents⁹
- The US proposal envisages empowering patent-holders to seek information of the entire supply and distribution chain in case of alleged infringement. The information so obtained could be used effectively to block the supply chain – transporters, warehousing agents and distributors
- The proposed border measures in the deal revive the fear of detention of goods in transit for alleged violations of patents and trademarks. The application of “confusingly similar” trademarks by the customs officials would most likely lead to seizure or detention of many generic consignments as it happened in case of a shipment of amoxicillin from India to Vanutan. The use of INN appeared confusingly similar to GlaxoSmithKline's brand Amoxil¹⁰

Thus, generic industry and the public health will be severely impacted. The generics decline will be discernible from the end 2017, if the TPPA is signed in 2015. It would begin from 11 Pacific Rim countries and accelerate with the

⁷ <http://bloodjournal.hematologylibrary.org/content/early/2013/04/23/blood-2013-03-490003.full.pdf>

⁸ UNTAID – The Trans-Pacific Partnership Agreement: Implications for Access to Medicines and Public Health March 2014

⁹ Ibid.

¹⁰ Ibid.

conclusion of TTIP in 2016. The decline will extend to the US and 28 EU countries, besides members of NAFTA (2) and EFTA (4). The full blown impact of these mega trade deals will be felt by 2020.

Encouraged by its success, the brand-name industry will be ready by 2020 to push the USTR to seek amendments to the TRIPs Agreement. Backed by some 50 signatories to TPPA and TTIP, the USTR will push for maximalist standards of protection and enforcement in the TRIPs Agreement. The moot question is if BRICS or any other new alignment of the developing countries would be able to thwart this grand design.

DGS:lf:27VII15



PANEL MEMBER

Vivek Sharma CEO – Pharma Solutions, Piramal Enterprises Ltd

The Fertile Market of Sterile Injectables

Introduction

As life sciences firms have increasingly shifted their focus to therapeutic segments like Oncology, biologics have become a larger component of the pharmaceutical industry’s development pipeline. Further, novel drug delivery systems that provide targeted therapies are gaining prominence. These two factors, among others, have led to a rapid growth in the Sterile Injectable technologies and formulations’ market.

In this article, we provide an overview of the sterile injectable dose formulation market, the drivers behind its growth, and the various types of dosage forms that constitute the market. Following which, we assess the reasons for demand-supply inequity and the acquisitive strategies that have resulted thereof. We then conclude with a service provider’s view that summarizes how providers have responded to client needs and market trends.

Market overview

The global sterile Injectable market is at circa \$312 billion in 2014 and is projected to reach \$363 billion by 2017. The two largest segments are Biologics (52% share) and Small Molecule injectables (38% share), with a CAGR of 7% for the latter. Within Biologics, monoclonal antibodies (mAbs) account for the largest market share, followed by vaccines and insulin (see Chart 1). In the Small Molecule segment, Oncology and Anti-Infectives are the major contributors of the market (see Chart 2).

(Source: IMS, 2014)

Chart 1. 2014 Sterile Biologics Market US\$ 162 B

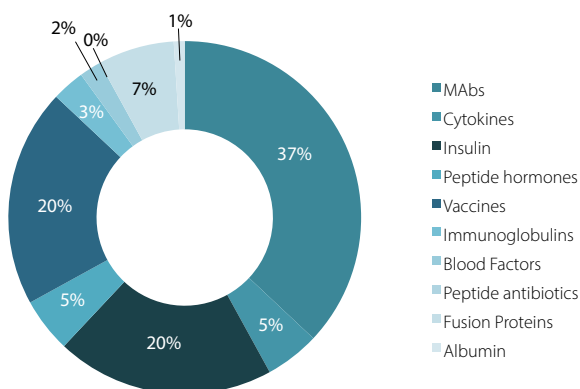
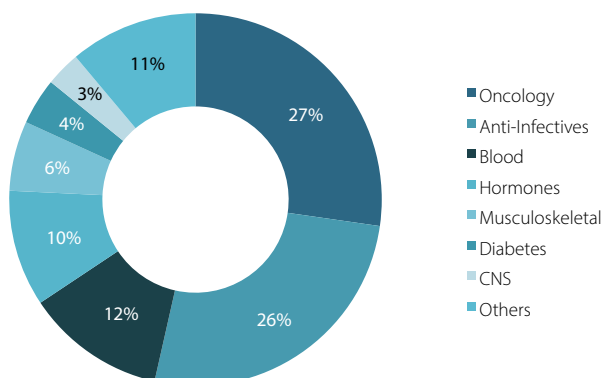


Chart 2. 2014 sterile Small Molecule Market US\$118 B



Market drivers

Approximately 2,400 injectable products are currently in the development pipeline (potent and non-potent), leading to growth on the innovative side of the market. Demand for cutting edge injectable capabilities should grow as ADCs and other high value products dominate the 'potent' development space. Nevertheless, the primary driver behind the growth in injectables is the generic market. Growth in the generic injectables is outpacing growth on the innovator side: The global, generic, sterile injectables market is projected to grow from \$37 billion in 2013 to \$70 billion in 2020 - a growth rate of 10%.

Market segmentation by technology

The Sterile Injectables formulation technologies market can be segmented into conventional and novel formulations. The 'Conventional Dosage' forms can be further categorized into Solutions, and Lyophilized / Water for reconstitution. Novel Drug Delivery Formulations have gained prominence in the last few years for enhanced disease targeting and to increase patient compliance. Some of them are:

- **Depot Injections – Microsphere & oil based:** A depot injection is an injection, usually subcutaneous or intramuscular, of a pharmacological agent which releases its active compound in a consistent way over a long period of time
- **Liposomes:** Liposomes are being used as carriers of various pharmacologically active agents like anti-neoplastics, antimicrobials, steroids etc. Liposome formulations are used to reduce toxicity and increase accumulation of the drug at the target site

- **Nanoformulation:** Nanoformulation enables the sheathing of drug particles with polymeric surfactants, which can then be layered onto a substrate for future delivery. This has helped in effective formulation of many insoluble molecules
- **PEGylated formulations:** PEGylation is the covalent attachment of Polyethylene glycol (PEG) to molecules of interest. It is the most commonly used non-ionic polymer in the field of polymer-based drug delivery. It increases solubility of the drug in aqueous medium, increases the half-life of the drug, reduces toxic side effects, stabilizes and improves therapeutic activity of the drug
- **Implants:** Implants are sterile solid preparations containing one or more active ingredients. They are of a size and shape suitable for parenteral implantation and provide release of the active ingredient(s) over an extended period of time

Key players in the innovator and generic space

Some of the large injectable players in the innovator (pharmaceutical and biotech firms) space are given in Table 1. Teva, Hospira, Hikma, and Fresenius Kabi, are some of the major generic players in this space.

Table 1: Key pharmaceutical and biotech firms with injectable products

Amgen	Genentech	Novo Nordisk
J & J	Sanofi	Abbvie
Eli Lilly	Pfizer	Roche Biogen

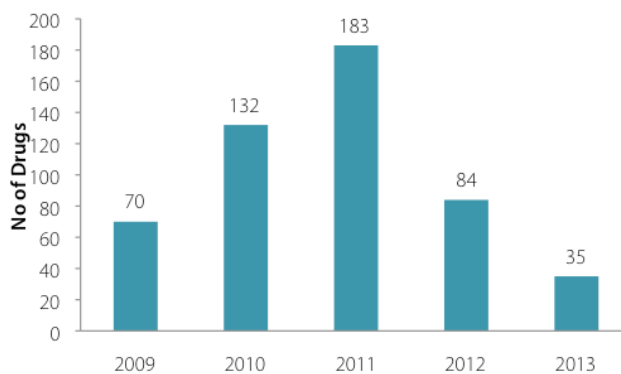
Market demand-supply equation

The development and manufacturing of sterile injectable products is both, complex, and capital intensive. Operational costs are high since injectables are toxic and infectious in their natural state and hence require a higher degree of quality and care in their manufacturing, packaging, storage, and distribution. Stringent regulations from FDA on manufacturing sites, pose a major challenge for both existing players, and for potential new market entrants. Competition from low cost manufacturing zones like India and China in the generic market has led to discontinuation of many products in the segment for economies of scale. Consolidation of captive/in-house manufacturing capacities have resulted in closure of many sterile manufacturing sites in the US and elsewhere which, in turn has led to product shortages in the US. Some of the other reasons for these shortages are:

- Mergers & Acquisition activities have resulted with single supply sources and capacity constraints
- FDA regulatory violations leading to Import alerts/bans at manufacturing sites
- Discontinuation of older injectable drugs in favour of newer, more profitable drugs
- Consolidation of supply chain by large pharma companies leading to shut down of their existing manufacturing sites
- Relatively less number of in the sterile injectable market that cater to the increasing demand of sterile dosage forms. The complex manufacturing process makes it even more difficult to transfer technologies freely between the sites. Some of the process related challenges are:

- Sterility: Bacterial and Fungal contamination
- Stability Issues (Crystallization)
- Extractables and Leachables from packaging materials: glass, metal or fibers in vials
- Transportation & Logistics

Chart 3: Sterile Injectables in short supply (Source: US FDA)



FDA has begun responding to shortages by expediting generic approvals for drugs that have shortages, shortening approval times for new production lines/new raw material sources to help increase supplies, and also allowing imports into the US for drugs under shortage from approved suppliers. This seems to be alleviating the problem, with the number of shortages reducing to 35 in 2013, from a high of 183 in 2011.

