Industry Visionaries Weigh In On Pressing Trends

What does the future hold for the CMO and CDMO sector?

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

CMO/CDMOs: Looking Ahead

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

Consolidation

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

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

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

Buy In

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

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

Cash Out

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

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

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

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

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

Conclusions

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

All predictions null-and-void if Trump wins the US Presidential election against Democratic challenger Hillary Clinton.

Editor's note:

Below are abridged articles from the annual report. The full, unedited versions are available at: http://www.cphi.com/europe/cphi-annual-report

Licensing of Generic: Needs and Expectations of Industry

Dilip Shah, **CEO At Vision Consulting Group**

Introduction:

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

Cost Containment:

The foremost among them is cost containment through regulatory approval process.

It is difficult, but is doable. The five key areas are:

A Single Reference Product: Regulators in several markets approve a new product based on a global multicountry clinical trial. The innovators use one product in all countries for its trials and subsequent registration. However, this results in testing of multiple reference products for a company seeking regulatory approvals in more than one market.

Uniform Product Standards: Some product monographs vary according to the pharmacopeia; e.g. USP, BP, JP. All of these variations are not necessarily based on science alone. The variations reflect mindsets of different markets. The monographs usually incorporate the originator's standards. If only the regulators were to agree to a common standard for a product, instead of multiple pharmacopeias.

Common Packaging Specifications: Like product standards, the packaging specifications vary according to markets. The variations in different jurisdictions are mostly linked to the regulatory and/or marketing needs. Common standards could help reduce variability and cost.

Timely Product Approvals: Currently, the time taken for approval of generics varies from 4 months to 36 months in various jurisdictions.

Establishment Inspection & Report (EIR): The time taken by the regulators for inspection of new manufacturing facilities and re-inspection of old facilities under warning letters/import alerts is a major cost.

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

Compliance:

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

Quicker Resolution of Remedial Actions:

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

Capability Building:

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

High Potency API growth trajectory

Vivek Sharma, **CEO at Piramal Enterprises Ltd.**

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

Market size and drivers for growth

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

The anti-cancer market with its unprecedented growth is the engine that fuels the High Potency Active Pharmaceutical Ingredients (HPAPI's) market, since 60% of highly potent APIs are targeted towards oncology. The global HPAPI market, which was $12.6 billion in 2014, is projected to reach $25.1billion by 2023, at an estimated CAGR of 7.8%.

Regulatory and Manufacturing guidelines

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

In general, good manufacturing practices (GMP) apply to the production of highly potent and cytotoxic compounds. The only regulatory body to have flagged up the importance of bringing in updated guidance for safely dealing with HPAPIs is the European Medicines Agency (EMA). In 2005, EMA (European Medicines Agency) published a concept paper on HPAPIs, though it was mainly focused on high potent product segregation rather than classification. The concept paper primarily addressed the need to update GMPs and have better clarity on classification systems in order to determine requirements for working with specific compounds.

In 2011, EMA introduced another concept paper mentioning the requirement for a toxicological tool and a risk-based scientific approach to establish exposure limits. Then, in January 2013, EMA published a draft guideline on setting health based exposure limits. The primary purpose of this guideline was to advocate the assessment of pharmacological and toxicological data of individual active substances, which would allow establishment of safe threshold levels as mentioned in the GMP guideline. Around the same time, the EU came up with proposed amended text for managing the concern of cross-contamination in chapters 3 and 5 of GMPs.

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

Manufacturing HPAPI's: Captive and Contract

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

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

Conclusion

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

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

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