

INDUSTRY GRAPPLES WITH THE GROWING COMPLEXITY OF CONTRACT MANUFACTURING SUPPLY CHAINS

While all the market indicators point to healthy growth, managing the CMO relationship is a challenge. Industry collaboration might fill in the regulatory gap

On the surface, the business of contract manufacturing for life sciences should be nothing but good news. Big pharma continues to divest hard assets like manufacturing plants; startup companies tend to favor “virtual” organizations that hand off manufacturing responsibilities to partners; and meanwhile the volume of pharma and healthcare products globally continues a steady ascent (even if their prices are under pressure).



While all this is true, the road ahead is not a uniformly smooth one. In 2009, according to various market analyses, the US industry saw growth of barely one percentage point; a tough adjustment for an industry accustomed to growing at around 10-12% per year, as it has been since early in this century. But that was a year when many industries showed double-digit declines as the recession took hold, so the performance might not be so bad in context. Last year and continuing into this year, there is still a broad trend of manufacturers outsourcing manufacturing.

Most recently, Amgen has sold its Fremont, CA plant to Boehringer Ingelheim, one of its longterm CMOs. Dr. Wolfram Carius, B-I managing director, said that the “state-of-the-art facility will enable us to further strengthen our global contract manufacturing business including new biological entity process development and manufacturing.” The Fremont facility had been acquired by Amgen when it purchased Abgenix in 2006.

Besides overall business conditions, the CMO industry, at least in the industrialized nations, deals every day with the looming presence of “offshored” outsourcing, to China and India in particular, where recent growth rates on the order of 20% have been projected. Multinational pharma companies are still wrestling with how quickly they can build up their presence there, both to serve local markets and to obtain low-cost manufacturing. This trend, which has been occurring for a decade or more, is creating a dynamic that could change the shape of the entire industry in the future.

Continuing trend

Market forecasts of the CMO space are sketchy; different organizations count the business different ways, or include contract research organizations (CROs) which are a quite large business of their own. Global Industry Analysts (San Jose, CA) has just published a study that measured the world CMO business at \$20.8 billion in 2008, growing to \$40.7 billion in 2015. BCC Research (Wellesley, MA) measured it at \$44 billion in 2009, growing at a CAGR of 10.8% to \$73 billion in 2014, while BizAcumen, Inc. (San Francisco) measured it at \$22.5 billion in 2009. All agree, however, that growth rates of 10-12% will be the pattern for the next several years.

PharmSource (Springfield, VA), a market research firm specializing in outsourcing, reported in mid-2010 that, of the 487 NDAs and BLAs approved by FDA in 2005-2010, 200, or 41%, involved a CMO. Within those 200, 72 CMOs were involved in at least one approval; and 12 companies had a cumulative total of 105 approvals, or 52% of the approvals—indicating the degree of consolidation in the CMO market. (This analysis leaves out, however, the significant volume of CMO business for already approved drugs, as well as generics.)

Some of the leading CMOs have integrated vertically, looking very much like a traditional pharma company except for research on new molecular entities: Patheon (Research Triangle Park, NC), for example, touts a “molecule to market” service that entails manufacturing for clinical trials, formulation services and a wide range of dosage forms (solid, liquid, injectable) at commercial scale. The company has just bagged a new CEO, James Mullen, former CEO of Biogen Idec.

“The belt-tightening for life sciences companies across the board drives much of the outsourcing trend,” says Mike Leary, a partner at Clarkston Consulting’s (Horsham, PA) Life Sciences practice. “In addition, pharma are getting more comfortable with the concept of ‘extended networks’ of outsourced providers,” by which he means multiple providers who represent a network of sourcing, manufacturing and packaging services. “This has become a conventional practice in consumer packaged goods; now the challenge is for life sciences companies to manage these networks effectively.”

Marie McDonald, a coworker at Clarkston, notes that the trend is even more pronounced among biotechs. “Startup biotech companies are asking themselves, ‘How far can we go in minimizing additions to staff or capital assets’ in looking for partnerships to assist them toward commercialization.”

Perhaps the best example of these extended networks is Eli Lilly’s FIPNet—fully integrated pharmaceutical network—which includes partnerships with CROs and widely dispersed materials sourcing.