M & A Activity

The last few years have seen significant M & A activity in the sterile Injectable space. In a bid to quickly participate in a rapidly growing market, firms are acquiring specialist sterile injectable players to enhance their product portfolio and manufacturing capabilities. Some of the recent key deals are listed below:

- **Pfizer- Hospira (\$17 billion):** This provides a growing revenue stream and a platform for growth for Pfizer’s Global Established Pharmaceutical (GEP) business by combining Hospira’s generic sterile injectables products, including acute care and oncology injectables
- **Pfizer – InnoPharma (\$360 million):** At the time of the announced acquisition, InnoPharma’s portfolio included 10 USFDA approved generic products, a pipeline of 19 products filed with the FDA, and more than 30 injectable and ophthalmic products under development
- **Hikma - Bedford laboratories (\$300 million):** Hikma acquired Bedford’s product portfolio, intellectual property rights, contracts for products marketed under license,

raw material inventories, R&D and business development pipeline. This strengthened Hikma’s position in the US generic injectable market

- **Sun Pharmaceutical - Pharmalucence Inc.:** Pharmalucence was a privately held company based in Billerica, Massachusetts, which has sterile injectable capacity supported by R&D capabilities
- **Mylan – Strides Arcolab:** In December 2013, Mylan Inc. completed the acquisition of the Agila injectables businesses from Strides Arcolab Limited for up to \$1.75 billion. Through this acquisition, Mylan expanded its injectable product portfolio, pipeline, and capabilities, and as of December 2013, had more than 1,200 approved injectable products globally and more than 900 injectable products pending global approvals
- **Piramal - Coldstream Laboratories:** In early 2015, Piramal acquired Coldstream Laboratories, a Kentucky based injectable manufacturer to augment its formulation offering, while augmenting its ADC fill finish capabilities

Sterile CMO Market

Presently, the injectable CMO market is at US\$6bn and growing at a CAGR of 11% compared to the overall global CMO market which is growing at a CAGR of 7%. Outsourcing in the Sterile Injectable segment is still skewed towards US, followed by the EU. We anticipate this market to continue growing at 10% annually for the next 5 years and US to remain the most preferred outsourcing destination.

Some factors driving the growth are,

- Specialised technologies and dedicated capacities required for biopharmaceuticals products leads to high outsourcing of these products

- Preference to outsource products that require handling of high potency materials and containment suites
- Rapid growth of Pre-Filled syringes’ market leading to spike in the demand of CMOs
- De-risking of supply chain by brand manufacturers by adding a second source to their product manufacturing
- High growth in emerging markets resulting in local players looking at local CMOs to enter the geography

The major CMOs in the sterile injectable space include: Catalant, Baxter, Pfizer Centertsource, Akorn, Althea, Vetter, Piramal Pharma Solutions (ColdStream Laboratories), and IDT Biologica.

The Future

With over 900 approvals in the injectable space since 2000, the market is growing rapidly as firms invest more into development of new molecules and generics and ramping up their production capacities through acquisitions.

- Drug Delivery Systems like Liposomes, PEGylation, Depot Injections will see a spurt in the growth – especially in therapeutic segments that require efficient targeting of drugs
- Compliance issues and the high cost of injectable drugs will

- propel the Pre-Filled syringe market to attractive growth
- Biologic molecules will contribute to more than 50% of the research spend by top 15 companies globally, serving as a macro catalyst for injectables long term prospects
- Generic segment will continue its growth, and we expect that top generic players will consolidate their position with adding manufacturing infrastructure
- Emerging markets will drive the generic market expansion, with China and India leading the pack

Summary

The increase focus in biologics and targeted therapies, especially in the area of cancer has led to an increase in the need for injectable drugs. While biological drugs have a larger part of the injectable market, the small molecule injectables will have the higher growth. The complex process of manufacture, high capital and operational costs, and the compliance requirements for success has

led to a smaller number of players. These firms are being further reduced due to acquisitive activity in a sector that is rapidly consolidating. The supply crunch that was present a few years ago has been mitigated to some extent by FDA actions. In the future, we see a continued demand for injectable drugs especially in drug delivery systems and Pre-Filled Syringes.

References

- IMS World Review Molecule, 2014
 "Injectable Drug Delivery Market – Global Forecasts to 2017" by Markets and Markets

**PANEL MEMBER****Prabir K. Basu** President, Pharma Manufacturing, OPEX and cGMP Consultant

Innovation – can Pharmaceutical Manufacturing learn from the lessons in Auto Manufacturing in the US?

Introduction

In a 2008 article¹ titled, “Arguing by Analogy: What Pharma Can Learn from the Car Business,” the author of that article identified several key lessons that the pharmaceutical industry can learn from the automobile industry. At that time, the US auto industry was making a lot of headlines due to their business insolvency and related issues. Who could have imagined that companies like GM and Chrysler would be in such dire financial situation? The key lesson of the above mentioned article was that the pharmaceutical industry could possibly learn from what has happened to the US auto industry in the recent years.

Some characteristics of the auto manufacturing industry in the US that led up to the crisis in 2008, appear very similar to those that exist today in the pharmaceutical manufacturing business in the US and Western Europe:

1. Inefficiencies in manufacturing and the inability to streamline manufacturing.
2. Older plants and lack of investment in plant and technology.
3. Lack of innovation – age-old batch processes are still being used to make pharmaceuticals. The focus of pharmaceutical companies is in marketing and sales. Manufacturing assumes a secondary role.²
4. To stay competitive, the focus was on outsourcing to markets with cheaper labor rather than investing in modernization, new technology and improving efficiency and quality.
5. Lack of customer focus – pharma has two customers viz. the FDA and the patient. The patient is often forgotten. The patient relies on the FDA to ensure that the medical product is safe and effective. However, FDA does not even inspect many of the plants where our pharmaceutical products and the ingredients to make them are manufactured.
6. Lack of focus on quality and measurement of quality.
7. A reactive approach to problem solving rather than being proactive to solve their own problems. The auto industry blamed the unions for their decline and all their woes. Pharma today thinks FDA and the regulations are the major source of all their manufacturing problems. As if, if the FDA did not exist all, the plants would immediately upgrade their plants and processes and manufacture product that would be of very high quality.

¹Roger Longman, “Arguing by Analogy: What Pharma Can Learn from the Car Business”, The RPM Report, November 20, 2008

²Robin Pagnamenta, AstraZeneca to outsource manufacturing”, Times Online, September 17, 2007.

In the late fifties and early sixties, the automobile industry in the US was highly profitable and Japan had then just started entering the automobile manufacturing business. The automobile industry in the US was focused on engine power, vehicle speed, artful design, luxury and size of cars, but not so much on reliability and defects. Quality was of lesser importance. US automobiles were then generally competitive with European products and superior to Japanese products.³ In fact, people like Edward Deming found a voice in Japan rather than at home, here in the US. Deming championed statistical process control and started working with Japanese companies as early as 1947-1950 to better design products and improve product quality.

Rather than trying to improve quality by improving manufacturing through innovation and investment in new technology, the US auto manufacturers responded to the competition by shifting manufacturing to low labor-cost countries like Mexico. The main difference between the Japanese automakers and the US automakers, was that the Japanese implemented state-of-the-art quality management programs, measured quality and invested in innovative technologies to continuously improve the quality of their automobiles. Meanwhile, the US automakers pursued cost savings by looking for cheaper sources of labor.

Rather than trying to improve quality through innovation and investment in new technology, the US auto manufacturers responded to the competition by shifting manufacturing to low labor-cost countries like Mexico

As the result of nearly one hundred years of experience with many ups and downs, the US pharmaceutical manufacturers today undoubtedly have attained a higher regulatory and compliance standards compared to those in Asia. In addition, the FDA inspects US plants quite frequently, on an average once every two and a half years.⁴ However, the current trend is that pharmaceutical manufacturing is gradually being outsourced to countries with lower labor

cost without due consideration of regulatory standards in those countries, which have far less cGMP and regulatory history and experience. Facing cost pressure, rather than investing in quality, technology and innovation to reduce cost, the industry is relying on outsourcing where quality is far less guaranteed, as opposed to if the same products were manufactured in the US. Those of us, who have been involved with cGMP and regulatory compliance for a number of years in pharmaceutical manufacturing, know that the high quality standards and quality cultures cannot be achieved overnight by reading some books, manuals or FDA Guidance Documents. It is a culture that requires a number of years of training, experience and practice. Usually, a site or a manufacturer evolves into a high quality one over time, sometimes even through making some unfortunate mistakes. Pharmaceutical manufacturers in countries with cheaper labor are primarily in business by providing lower cost and are facing competition even internally in their own countries. Any experienced pharmaceutical manufacturing expert will agree that it is difficult to maintain low cost while investing in compliance. There is a cost to compliance. Quality is not cheap. I visited an Indian pharmaceutical plant in 2008, which exports several products to the US market, and while the manufacturing facility was very impressive, the lack of knowledge and the true spirit of cGMP, even among senior quality and regulatory staff was apparent.

It is well known that cost of labor is only around 20% of the entire COGS for pharmaceutical products.⁵ Thus, it is difficult to understand how the cost of labor alone can justify the significantly lower cost of manufacture of pharmaceuticals in countries where outsourcing currently is predominant. One might then ask the question as to why there is such a rush to outsource? Is the cost saving really due to cheaper labor, or is it due to being able to manufacture in a less regulated or unregulated environment?

Many of the countries which have lower labor costs are in the process of evolving into regulatory cultures, however, it will probably take them several years before they can attain comparable regulatory standards that have already been achieved by many US pharmaceutical manufacturers. FDA's inspection of foreign facilities has always been an issue. On April 24, 2008, during Senate hearings on the heparin fiasco, Dr. Janet Woodcock, the FDA stated that the FDA's

³Joseph M. Juran, "Made in USA: A Renaissance in Quality", Harvard Business Review, July-August, 1993.

⁴GAO-10-961

⁵Prabir K Basu, et al, "Analysis of Manufacturing Costs in Pharmaceutical Companies", Journal of Pharmaceutical Innovation 3(1):30-40 - February 2008

capacity to inspect generic drug manufacturing facilities “has not been commensurate with this global expansion”⁶. According to Dr Woodcock, “We cannot be the quality-control unit of the world.” Dr Woodcock also mentioned that with increasingly large numbers of pharmaceutical ingredients manufactured abroad, it makes it nearly impossible for the agency to ensure the safety of the drugs sold in this country.

The FDA inspect foreign plants at a much lesser frequency than domestic plants. A US Government Accountability Office Report issued in September, 2010 stated:

“Using a list the FDA developed to prioritize foreign establishments for inspection, the GAO estimated that the FDA inspected 11 percent of foreign establishments on this list in fiscal year 2009. At this rate, the GAO estimated it would take the FDA about 9 years to inspect all establishments on this list once. In contrast, in that same year, the FDA conducted 1,015 domestic inspections, inspecting approximately 40 percent of domestic establishments. The GAO estimated that at this rate the FDA inspects domestic establishments approximately once every 2.5 years. Further, FDA’s approach in selecting establishments for inspection is inconsistent with GAO’s 2008 recommendation that the FDA inspect, at a comparable frequency, those establishments that are identified as having the greatest public health risk potential if they experience a manufacturing defect, regardless of whether they are a foreign or domestic establishment. Instead, its foreign inspections continue to be driven by the establishments listed on an application for a new drug, instead of those already producing drugs for the US market.”

