Industry Visionaries Weigh in on Pressing Trends

Editor's Note Below are abridged articles from the annual report. The full, unedited versions are available at: www.cphi.com/europe/networking/cphi-pharma-insights

Expert Warns Urgent Regulatory Change Critical to Improving Quality

Girish Malhotra, President & Founder, Epcot International

Regulations are necessary for quality assurance of drugs. FDA established 21CFR314.70 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.

The FDA rule 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.

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. 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 more than 60 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

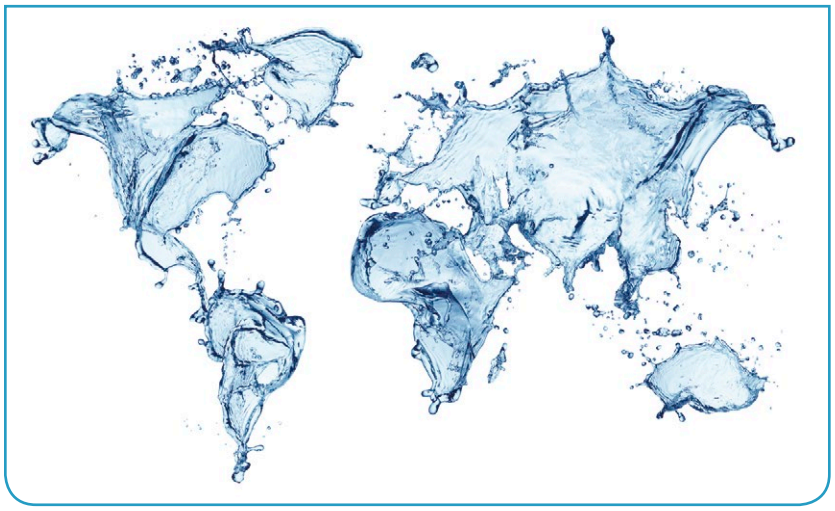
I would propose the following. I am sure there will be plenty of scrutiny and naysayers— unless we take bold steps, not much changes. If there are better ideas, let's discuss those as well. ► 12

Quality Metrics: Carrot & Stick

Brian Carlin, Director—Open Innovation, FMC

Report highlights:

- The FDA quality metrics initiative has elements of carrot and stick: compliance with baseline metrics (stick?) and optional metrics to demonstrate quality culture (a do-it-yourself carrot?)
- In practice, not all critical sources of variability will be identified, and explained at time of filing, although QbD assumes this
- The 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. The FDA should recognize and reward best practices, as well as enforcing minimum standards.
- 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.
- 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 a source of unknowns which confound design and risk assessment. Unknowns lead to rare and unpredictable "Black Swan" events with disproportionate impact, subject to post hoc rationalization. Oversimplification may be the reason for so many Black Swans in the pharmaceutical industry.
- Building variability and flexibility into your system can be used to offset raw material variability.
- If so-called "non-critical" excipients are present in DOE and production batches without incident may be misinterpreted as proof of non-criticality: the white swan argument. When a product failure is associated with a "non-critical" excipient, it is often 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."
- In practice, 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.
- 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.
- Moving towards a more metrics-driven regime should mean some measure of the degree of user-supplier joint due-diligence is included.



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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 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 would be excluded. This would apply to OTC, brand and generic products also.

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 the 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 percent 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.

Mega Trade Pacts, Their impact on Pharmaceutical Markets

Dilip Shah, CEO, Vision Consulting Group, and a regulatory expert

The passage of the Trade Promotion Authority (TPA-2015) Bill by the U.S. Congress gives powers to the president 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 U.S. Trade Representative (USTR), Michael Froman, 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."

The "companion agreement" to TPPA is TTIP. President Obama is aiming to conclude the trans Pacific deal in 2015 and 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
- 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

This deal would favour big companies like Pfizer, Roche, and Novartis and would slow down the 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 Pharmaceutical Research and Manufacturers of America (PhRMA) have been lobbying for the TPPA.

It is a different matter that the US domestic laws do not have some of these provisions. 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 U.S. domestic law could lead to one or more of three potential outcomes:

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

The third is the most likely outcome of the TPPA.

TTIP–Five Key Provisions:

The U.S. and the EU represent 60 percent of world GDP. They share 33 percent of world trade in goods and 42 percent of world trade in services, and yet they are home to only 20 percent of world population. A free trade agreement between the two, covering 46 percent of world GDP, will potentially be the largest regional free-trade agreement.

Unlike most free-trade agreements, the TTIP aims to remove non-tariff barriers. Its societal impact on labor, employment, public health, and more, are very deep, widespread and 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 harmonization 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:

- 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

The intention is to push the EU to adopt U.S. 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 also extend to developing countries and their generic industry. The new "standards" of IP, Drug Registration, Protection and Enforcement will hit the generic industry across the world.

The Fertile Market of Sterile Injectables

Vivek Sharma, CEO. Piramal Critical Care & Pharma Solutions

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.

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 percent share) and Small Molecule injectables (38 percent share), although the Small Molecule injectables are the faster growing segment, with a CAGR of 7 percent. Within biologics, monoclonal antibodies (mAbs) account for the largest market share, followed by vaccines and insulin. In the Small Molecule segment, oncology and Anti-Infectives are the major contributors of the market.

Sterile CMO Market

Presently, the injectable CMO market is at $6 billion and growing at a CAGR of 11 percent compared to the overall global CMO market, which is growing at a CAGR of 7 percent. Outsourcing in the sterile injectable segment is still skewed towards U.S., followed by the EU. We anticipate this market to continue growing at 10 percent annually for the next five-years and the U.S. to remain the most preferred outsourcing destination.

Some factors driving the growth are:

- Specialised technologies and dedicated capacities required for biopharmaceuticals products leading to high outsourcing of these products
- Preference to outsource products that require handling of high potency materials and containment suites
- Rapid growth of the 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: Catalent, Baxter, Pfizer Centersource, 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, generics and ramping up their production capacities through acquisitions.

- Drug Delivery Systems like Liposomes, PEGlyation, 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 attract growth
- Biologic molecules will contribute to more than 50 percent of the research spent by top 15 companies globally, serving as macro catalyst for injectables long term prospects
- Generic segment will continue its growth, and we expect that top generic players will consolidate their position by adding manufacturing infrastructure
- Emerging markets will drive the generic market expansion, with China and India leading the pack

Summary

The increased 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 successful players. These successful 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 some by FDA actions. In the future, we will see a continued demand for injectable drugs, especially in drug delivery systems and Pre-Filled Syringes.

Report highlights:

- Life science firms shifting their focus to therapeutic segments and increasing prominence of Novel Drug Delivery Systems has led to rapid growth in the sterile injectable technologies and formulations' market.
- The global sterile injectable market is at circa $312 billion in 2014 and is projected to reach $363 billion by 2017.
- M & A activity has significantly increased in the sterile injectable space over the last few years. 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.
- Increased investment is being supplied into the development of new molecules and generics, and production capacities are rising due to more acquisitions.
- The increased focus in biologics and targeted therapies, especially in the area of cancer has led to an increase in the need for injectable drugs—biological drugs have a larger part of the injectable market, but 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 successful players.
- The supply crunch that was present a few years ago has been mitigated some by FDA actions.
- In the future, we will see a continued demand for injectable drugs, especially in drug delivery systems and pre-filled syringes.