Fig. 1. FDA inspections of foreign and domestic manufacturing sites

Countries with the largest number of establishments in FDA’s inventory that may never have been inspected	Number of establishments in FDA’s inventory that may never have been inspected	Estimated number of establishments in FDA’s inventory	Percent of establishments in FDA’s inventory that may never have been inspected
China	811	920	88
India	323	502	64
Canada	206	310	66
France	107	188	57
Japan	99	207	48
Germany	97	228	43
United Kingdom	82	191	43
South Korea	69	75	92
Mexico	57	76	75
Italy	55	168	33
All other countries	488	900	54
Foreign total	2,394	3,765	64
Domestic total	253	2,498	10

Source: GAO analysis of FDA risk-based process data

FDA inspections

The collaborations are further complicated by the offshoring trend to Asia. US CMOs have a legitimate beef with how level the playing field is, as FDA looks a lot closer at domestic CMO operations than it does overseas locations. This has been a well-known situation for years. A Government Accountability Office (GAO) study issued this fall noted the same imbalance was in place in 1998, and has changed only slightly since then. The report, “FDA Has Conducted More Foreign Inspections... but More Progress is Needed,” (GAO 10-961) found that, on average, 64% of non-US facilities had never been inspected at all, while only 10% of US facilities had not been inspected (Fig. 1). Moreover, most non-US inspections (83%) occur as part of a pre-approval process for a new drug, compared to 18% for US inspections. “While FDA mainly selected domestic establishments for inspection to examine the manufacture of drugs already marketed in the United States ... FDA is still unlikely to select [a foreign] establishment for inspection” unless a pre-approval is involved.

From a CMO perspective, it might not matter too much that they’re competing for producing new or already-commercialized

drugs, but the obvious hole in the regulatory process is worrisome. “FDA officials acknowledged that the agency is far from achieving foreign inspection rates comparable to domestic inspection rates and, without significantly increased inspectional capacity, its ability to close this gap is highly unlikely,” the GAO report concluded.

“Five or so years ago, many US manufacturers went to China for the lowest prices, but now that driver is slowing as the costs begin to balance,” says Tee Noland, VP of business development at Pharma Tech Industries (Royston, GA) a US CMO.

“While offshoring always represents a threat, we plan to get better at what we do as our competitors make such plans. The companies we deal with value the benefits of not having to fly around the world, and to be able to manage their supply chains more closely.”

Quality rules

Indeed, quality concerns might be trumping economics in manufacturing costs these days. That GAO report came out of a request from the Committee on Oversight and Regulatory Reform in the House of Representatives, whose chairman, Eudolphus Towns, held hearings early last summer on the woes of Johnson & Johnson’s manufacturing problems, both in its own facilities and those of its CMOs.

“Quality assurance is the big differentiator among CMOs,” says Clarkston’s Leary. “The companies that can maintain their quality commitments and pass audits are the ones that will be retained by their clients.” Leary says that a growing trend among brand owners is to set up “quality liaison” functions—a team whose primary responsibility is to ensure that quality standards are met by CMOs. The quality liaison reports to a quality assurance office at the brand owner, but could be stationed at the CMO. Regular audits, and the ability to produce the necessary audit data, are the focus of the liaison’s attention.

“More so than CPG, life sciences companies have heavy regulatory burdens, so an approved manufacturing process in an approved facility is not something to switch out lightly,” says Leary. “That puts the onus on the brand owner to ensure that quality measures continue to be met.”

Pharma Tech’s Noland emphatically agrees, noting that “the trend we see is a higher interest in longterm, strategic partnerships, checking constantly on the service levels and quality assurance with our clients.” Cost is still an issue, but quality is what shapes our organization.”

Quality collaboration

The combination of quality assurance concerns and CMOs is driving several efforts to enable the life sciences industry to manage its business processes better. One effort in this regard, the Rx-360 organization (rx-360.org) was formed in the aftermath of the contaminated-heparin scandal from 2008; it has held several meetings over the past couple years, and is developing a “shared audit” program whereby brand owners can share their internal audit data with each other to qualify CMOs that they (individually or collectively) might be using. In October, the group got a clearance from the US Federal Trade Commission to address antitrust concerns. The current board of Rx-360 has representation from Amgen (which originated the effort), Baxter, GSK, Abbott, Merck, Novartis and 14 other life sciences companies. It is still unresolved, however, whether manufacturers will actively cooperate with each other in this manner.

Another, newer, effort has apparently just got under way by a group called The Quality Advisory Board (theqab.com) to provide “realtime, actionable intelligence and a better toolset to manage the risks inherent in the expanding pharmaceutical supply chain.” The group has sketchy details of a pilot program being initiated. PC