Thus, unless a serious quality issue arises, the probability that a foreign plant will get inspected while it is manufacturing product for the US market is very low (perhaps once every 11 years!). The FDA has considerably increased its resources for inspecting foreign pharmaceutical plants. However, it still has a considerable way to go.

When a product is outsourced, it is likely to be due to it being inefficient to manufacture in-house because the process is old and it has a poor performance record. Therefore, plants in countries like India and China are inheriting the poor technology from the West while they are evolving in their regulatory cultures. This is not improving

quality of the pharmaceutical products, but is in fact creating quality risks instead.

The status of science and technology of pharmaceutical product development and manufacturing is antiquated compared to other industries. Lack of research, innovation and publicly available knowledge base or “Technology Commons” in manufacturing science is startling for an industry so critical for the wellbeing of people. Will the increased reliance on outsourcing have the same consequences for the pharmaceutical industry as that of the US auto industry? If a major incident several times bigger and more severe than the heparin incident happens, will there be knee-jerk reaction from the FDA or the US Congress about outsourcing and quality of outsourced drugs? Will that lead to severe drug shortages in the US?

When a product is outsourced, it is likely due to it being inefficient to manufacture the product in-house

If the main driver for the pharmaceutical industry to outsource is to take advantage of cheap labor, then within a few years, is it likely that even India and China may face competition from other countries around the world with even cheaper sources of labor. How many foreign offices will the FDA have and how many inspectors will the FDA need in 2050 to assure the quality of our drugs? What the US corporations save in cost of pharmaceuticals by outsourcing is ultimately outweighed by the increased headcount and increase of the FDA budget. We have to remember that it is the US taxpayer who funds the FDA. The patient is not only saving money, but is also now at the risk of receiving a lower quality product.

Promoting “Quality by Design” (QbD) in developing and manufacturing medical products, using Process Analytical Technology (PAT) etc. and pushing for Quality Metrics in manufacturing are therefore the right approaches to the problem at hand. Approaches like QbD and PAT are proactive and they attempt to fix problems before they occur rather than the current reactive approach of assuring quality through inspection of the products after they

⁶Jesse C. Vivian, “FDA Inspection of Foreign Drug Companies”, e-Connect, December 15, 2008.
⁷GAO-10-961

have already been manufactured. According to Deming,⁸ “Inspection does not improve quality, nor guarantee quality. Inspection is too late. The quality, good or bad, is already in the product.” Quality by Design is practised by other industries such as the Japanese auto industry since the early 1960’s or perhaps even earlier. If products are designed and manufactured using the 21st century principles of science and engineering, then quality can be designed into the products and thus quality can be assured no matter where the product is manufactured. Therefore, implementing QbD will reduce the need for inspection by the FDA of manufacturing facilities, while ensuring a greater degree of quality of the medical products for our patients.

The main impediment to implementing QbD in pharmaceutical product development and manufacturing today is that the 21st century science, required to design

and manufacture our medical products by QbD, are not available. Therefore, the US government and the pharmaceutical industry should learn a lesson from the current situation of our auto industry and encourage investment in fundamental science and engineering to design and manufacture pharmaceutical products so that robust and cost-effective manufacturing processes can be developed. Greater savings can be easily achieved with innovative science and technology. It is important for the pharmaceutical industry to learn from other industries such as the automobile industry and invest in research and innovation to ensure that our medical products continue to be safe and of high quality. Like other industries such as the chemical and petrochemical industries, pharmaceutical research results should not be proprietary, but should be shared in public to create a viable knowledge base for the common good.

Addendum: Follow up Q&A on future trends

1. *Do you think quality cultures should come from the industry or the regulators?*

Quality culture is ultimately the responsibility of the industry. However, the FDA’s enforcement is weak. I often wonder (theoretically of course), what would happen if the FDA did not regulate manufacturing at all. In that case, I think the consumers will become more alert and will ask questions as to where and how the drugs are being manufactured. If I had a choice between buying a prescription drug from Pfizer or an unknown generic in a foreign country, I would not hesitate to pay a higher price to buy it from Pfizer for example. Today, consumers perhaps falsely think that since FDA regulates manufacturing, all manufacturing is equivalent.

2. *Do you know any manufacturers trying to implement any initiatives from the car industry?*

I know that some of the manufacturers have been inspired by the car industry experience. But, I cannot give you specific examples of direct one-to-one relationship between the OPEX or quality initiatives between the two.

a. *Can you predict if this will happen?*

It is already happening. Deming’s work with the car industry in Japan is being followed in most six sigma

and lean initiatives. Quality management principles are the same.

3. *Chinese and Indian industries are becoming gradually more expensive, do you believe that within the next 5 years cheaper industries will open up, or do you believe manufacturing will continue in China/India and that their regulations will improve?*

Chinese and Indian industries are going to become increasingly expensive as they try to comply with the regulations more and more, in addition to their labor costs increasing. Manufacturing will continue in India and China for several more years. However, I will not be surprised to see that other countries, with cheaper labor costs, becoming outsourcing partners for the western manufacturers. Isn’t it the most logical thing to happen? Why not? Also, if continuous manufacturing technology becomes well established, it will lead to manufacturing returning to the west.

a. *Can you make any predictions about outsourcing?*

It will continue to grow. There is no incentive or disincentive currently for the industry otherwise.

4. Just as a general thought, you mentioned that FDA costs are becoming increasingly high, do you believe the industry should support its costs e.g. through a levy? (Would this help.)

I think if a company decides to source an ingredient, intermediate or a final product from a company outside the country, then they should submit a proposal for that to the FDA. FDA should train and support private certified inspectors, who would be assigned to inspect and certify to the FDA that these outsourcing partners are qualified to do so. FDA can review and spot check on these inspections. These facilities abroad should be inspected at least once a year. The entire cost of this should be borne by the industry. There are a large number of qualified and well-trained people with experience available today. The FDA just needs to develop a program for training and certification. Pressure vessels, such as boilers, are inspected and certified by reputed inspection agencies, such as Lloyds of London. Why can't we develop a similar system? Why do taxpayers have to pay for the cost of inspection?

5. Overall, the context of the article puts a compelling (and worrying) case for the future if nothing changes, what do you predict the consequences for this will be?

a. Will the industry gradually improve its standards abroad?

Some of them definitely will do.

b. Will the FDA become further over stretched and fail?

FDA will undoubtedly become further stretched, but I cannot say that they will fail. However, if a catastrophic incident occurs, then I am not sure what the reaction of the public and the congress will be, a knee-jerk reaction may lead to severe drug shortages.

c. Will even lower cost markets emerge?

I firmly believe that they will.

d. Will the industry take the lead on pushing quality cultures?

Big pharma, which has a lot at stake, has already been pushing for quality cultures for a long time. They are also leading most of the OPEX efforts. However,

most of our drugs are generics and they are being outsourced. I am not sure about that part of our manufacturing.

e. Will manufacturing begin to return to the US and Europe?

Only if continuous manufacturing takes hold. Then we can have manufacturing on-demand on-site.

f. Do you think the patient may instigate change at all?

Only if a catastrophic incident occurs. Today, a patient thinks since he/she is buying the drug from a pharmacy, and the FDA is there to protect them; the drug must therefore be safe. Very few know how the drug is actually made, what the GMP's are, where the drug is made and whether the plant was even ever inspected. Even when we buy a piece of clothing, the label says where it was made, but not for a drug. Isn't that strange?

6. Any general thoughts on how this will develop over the next few years (5-10)?

Nothing much will change unless there is a serious or catastrophic incident. (Which I sincerely hope does not occur). The recent quality metrics guidance will not ultimately make a particularly large impact, as the metrics does not have any teeth, it does not reflect the quality culture. Manufacturing the metrics to look good is easy.

7. If you are not sure how the industry will change, how do you think the industry should be improved? (there may be no easy fix).

Outsourcing has to be regulated. I am not against outsourcing, however, outsourcing should only be approved if the company responsible for it can demonstrate that the outsourced product will have a superior quality, or at least an equivalent quality.

8. Any further information on how we might set up a technology commons ground (are we any closer to this than last year)?

The industry has to take the lead here. It can learn from SEMATECH, the semiconductor industry. Currently, the industry is too protective about its technology. They should come together and develop technologies

that can be widely used by everyone. Industry and government should support research in academia, to conduct research and develop new technologies or fill the gaps in technology. There should be texts, rules and procedures as to how to design equipment and processes. Pharma needs to learn from the chemical and petrochemical industries, which have invested in research into how to design and operate equipment, how to estimate physical properties of raw materials and mixtures, etc.

9. We are just really looking for your thoughts and predictions on how you think this situation will now evolve over the next few years.

I may be totally wrong. So, you must take my opinions with a grain of salt. But, I do not see things changing much unless there are some major problems with drug quality or drug supply.



PANEL MEMBER

Alan Sheppard Principal, Global Generics, Thought Leadership at IMS Health

The real need for generic medicines

Introduction

In an ideal world, there would be total freedom of access to healthcare with safe, effective, and affordable medicines available to all. Unfortunately, this is not – and cannot be – the reality. An aging and increasing population places ever greater demands on healthcare systems that have already been strained for several years. Add to this the economic stresses of recent times, and the rising burden of cost to health systems appears unsustainable.

Meeting the challenge requires a holistic approach, although one key area of focus remains controlling pharmaceutical costs. European countries have employed a multitude of tactics, including mandatory price cuts, changes in reimbursement levels, delisting of products, prescribing formularies, tendering for medicines supply, and increases in patient co-payments. These have worked to some degree, actually decreasing the growth in pharmaceutical expenditures in some countries.

In the EU, generic medicines have played a significant part in this aspect of cost control to date. However, given that over the next 10 years, the number of original brands losing their market exclusivity – and the savings opportunities to be had from generics – will be dramatically reduced,

the role that generic medicines have historically played in sustaining health systems in the EU will be diminished.

Providing affordable healthcare that meets acceptable standards is a major challenge in most European countries. Resources are pulled in many directions, and European economies struggle to raise sufficient funds from taxation to cover their budgets.

Providing affordable healthcare that meets acceptable standards is a major challenge in most European countries

Public expenditure on health in the EU reached an average of 8.7% of GDP in 2012,¹ having increased from 5.7% in 1980. On average, Western European countries spend 8 to 12 percent of their gross domestic product on healthcare – a proportion that has remained stable despite the global economic crisis, according to the Organization for Economic Cooperation and Development—despite the increasing demand. The specific proportion of GDP spent

on healthcare varies widely between Member States: it is above 11% in Austria, Denmark, France, Germany, and the Netherlands; below 6% in Estonia, Latvia, and Romania.²

Spending on pharmaceuticals, on average, accounted for almost a fifth of all healthcare expenditure across EU member states in 2012, making it the third largest spending component after inpatient and outpatient care. The economic crisis has had a significant effect on the growth in pharmaceutical spending in many European countries. Between 2000 and 2009, annual pharmaceutical expenditure per capita grew on average by 3.7% in real terms in EU member states, but fell in the following three consecutive years. On average, pharmaceutical spending fell by over 2% per year in real terms between 2009 and 2012 across EU member states.³

Pharmaceutical spending is closely related to GDP per capita and, over time, tends to follow GDP growth which in the current economic climate will fail to deliver sufficient funds to support the growth in healthcare costs.

Lowering pharmaceutical costs is seen as an important element of achieving sustainable healthcare, and even before the recession, many European countries attempted to control pharmaceutical expenditures via a mix of price and volume controls directed at physicians and pharmacies. They also relied on policies targeting specific products. In Germany, pharmaceutical companies must now enter into rebate negotiations with health insurance funds for new innovative medicines, putting an end to the previous free-pricing regime. In 2010, Spain mandated a price reduction for generics and introduced a general rebate applicable for all medicines prescribed by NHS physicians. In France, price reductions or rebates on pharmaceuticals have often been used as adjustment variables to contain growth in health spending, while in the United Kingdom, caps were introduced on pharmaceutical companies' profits on sales to the National Health Service (NHS).⁴

Some countries have started to shift healthcare costs to patients, via co-payments, new reimbursement policies and deregulation of certain therapies in order to reduce the burden on the provider. However, savings produced by all of these efforts can quickly be eradicated by changing

demographics and the availability of new, more expensive medicines.

Population aging is one of the greatest social and economic challenges for the European Union and is the result of a low fertility rate, the gradual progress of baby boomers toward retirement age, and increased life expectancy at birth. It is estimated that the increase in the proportion of people aged 65 and over will rise from 17.4 % in 2010 to 25.6 % in 2030 and to 29.5 % in 2060.^{5,6} Because an aging population has different healthcare requirements – such as a higher demand for mental health care, homecare and assistance and social capital and self-management services – health systems will need to adapt so they can provide adequate care and remain financially sustainable. Another consequence of the changing demographics is that the workforce will increasingly consist of older workers. This will in turn put pressure on healthcare systems as they attempt to cope with the need to maintain a healthy workforce.

Some countries have started to shift healthcare costs to patients, via co-payments, new reimbursement policies and deregulation of certain therapies

EU countries have seen an improvement in lifestyle trends such as a reduction in tobacco consumption and occupational injuries. Nevertheless, much of the burden of disease in EU countries is still linked to lifestyle factors, such as alcohol consumption, unhealthy diet, lack of physical activity, and obesity. Although there is considerable variation between countries, the EU currently has the highest level of alcohol consumption in the world (an average of 10.1 litres per person per year), while 53% of adults are either overweight or obese, and 16.7% are considered obese.

An aging society and poor lifestyle are linked to chronic diseases and conditions that have traditionally included cardiovascular disease, diabetes, and asthma/COPD. As survival rates and durations have improved, this type of disease now also includes many varieties of cancer, HIV/

AIDS, mental disorders (such as depression, schizophrenia and dementia), and disabilities such as sight impairment and arthroses. Chronic diseases are now responsible for most of the disease and deaths in Europe. Expenditures on chronic care is rising across Europe, consuming increasingly greater proportions of public and private budgets.⁷ Many of the diseases of ageing however, can be managed by the prescribing of a generic medicine.

New diagnostic and treatment options are improving survival rates for patients in many chronic diseases such as cancer, HIV/AIDS, and they are, in turn, driving demand for new medicines. For example, the new wave of treatments for hepatitis C offering the promise of halting disease progression, preventing the occurrence of end-stage renal disease and liver cancer. Such innovations, however, often come at a high price.

So where do generic medicines fit in? The value of generic medicines does not just lie in the role that they play in reducing the cost of therapies for post patent expiry usage of key medicines. They increase patient access to well established and proven therapies in many disease areas, however they represent only a very small part of the healthcare budget. In Europe, over half of prescription medicines are generic, but these only represent 25% of the

total medicine expenditure. As a tool, generic medicines provide a cost-effective solution to managing the budget spent on medicines, without compromising prescription freedom or therapeutic choice. Generic medicines stimulate innovation, both within the generic sector and the discovery and development of new medicines. With drug budgets under scrutiny, generic medicines can help control costs whilst still allowing headroom for additional expenditure required for new medicines, addressing unmet clinical needs. Generic medicines represent many of the therapies required for the treatment of diseases in an ageing population and as such provide a safe, effective and affordable solution. Growth in the generics sector should be seen as a positive step and as essential component of cost containment. Any existing negative incentives should be removed without delay if the full benefit of generic medicines is to be realized. Positive measures aimed at increasing usage of generics can provide a far more sustainable solution to cost containment rather than the arbitrary lowering of prices of generic medicines which may only result in marginal savings and could act as a disincentive for increased usage. Sustainable policies for pricing and reimbursement are essential if generic medicines are to be an effective resource in controlling long term costs. Without generic medicines, the cost of healthcare would surely be unaffordable.

References

¹World Bank

²OECD Health Data 2012

³OECD

⁴OECD

⁵European Commission

⁶OECD Health Data 2012

⁷http://www.euro.who.int/__data/assets/pdf_file/0008/96632/E93736.pdf (Gaining Health – The European Strategy for Prevention and Control of Non-communicable diseases. WHO, 2006)

Part 4.

The outsourcing perspective

**PANEL MEMBER****Gil Y. Roth** President, Pharma and Biopharma Outsourcing Association

CMO/CDMO Challenges and Opportunities

Introduction

The market for outsourced services and technologies is at a crossroads, but then, it always is. Estimates of the size of the global market for Contract Manufacturing Organizations and Contract Development and Manufacturing Organizations (CMO/CDMOs) in the dosage form space tend to vary widely, sometimes by an order of magnitude. This is due to a number of factors, including differences in methodology, ambiguities in terminology and definitions, the preponderance of privately-held players in the market, and the shroud of confidentiality agreements that covers the industry.

For our purposes, we'll use information from PharmSource, a provider of market intelligence, data and analysis for the global contract bio/pharmaceutical industry. According to PharmSource's information, total global bio/pharma R&D spend in 2014 was between \$125 and \$160 billion. Estimated CMC development outsourced spending was approximately \$6.7 billion in that year, while clinical research spending was approximately \$28 billion for 2014. PharmSource's recent research indicates that the contract manufacturing of

drug product for developed markets was \$16.5 billion, following two years of mid-single-digit growth.

Even without a firm set of numbers, general conversations with industry players indicate that revenue is trending up. A recent presentation by ICON Plc, a large Contract Research Organization (CRO), notes that overall bio/pharma R&D spend is growing at 2% to 3% annually, while numerous reports illustrate the flood of venture capital funding into the early-stage bio/pharma market. This signals increased outsourced spending across the spectrum, even without greater market penetration by CMO/CDMOs. Combined with a savvier understanding of outsourcing by large and small bio/pharma companies, and the future looks bright for CMOs/CDMOs.

A number of factors will help shape the future for this market, including growing funding in the emerging bio/pharma space, shifts in customer attitudes and practices, regulatory compliance, globalized supply chains, niche technology offerings, new and previously untapped markets, and perhaps most critically, the ways in which CMO/CDMOs learn from the industry's past.

Consolidation

The key trend for the industry is consolidation among CDMOs. By some accounts, as many as 600 companies engage in CDMO activity, including pure-play providers and hybrid business units of larger bio/pharma companies. Such a fragmented playing field virtually necessitates consolidation, especially since so many CMO/CDMOs are owned by private equity firms that have relatively fixed timelines for sale once they acquire a company. In some cases, these firms combine the assets of several CMO acquisitions in order to make them more attractive to a larger buyer. PharmSource reports that there have been 18 acquisitions of one CMO by another in the past three years.

In previous periods of consolidation, companies appeared concerned chiefly with achieving scale, breadth of services, and (for some) geographic reach. It was believed that an integrated, global set of offerings would appeal to the large pharma companies that spent the past decade-plus winnowing their internal manufacturing networks and were looking to reduce their number of external suppliers.

Today's CDMOs typically are neither acquiring companies solely to expand their footprint nor taking over pharma's unwanted facilities (except in highly specific cases). Some European CDMOs have expressed interest in acquiring U.S. facilities in order to get a greater toe-hold in the world's largest bio/pharma market, but such moves tend to reflect the moribund state of Europe's market than the tenor of the CDMO industry overall.

Rather, this current phase of consolidation shows CDMOs being more interested in integrating their service offerings or acquiring niche technologies or platforms that can bring

in earlier phase clients, who are more likely to stay with a CDMO into commercial manufacturing. With bioavailability as the key challenge for many therapeutics in development, savvy CDMOs are positioning themselves to offer specialized drug delivery technology solutions.

In the case of the largest recent consolidation – the Patheon-DSM pact (announced in Nov. 2013) – this move satisfied a unique set of corporate and financial goals, but was also a transformative event that created a global mega-CDMO with expertise and capacity across the bio/pharma spectrum. Patheon's recent divestitures of non-core, non-pharma assets have helped define this combined firm in the CDMO space. However, a smaller move more recently by Patheon, the acquisition of Agere Pharmaceuticals and its spray-drying technology, may be more indicative of the industry's future, in which specific technologies are added to companies that already possess global scale and an extensive bio/pharma clientele.

Diversification has also driven the consolidation efforts of AMRI, which in recent years has acquired Oso Biopharmaceuticals Manufacturing, Cedarburg Pharmaceuticals, and Gadea Pharmaceutical Group, as well as a pair of facilities from Aptuit, including an aseptic clinical manufacturing site. These moves boosted the company's API offerings and helped solidify the company's position in the finished dose manufacturing sector.

Consolidation presents challenges to the CDMO industry, to be sure. Unlike the less capital-intensive clinical research organization (CRO) industry, major roll-ups have been few and far between, but we have arced toward a market dominated by a few key players.

Client demands

The wave of consolidation is frequently framed as a response to large pharma client demands for fewer CMO/CDMOs with more comprehensive offerings. Since the late 1990s, there has been talk of bio/pharma customers moving from tactical to strategic relationships with their CDMOs. Major pharma companies have shown more initiative

in winnowing their list of contract service providers and working with preferred partners, but the CDMO industry lags behind the CRO sector when it comes to strategic partnerships. This is due mainly to the differing business models of these sectors, and the arrays of services provided. CROs, with lower fixed costs than CDMOs, have greater

flexibility for staffing and ramping up services for their strategic partners.

Sizeable (perhaps strategic) relationships with top pharma clients, while a major source of revenue and growth, can also be fraught with peril, as those companies continue to evaluate their supply networks and make strategic internal investments. One major CMO recently reported that it will lose as much as 10% of its annual revenue because of a client's decision to move manufacturing in-house.

In a recent article on biopharma-reporter.com, Roche chief operating officer of Pharmaceuticals, Daniel O'Day, remarked, "We continue to have about 80% of our biological manufacturing internally [and] about 20% externally – we think that's a good mix for our high-value manufacturing segment."^[1] That statement was in the context of a report on Roche's increased investment on internal bio-capacity. A variation of a few percent here or there may not be critical to a top bio/pharma company's bottom line, but could have huge ramifications on the CDMOs it works with.

Similarly, Biogen's recent move to acquire in-house capacity from Eisai may affect the relationship that company traditionally held with CMOs. The industry will have to balance reliance on major customers with the risks of strategic shifts.

In addition, the latest drug developments can present challenges to CMOs. Some report that the upswing in orphan drugs has led to smaller batch sizes, as these products have limited patient groups. While these products can be inordinately profitable to their license-holders, they pose problems for CMOs that have a more limited revenue horizon.

Some CMOs also contend that clients have become more circumspect about long-term contracts; where manufacturing pacts may once have run for five to eight years, clients are now asking for two-to-four-year deals. This trend can be a result both of specialty runs of drugs and of more sophisticated outsourcing practices on the part of clients.

Regulatory issues

The regulatory environment will also play a strong role in the future of the CDMO industry. Local content laws, supply chain compliance and other regulations may impact CMO/CDMOs, particularly as they serve an increasingly global marketplace. At the same time, these companies can be victims of the unintended consequences of well-intended regulations.

In the U.S., the Generic Drug User Fee Amendment of 2012 (GDUFA) was enacted to enhance the FDA's ability to review Abbreviated New Drug Applications (ANDAs) and inspect facilities that manufacture generics, similar to the prescription drug user fee (PDUFA). The fee structure of GDUFA differed from that of PDUFA in two significant ways: it contained no reductions or waivers for small companies, and it levied fees directly on manufacturing facilities, rather than on the filers of each drug. As a result, CMO/CDMOs found themselves being charged the same rate per facility as an in-house generic company, regardless of the number

or volume of generic products manufactured there. That meant that a CDMO that produced a single generic product for one week in a year was paying the same fee as an in-house facility for a major generic company that worked three shifts regularly to produce millions of doses. Further, CMOs that aren't manufacturing a generic drug but are listed on a client's ANDA have been paying full GDUFA fees each year, despite the absence of revenue.

This type of disincentive can have negative consequences on the manufacturing landscape. Based on the FDA's Self-Identified Facilities List under GDUFA, there has been a net decrease from fiscal year 2013 to 2016 of 7% in the number of facilities subject to Final Dosage Form fees, and 6.7% in the number of sites that are charged API fees. Domestically, the decreases were more severe: 13% fewer U.S.-based Final Dosage Form sites, and 14% fewer API sites, respectively. If GDUFA doesn't undergo structural changes for its 2017 reauthorization, we could see greater long-term impact on

CMOs, despite the fact that generics currently account for far less CMO industry revenues than branded drugs do.

Serialization and track-and-trace regulations also threaten upheaval in the CMO/CDMO industry, as manufacturers race to beat various regions' deadlines to comply with new regulations. Industry watchers are skeptical that U.S. regulations will be implemented on time under the Drug Supply Chain Security Act, but no one doubts that serialization will become the norm in the years ahead.

Implementing such systems will require a level of cooperation between clients and CMOs unprecedented in its breadth. CMOs will have major investments to make in terms of equipment and training, but if they can use serialization and its data-driven processes to build a greater

understanding of clients' manufacturing needs, the benefits could greatly outweigh the short-term pain in time and money.

CMO/CDMOs are benefiting from a strong business environment and a degree of foresight regarding investments in the post-fiscal-crash world. There are significant challenges ahead, in terms of consolidation, client focus, and regulatory compliance among other factors, but the best-managed firms will navigate potentially treacherous waters.

Gil Y. Roth is the President of the Pharma & Biopharma Outsourcing Association, a U.S.-based trade group for CMOs and CDMOs. From 1999 to 2014, he was the Founding Editor of Contract Pharma magazine.

References

¹<http://www.biopharma-reporter.com/Upstream-Processing/Roche-expanding-capacity-40-across-network-but-will-still-use-CMOs>



PANEL MEMBER

Hedley Rees Managing Consultant at PharmaFlow Ltd

What does the future hold for biopharmaceutical outsourcing?

Introduction

There is a something of a buzz around Pharma these days about the potential for biologically derived substances to transform the world of medicine. On the back of successful branded biologics from the biopharma innovator community, biosimilars have become hot news, and the potential afforded by stratified and precision medicine seemingly on everyone's lips.

It will have escaped the notice of few that the manufacture and supply of large molecule, biologic products, is very different to small molecule. Even seemingly minor changes in the production process can result in the product changing from what it was into something different, with potentially devastating effect for companies operating in the field. The biopharmaceutical mantra 'the process is the product' holds as true today as it ever did; and the analytical methods used to pick up potential differences in biopharmaceutical outputs are challenged, to say the least.

That is not the end of it. The sensitivity of biologics to temperature variation and other factors in the environment mean they can be lost in the blink of an eye. A moment's

loss of concentration from an operator or material handler can mean months of work going down the drain. A temperature data logger not properly validated, activated or downloaded can yield the same result – valuable product in the bin.

Even that is not the end of it. The potential for input materials to affect yield, potency and quality of output can be dramatic, as the titre of each new supply of materials can vary widely, dependent on factors not always obvious to the receiving company. Getting to the bottom of things with suppliers, especially when the upstream supply chain leads to seemingly anonymous donors, can be a nightmare and sometimes even impossible.

Wait for it, even that is not the end of it and this is the crunch. The cost of goods for biologics can often mean a promising compound becoming commercially non-viable. The net result of the factors above means that it is an order of magnitude more expensive to develop a biologic than it is a small molecule drug.

Now we come to the end of it, as we consider a new generation of biologically based therapies – advanced therapy medicinal products (ATMPs). As many will already know, ATMPs are made up of gene therapies, somatic cell therapies, and tissue engineered products.

These use the body's own healing mechanisms and often target conditions associated with a patient's genetic make-up. The potential to cure disease is phenomenal but it is still in its infancy; almost all the clinical trial work going on is at a very early stage, involving small numbers of patients in the hospital setting.

There is also a sub-set of ATMPs, autologous cell therapy, which is specific to an individual patient, whereby the patient's own cells are extracted, modified in some curative way, and then reintroduced into the patient's body. The potential for this type of therapy is further enhanced by the emergence of precision medicine, whereby patients with particular predispositions to certain conditions, can be diagnosed and a relevant therapy identified. Wikipedia defines it this way:

"Precision medicine (PM) is a medical model that proposes the customization of healthcare, with medical decisions, practices, and/or products being tailored to the individual patient. In this model, diagnostic testing is often employed for selecting appropriate and optimal therapies based on the context of a patient's genetic content or other molecular or cellular analysis"

When companies are faced with products that have such specific needs and there is such potential for things to go wrong, they need to be sure they have the necessary control of events through the end-to-end supply chain. Additionally, ATMPs and precision medicine are going to require far closer ties between manufacturers and the healthcare system. Traditionally, the industry has been producing one-size-fits-all products for global markets. Batch sizes have been huge, the customer base relatively contained to wholesalers, and three sigma quality levels have been sufficient to keep the wheels turning with the regulatory authorities, just.

It doesn't take a genius to work out that this not going to cut the mustard in Biopharmaceuticals. The current model of large manufacturing sites delivering finished products

to pre-wholesalers and wholesalers, who then deliver to hospitals and community pharmacies, is working for now, but it will start to creak at the seams, and possibly break, as innovator biologics, biosimilars and ATMPs grow further.

So what has all this got to do with outsourcing in Biopharmaceuticals, I hear you ask? An awful lot you hear me say! The banana skin waiting for the unsuspecting pharma is that this new era of biologics needs a different approach to outsourcing.

The banana skin waiting for the unsuspecting pharma is that this new era of biologics needs a different approach to outsourcing

The nature of a third party relationship is totally different to operations contained in-house. The outsourced relationship does not have the inbuilt linkages within the product license holder's or clinical trial sponsor's organisation. It is the quality and technical agreement (QTA) or supply agreement that determine what can, and cannot, be done. The contract acceptor has its own investors and boards of directors, stakeholders and cultures that have their own way of doing business. The service provider may also be supplying your competitors and your competitors' competitors too, even to the point where they are the only source of certain activities.

Whereas changes to plan can often be accommodated in-house by a shift of priorities, the very nature of the outsourced relationship means changes must be negotiated, with cost and lead-time implications to follow. Sometimes even there may be a failure to agree with a consequent 'costly divorce'.

The world of small molecule drugs has begun to see the potential downside if their outsourcing relationships are not properly set-up and managed. With biopharmaceuticals the issues multiply many fold, for the reasons below:

1. A Quality by Design (QbD) approach to drug development is the only way to guarantee the levels

of predictability and repeatability required in biologics. This will cost a lot of investment for a contractor, and additional cost with no immediate return, for the sponsor.

2. Each handover in the supply chain is an opportunity for things to go wrong and time to be lost on these often short shelf life products, measured in hours rather than days.
3. Contractors are going to want to patent their process knowledge to a far greater degree than with small molecule drugs. This will create potential 'lock-in' for Biopharma companies.
4. Similarly, the potential for lock-in is there even without patents in the process, due to 'the process is the product' effect.
5. Cost of costs is a critical part of commercialisation decision making, due to the inherent costs cost drivers with manufacture and distribution.
6. Tight control over the chain of custody is vital to avoid losing the product and meet the special regulatory requirements.
7. The skills required to manufacture, test and quality assure these products are in short supply, and there is certain to be competition for good people and the need to retain their services.

These factors, I believe, will start to drive discussions between biologics product license holders or clinical trial sponsor organisations, and their providers of outsourced services. Neither can do it on their own these days, as much of the technical expertise lies within the contractor base. There will have to be more in it for service providers, and sponsors will need to demand more from their contract acceptors than we currently see in the fee-for-service arrangement. Risk and reward sharing, whilst talked about widely these days, is not really happening to any degree, because fee-for-service is low risk. If the Big Pharma companies think more about expanding their own plants, as with the GSK in Ulverston, then the make/buy decision may become a lot more marginal and even swing back towards the in-house solution. This will make the contract sector think more carefully about models different to fee-for-service where more risks could result in much better returns if things work out.

Only time will tell how it all tracks out, but one thing is certain, there will be exciting times ahead in the new area of biologically derived drugs.



PANEL MEMBER

Arun Chandavarkar CEO & Joint Managing Director, Biocon

Access and affordability: The impact of biosimilars

Introduction

Globally, biologics are playing an increasing role in addressing unmet medical needs. These targeted molecules impact underlying disease pathophysiology in unique ways and in many cases can provide more safe and effective treatment than previously available small molecule therapies. That biologics are finding greater acceptance for treating a wide range of chronic diseases can be gauged from the fact that of the 41 new drugs approved by the U.S. Food and Drug Administration (FDA) in 2014, 11 were biologics. This was a big jump over 2013 when just two biologics were approved.¹

Biologics, like insulins and monoclonal antibodies (MAbs) have emerged as a class of highly effective transformational life-saving drugs targeted at chronic diseases like diabetes and cancer. Market trends point to the share of biologics expanding from 15% of the global pharmaceutical market in 2007 to 19–20% by 2017.²

Biologics differ from chemically synthesized drugs in that the regulatory, clinical and development requirements are considerably more exacting. The resulting high development and manufacturing costs imply that biologics tend to be 20 – 50 times more expensive than conventional drugs.

Today, there are a range of cutting-edge biologics to manage or cure a variety of conditions from orphan diseases to subtypes of cancer and autoimmune disorders. But more often than not, the high cost of these therapies push them out of the reach of many patients, especially those in low and middle income countries where common treatment regimens can cost several months' wages – making the treatment for chronic diseases simply unaffordable.

Research shows that the list prices for high-end medications including biologics do not vary substantially between developed and developing markets. This is despite the disparity in income and the high out-of-pocket expenditure in developing markets, where drugs account for 20–60% of healthcare costs and 50–90% of these costs are paid out-of-pocket.³

In developed countries, too, the increasing gap between drug prices and nationwide inflation rates has created an unaffordability gap.

Often these life-saving drugs are accessible only to the affluent.

As a result, millions of patients suffering from life-threatening or chronic diseases across the globe have to submit themselves to older generation drugs that may be less safe or efficacious as they don't have the financial wherewithal to afford these biological medicines.

The current scenario is untenable and has led to widespread demands for affordable generic versions of biologic drugs or biosimilars from patient advocacy groups, non-profits that support healthcare initiatives and governments with overstretched healthcare budgets.

The Cost & Time Factor

The reality, however, is that R&D costs for developing biosimilars are significantly high and time for development is extremely long in sharp contrast to the cost and time of development for conventional chemical synthesis based generic pharmaceuticals.

The development of biosimilars requires the confluence of multiple high-end skills due to the complexity involved in bioprocess development and significant investments in sophisticated manufacturing infrastructure including aseptic processing. Extensive physico-chemical and biological characterization, using sensitive orthogonal analytical techniques for demonstrating biosimilarity at the molecular level, as well as pharmaco-kinetic (PK) and/or pharmaco-dynamic (PD) studies against the chosen reference product are integral to the development process of biosimilars. Some regulatory agencies also require

comparative clinical assessments in Phase III trials in a local setting.

As a result, the cost of developing a biosimilar for global markets has been estimated at US\$ 75-250 million. This is in stark contrast to the estimated US\$ 2-3 million required to develop the much simpler, traditional non-biologic generics.⁴ In addition, the investment required for a complex biologics manufacturing facility ranges from tens to hundreds of millions of dollars.

The development of biosimilars requires the confluence of multiple high-end skills due to the complexity involved

The Growing Demand for Affordable Biosimilars

Nevertheless, 'biosimilar' products are expected to provide cost-effective alternatives to expensive reference biologics for patients and an opportunity for governments across the world to rein in their burgeoning healthcare spends. Cost savings from switching to biosimilars in the U.S. alone are projected to be US\$ 250 billion between 2014 and 2024.⁴ According to one study, the use of biosimilars in eight European Union (EU) countries can save up to EUR 33 billion by 2020.⁶

The European Medicines Agency (EMA) was the first authority to issue guidelines for biosimilars, which came into effect in 2005. The first biosimilar product to be approved by the EU was human growth hormone Somatropin in 2006. Since then, 21 biosimilars have been approved by the EMA, with 19 still marketed.⁷ These approvals were mostly for

'first-generation' biosimilars Erythropoietin, Filgrastim and Sompatropin, which have shown a significant reduction in cost compared to their reference products.

Biosimilar products have also been registered in Australia, Canada, India, Japan and South Korea.

The first-ever approval for a biosimilar in the U.S. came in earlier this year when the FDA allowed the commercialization of Zarxio (Filgrastim) from Sandoz via the 351(k) pathway.

On the other hand, the EU has moved on to approving the 'second-generation' of biosimilars e.g. MAbs and related molecules. Infliximab, the first biosimilar MAb, was approved by the EMA in 2013.

The approval meant that across 12 European countries patients suffering from certain autoimmune conditions could access a more affordable treatment option to manage their diseases. As Infliximab was offered to patients in Europe at a deep discount to the innovator product, biosimilar Infliximab has successfully captured a 70% market share in Norway and a 90% market share in Denmark.⁸ This kind of market penetration only goes to prove that the

market is ready to take advantage of the significant cost savings available to health care systems which biosimilar MAbs can provide.

While the positive experience that the European medical community with ‘first-generation’ biosimilars and the impact of market education are helping ‘second-generation’ biosimilars it continues to be a challenging landscape.

Biocon: Focused on Affordability

The EU has amply demonstrated that the presence of biosimilars enhances existing market competition, increases access to medicine to a larger set of the population and helps stabilize healthcare costs.

In India, companies like Biocon are trying to bring the same benefit of high quality yet affordable biosimilars to thousands of patients.

Towards this end, Biocon has successfully developed the world’s first follow-on Trastuzumab and introduced it in India as CANMAb™ in 2014, which provides an affordable treatment option for HER2-positive metastatic breast cancer patients and has helped increase patient access to Trastuzumab by nearly 30% in India.⁹ The global clinical development of Trastuzumab in partnership with Mylan to

provide access to this more affordable monoclonal antibody to patients in the U.S. and EU is also progressing well.

Today, Biocon has one of the largest portfolios of generic insulins and biosimilar therapeutics in advanced stages of development for approvals in the developed markets with five molecules in Phase III clinical trials, viz. rh-Insulin, Glargine, Pegfilgrastim, Adalimumab, and Trastuzumab. Three of these are already approved and launched in many emerging markets and are making a difference to patients in these lower income countries by providing a high quality affordable alternative.

We are confident that, together with our partners around the world, we can build a strong global presence in biosimilars to address the huge need for affordable access to these life-saving and life-enhancing biologics.

Smarter Regulations Can Facilitate Greater Affordability

As the number of biosimilars grow, the confidence in their safety and efficacy is getting built leading to a broader acceptance. Global regulations and guidelines therefore need to constantly evolve. The world over, there is a need to create a smarter regulatory pathway that not only cuts down the cost of development but also ‘time to market’, which in turn benefits consumers by improving access to affordable drugs.

This requires concerted efforts by global regulators and healthcare professionals to minimize development costs through greater harmonization, mutual recognition and abridged clinical development.

Abridged Clinical Pathway

Some recent instances of evolution in the regulatory pathway in developed markets hold promise for the speedier entry of biosimilars.

While the current regulatory practice generally insists on confirmatory clinical trials to compare efficacy and safety of a biosimilar with its reference product, in specific circumstances such trials may be waived. Already there is general acceptance of a risk-based approach that dispenses with animal studies in favor of non-clinical comparability exercises focused on in vitro studies, which are usually

more specific and sensitive to detect differences between a biosimilar and its reference product than in vivo studies. Similarly, there is a need for consensus among regulators over waiving off clinical trials for products whose structure, physicochemical characteristics and biological activity can be well characterized by state-of-the art methods and where clinically relevant PD parameters are available.

Interestingly the latest signals from the EU and U.S. regulators have also been encouraging in this regard. E.g.,

- The recent concept paper from the European Medicines Agency (EMA) on revision of the GCSF (granulocyte-colony stimulating factor) biosimilar guidelines explicitly raises the possibility of codifying the approach to waiving confirmatory clinical trials for biosimilar GCSF.¹⁰
- The U.S. FDA has also shown positive signs of reducing the need for clinical trials in certain cases, with evidence available that the FDA is not requiring a Phase III study in cancer patients for Pegfilgrastim biosimilars.

These are useful first steps and show that leading regulators recognize the fact that the biosimilars pathway can be made more efficient in light of the advancements in our understanding of these molecules. These developments also recognize the positive experience the healthcare community has had with biosimilars launched thus far. Over time, we expect that this kind of streamlining can be made a reality for a larger category of products.

Biosimilars And Interchangeability

One of the greatest challenges for biosimilars is to demonstrate whether or not they are substitutable with innovator products. "Interchangeability" or "substitution" 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. Without dealing with issues of "interchangeability," it is unlikely that the full potential of healthcare system savings from the use of biosimilars will be realized.

It is heartening to see that Australia has taken a lead in this regard with the country's Pharmaceutical Benefits Advisory Committee (PBAC) recently allowing biosimilar infliximab

to be automatically substituted for its reference product by pharmacists.¹¹

We are also seeing the "interchangeability" issue being discussed elsewhere in the world e.g. Finland and Netherlands, where recently published position papers from various medical associations have argued that biosimilars can now be considered as clinically equivalent to their reference products.¹⁴ What's more, the Norwegian government has taken the initiative to sponsor its own clinical trial to support switching.

Similarly, the U.S. FDA, on its part, is working on a set of guidelines for approving biosimilar substitution. These much awaited guidelines could determine the level of penetration that biosimilars can achieve in future.

One of the greatest challenges for biosimilars is to demonstrate whether or not they are substitutable with innovator products

Developed Markets Challenges

These positive events notwithstanding, biosimilars continue to be a challenging space in developed markets.

Naming Convention for Biosimilars: The U.S. FDA has recently issued long-awaited draft guidance and proposed rule regarding the non-proprietary naming of biological products, including biosimilars. However, in its current form these guidelines could complicate the uptake of biosimilars.

Long-drawn Legal Battles: Patent litigation is also acting as a significant roadblock, delaying the launch of biosimilars in developed markets like the U.S. Though the Inter Partes Review (IPR) proceedings have the potential to streamline legal pathways related to patent challenges in the U.S., we are yet to see a positive development on that front. The recent Amgen-Sandoz litigation has shown the high level of uncertainty associated with the U.S. "patent dance." The additional six-month post-approval notice a biosimilar player has to provide to the reference product sponsor, which is reflected in the most recent Amgen-Sandoz

judgement, will further extend the timelines for bringing the benefit of biosimilars to U.S. patients. The upcoming appeals in this case and the other ongoing litigation will be important precedent-setters.

Emerging Market Imperatives

While the growing need for biosimilars in emerging markets has opened up opportunities, these are throwing up their own set of challenges. Regulators in these jurisdictions will need to continue to develop capability and confidence to operationalize their biosimilars guidelines and implement

timely review processes in order to swiftly bring these important therapies to patients who need them the most.

Emerging market regulators should be empowered to make the risk-benefit decisions that are most appropriate for the healthcare system in their country, and in many cases, to carve out faster clinical pathways than used in other countries with different risk-benefit equations. However, in all cases, they will need to ensure that the standards of quality and compliance for biosimilar products are at par with the best in the world.

The Path Ahead

With experience biosimilars should be able to make as much of an impact as small molecule generics have in the past 25 years.

The fact that globally 57 biosimilars are in an advanced clinical development phase¹³ means that patients can look forward to enhanced access to otherwise expensive therapies in the near future.

The introduction of biosimilars, which offer comparable levels of safety and efficacy as original biologics, has transformed thousands of lives in some parts of the world. The challenge now lies in making these cutting-edge treatments widely available globally. Only then will competition among biosimilar players translate into benefits for patients, who will be able to access alternative lifesaving drugs that achieve better medical outcomes at affordable prices.

References

¹FDA Data;

²IMS Report on 'Global Use of Medicines Outlook Through 2017'

³WHO Data;

⁴Bourgoin and Nuskey, 'An Outlook on U.S. Biosimilar Competition,' April 2013;

⁵Express Scripts 2013;

⁶Research Paper: 'Saving Money in the European Healthcare Systems with Biosimilars,' Robert Haustein, Christoph de Millas, Ariane Hoer, Bertram Häussler. IGES. Berlin, December 6, 2011, published in GaBi Journal;

⁷'Challenges in Global Biosimilar Development: A Regulatory Per-

spective' by Joan Boren, Costantino Congiatu, Patricia Hurley;

⁸The Biosimilarz Blog;

⁹Internal company reports;

¹⁰Concept paper on the revision of the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant granulocyte-colony stimulating factor, European Medicines Agency, July 2015;

¹¹'Australian Regulators Recommend Biosimilar Substitution without Notification,' Institute for Patient Access, September 2015;

¹²The Biosimilarz Blog;

¹³Bernstein report;



PANEL MEMBER

Dr. Fiona Withey Managing Director, UK Clinical Services, PCI Pharma Services

Cold Chain Outsourcing: A Simple Answer to a Complex Question?

Introduction

Pharmaceutical manufacturers are facing a new challenge. The recent patent cliff and the exponential growth in the development of high value pharmaceutical products, biologically developed therapies and live vaccines in the last ten years, has resulted in a greater need for temperature-assured

handling of drug product, from active ingredients to finished dosage form. This can be demonstrated by the fact that in 2013, seven of the top ten highest selling pharma products were biologics,¹ with global sales contribution from biologic drugs forecasted to jump from 23% in 2014 to 27% in 2020.²

Side-effects of growth

There is a growing side-effect from the global expansion in demand for Cold Chain services for the pharmaceutical industry: a supply chain which is becoming more and more demanding and complex.

Causes for this increase in demand include the previously identified growth in the biopharmaceutical sector, driven by the industry's technological breakthroughs resulting in more effective treatments by virtue of more effective mechanisms of action. This is further complicated by industry trends in the size and complexity of clinical trials, and greater regulatory demands for safety and efficacy data prior to drug approval.

In particular, the growth in the Biologics sector has increased the importance of robust and carefully managed global supply chains. These temperature-sensitive biological products often have shorter shelf-lives than small molecule therapies and therefore require specialist handling. With cost pressures and readily available patient populations, clinical investigator sites are increasingly in developing markets and remote locations, geographies such as Ukraine and Russia, Asia Pacific, and Latin America.

Biologics add an increased complexity to the supply chain and require specialist handling during packaging, labelling, storage and distribution to ensure the product remains

within its specific temperature range, which can vary from controlled ambient to cryo-store at -196 degrees Celsius.

This is a crucial issue because Biologics are of extremely high value in terms of supply and cost, and are vulnerable to minor temperature deviations. Failing to maintain specific temperature ranges can have a negative effect on the efficacy of the drug. Additionally, the timescales

for manufacturing these materials are often very long and replacements for damaged products may not only be costly but could take many months, causing shortages in the supply chain.

This can potentially have a significant impact on the clinical trial supply chain and, most importantly, there is the ultimate consideration of the risk to the patient.

The outsourcing trend

Historically, the pharmaceutical industry has taken a short-term tactical approach to outsourcing clinical supply chain services by managing specific peaks in demand. This is now changing to align with the biotech sector which has developed a very different strategy: a large number of biotech companies have been founded on a 'virtual' model; outsourcing all manufacturing and distribution activities.

This often leaves the organization with little supply chain experience and no in-house clinical supply teams and services to support their requirements. They have had to rely extensively on external service providers to develop clinical supply chain strategies for the manufacturing, packaging (primary/secondary), labelling, storage and

global distribution of high value biological products.

This outsourcing trend is being continued by pharma companies which want to concentrate on what they do well and leave the specialist handling to the specialist outsourcing providers.

A large number of biotech companies have been founded on a 'virtual' model; outsourcing all manufacturing and distribution activities

Greater opportunity; greater risk

There is a lot at stake. To put it into figures: a recent Visiongain report highlighted that the global clinical trial supply and logistics market was estimated to have been worth \$11.6 billion in 2013, and is predicted to increase to \$16.34 billion in 2019 and further projected to grow to \$22.08 billion by 2025. Analysts attribute this strong growth to increased outsourcing of clinical trial supplies and distribution, which is expected to drive the market at a compound annual growth rate of about six per cent from 2015-2025.

However, this globalisation of the clinical trial supply chain and increased access to new markets could increase risk to the supply chain. It will demand the development of distribution strategies to mitigate this risk of potential loss of often high value product and, as a practical matter, effectively considered invaluable due to its limited supply.

A key part of this strategy would be a fully audited global supply chain with a consistent approach to managing shipments via both standard operating and specialist training procedures.

At the moment, for example, a temperature excursion during shipment is only recognised when the investigational product is received by the clinical site/end user and the temperature monitor graph is downloaded and reviewed. If there is an excursion, the product will remain quarantined until the sponsor confirms whether the temperature excursion is within allowable limits. If there has been a deviation and the product is deemed not suitable for use, this can result in a delay in patient dosing, postponement of patient enrolment, loss of the patients from the trial and/or trials to be delayed. Depending on scope and available supply, it may also warrant costly

new manufacturing activities to feed the supply chain for resupply to the investigator sites. With the high cost and often limited availability of biopharmaceuticals, entire shipments may need to be rejected.

The development of truly strategic partnerships including a robust and simplified supply chain is crucial to limiting risk. The aim is to reduce the number of 'touch points' where things can go wrong,

Selection of an outsourcing vendor is an important consideration in the clinical supply chain. Importantly this relationship should be evaluated in the context of a trusted strategic partnership. There are a number of questions to ask to verify their expertise in Cold Chain management and distribution:

- Are they a specialist in this area?
- Do they offer a range of shipping solutions?
- Do they conduct their own shipper validation or do they rely on data provided by the shipper supplier?
- Are they capable?
- Do they have capacity, even at short notice?
- Are they flexible?
- Do they contract out to any third party vendors and how are these relationships managed?
- If shipments have deviated from specified temperature ranges, how will this be managed and how will it be addressed to reduce risk with future shipments?
- In the spirit of a true partnership model, what ownership and accountability do they take to ensure safe packaging, labelling and effective logistics to the patient?

Responding to change

The response to the new pressures on Cold Chain services can be demonstrated by the drive of sponsor companies turning to specialist outsourcing providers to fulfil the needs of their temperature sensitive materials.

Proactive and collaborative management of Service Level Agreements and Key Performance Indicators is essential to ensuring the patient receives the right product, at the right time and in the right condition (temperature maintained through the supply chain). Such performance indicators include operational metrics such as On Time Despatch, On Time Delivery, Volume of Temperature Deviations, and gauging the overall safety and reliability of their logistical operations.

An additional strong focus is the financial analysis in terms of spend on individual clinical trial activities. Setting and managing a clinical trial supply budget is an ever-evolving

task, especially for global studies with distribution strategies which are focussed on responding to the requirements of patient enrolment.

Online portals integrated into supply chain operations present opportunities to extend visibility to sponsor companies into logistical touch points. This visibility can help foster a partnership model by providing real time information about inventories and locations, shipment status, and acceptance at the investigator sites, thereby reducing study lead-times and consolidating communication channels. Software can be extended to electronic document approvals and sharing, order transactions, integration into IRT technologies and so many other facets of business integration. This integration fosters a more effective supply chain and ultimately a more effective study execution.

Smarter technology

A smarter supply chain has many facets, but central to the entire process is the refrigerated packaging and labelling of products that have limited stability data outside of refrigerated temperatures, and when refrigerated room space may be at a premium.

When packaging and labelling Cold Chain products, it is crucial that the total time the product is outside of the appropriate storage temperature is minimal. The preferred packaging option delivered by the majority of vendors offers limited packaging suites for refrigerated labelling

and packaging operations. Cold room space is often at a premium. To address this and to ensure secure and efficient packaging, the industry must look for innovative and smarter ways to address these challenges. One such method is the use of a fully validated cold plate technology in which the product is stored whilst being packed and labelled. This method offers a unique solution to overcome the standard hurdles. This is specifically favourable when a just-in-time service is required and removes the need for personnel to physically conduct labelling and packaging in a dedicated 2-8°C packaging room.

Investigational therapies can be extremely invaluable, or practically immeasurable, in the case of cell therapy. Supply chain visibility can help mitigate risk. Technologies exist for an integrated electronically monitored platform that orchestrates supply chain activities for Advanced Therapeutic Medicinal Products, utilizing a single, compliant and FDA-validated technology platform. These combine proven technologies that economically and effectively integrate and risk-manage the cell therapy supply chain. Any paper-managed cell therapy supply chain quickly becomes inefficient and risk-prone due to shifting regulatory requirements and linear complexity as demand scales up and scales out. A successful and scalable cell therapy supply chain demands standardised processes, automated electronic records, integrated temperature-sensitive logistics, real-time visibility and end-to-end traceability, to ensure final product quality.

In some instances reversing the logistical order of standard practices can help mitigate risk and drive efficiencies. For example, storing vials at temperatures as low as -196°C also presents huge challenges for ensuring the all-important labels are able to be applied. Bespoke solutions have been developed by working with the product manufacturer to design, print and pre-label vials prior to filling and freezing.

Non-standard temperatures

The growth of the pharmaceutical industry has brought with it the development of new drugs which may require non-standard storage temperatures, for example -40°C. The requirement for this temperature range is increasing as biologicals are inactive below -35°C and it is possible to build pallet storage

As another example of adding visibility and safety to the supply chain, bespoke barcoding systems have also been developed to incorporate cold-chain traceability during the picking and packing of products and to reduce errors. This forces the operator to scan individual identifiers ensuring the correct kit is picked at every stage of the shipper packaging process, and confirms the 'start' of the temperature monitor.

Partnerships leverage innovative logistical models to ensure success. Flexible and just-in-time strategies must also be applied, taking into account the availability of the product, multiple protocols and the possibility of additional countries being added after the trial has commenced. For example, multi-language booklet labels can provide flexibility but are typically produced based on the countries planned at the commencement of the study. If unplanned countries are introduced during the trial, this can make the existing labels redundant and add time and expense due to requiring updated booklets and the subsequent relabelling of inventory.

A successful and scalable cell therapy supply chain demands standardised processes to ensure final product quality

An alternative strategy is to label supplies on a just-in-time basis, whereby supplies are labelled with country-specific labels only after distribution orders are received for shipments to clinical sites. Just-in-time labelling can be performed as either a discreet labelling operation in a packaging suite, or may be integrated into the distribution process, in some instances in an approved regional depot closest to the remote investigator site.

warehousing at this temperature for the storage of bulk materials prior to fill finishing, therefore maximising the shelf-life of these expensive products. These very specific product needs may warrant construction of a bespoke solution from the outsourced partner in the form of a tailored stand-alone facility.

Speed and control

The emerging need to improve distribution strategies is why cold chain specialists are striving to identify innovative methods to improve temperature-controlled shipping systems. Instead of relying on validation data from the traditional suppliers of shipping containers, logistics providers are looking at their own methods of validation of shippers to ensure the integrity of the Cold Chain under ‘forced’ demanding conditions.

For example, a new phase-change frozen shipping system (-15 to -25°C) has recently been validated, which involved extended conditioning times for the frozen plates, requiring one-month storage at -30°C. The clinical market is so fast-paced, dynamic and difficult to forecast that actually one month conditioning is completely inefficient.

With the aim to speed up the process, suppliers’ validations are being challenged and new custom methods for conditioning these systems have been created which

enable a significantly reduced conditioning process for the frozen shipping systems: from one month to 48 hours.

This can be achieved by employing ultra-low temperature conditioning of the plates at -70°C for 48 hours compared to the supplier’s method of one month at -30°C. Coupled with increasing the conditioning time at ambient (in order to expel the required amount of energy prior to pack-out), this ensures controlled frozen temperatures are maintained during transit.

This ability to continually challenge the supply chain by qualifying shipping systems on-site and utilising bespoke test environments, may prove to be a crucial capability for successful operators in the future, and result in completely removing temperature deviations from incorrect packaging of shippers. These solutions continue to be developed in the spirit of partnership and prevention.

Cold Chain conclusions

An increasing proportion of worldwide drug sales are forecast to be derived from biological products. As the biopharmaceutical market is growing rapidly, outsourcing/partnering Cold Chain activities to specialists is critical as a result of the increasing complexity of the biopharmaceutical supply chain.

In an industry where the patient is at the forefront of everything that we do, developments in activities such as packaging, storage and shipping technologies will continue to be made in response to the unique challenges this sector provides, to ensure that the right drug gets to the right patient at the right time and within the right temperature range.

Longer term development of the Biologics supply chain?

As we have seen, the current supply chain is constantly evolving to cater for – and predict – the pharmaceutical industry’s developing technology and requirements. We are currently seeing the trend towards custom parenteral delivery forms such as the auto-injector, to aid patient convenience for injectable medicines. This trend further complicates the temperature controlled supply chain for biologically developed medicines because of the unique nature of these devices.

On the horizon, however, is the even longer-term prospect of a radical upheaval, that could bring a step-change in the

supply chain – the oral biologic. If injectable Biologics – with all their Cold Chain supply implications – are replaced by tablets which are able to be packed and shipped at room temperature, that would be a revolution which would provide the possibility of a vastly less expensive supply chain, which is faster, and easier to manage.

That is some way off. One of the problems that must be solved is that, unlike current methods, orally delivered Biologics breakdown in the gastrointestinal tract and become inactive.

But if this roadblock is cleared, it would remove the need for Cold Chain packaging, labelling storage and distribution strategies, and eliminate associated complexities. It would be the ultimate simplification of the supply chain.

Just as Biologics are now enabling new research and treatments, so new developments could utterly reshape the supply chain. For progress to continue, each side must keep pace with the other.

References

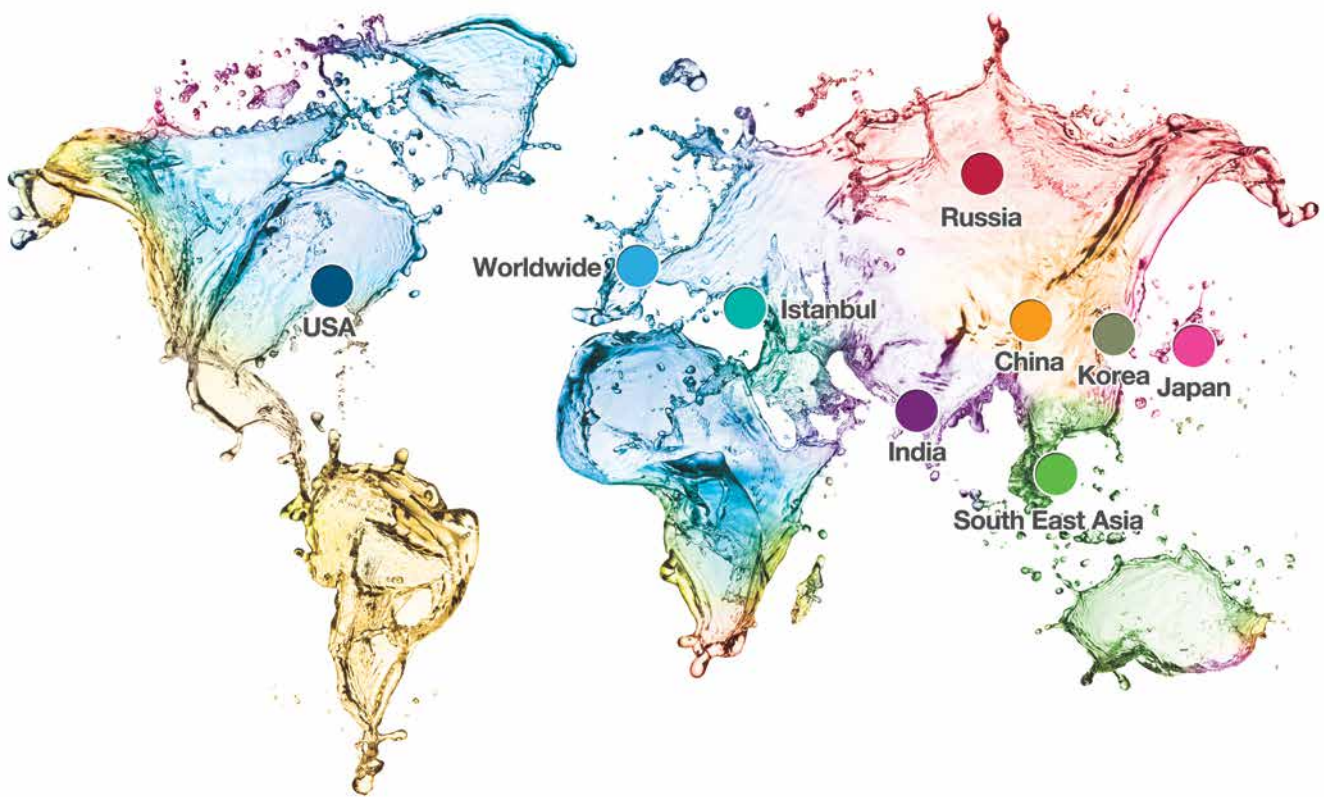
¹The Global use of Medicines: Outlook through 2017. Report by the IMS Institute for Healthcare Informatics

²EvaluatePharma, World Review 2015, outlook to 2020, June 2015

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.

For more information visit: www.cphi.com



CPhI Global Events

CPhI Worldwide	13–15 October 2015
CPhI and P-MEC India	1–3 December 2015
InformEx	2–4 February 2016
CPhI Russia	30 March–1 April 2016
CPhI Southeast Asia	6–8 April 2016
CPhI Japan	20–22 April 2016
CPhI Istanbul	1–3 June 2016
CPhI and P-MEC China	21–23 June 2016
CPhI Korea	23–25 August 2016
CPhI Conferences	year round

