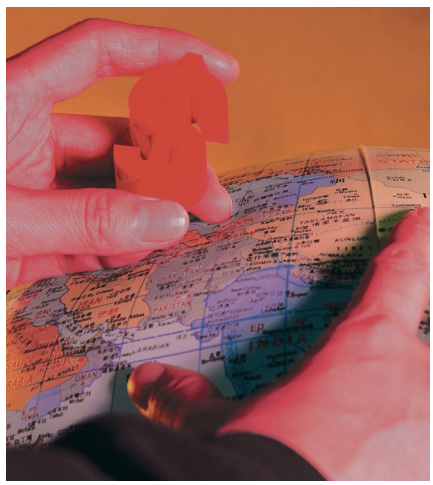
Selection and Oversight of Domestic and International CMOs

by Michael Strauss and Jeanne Novak

Contract manufacturing is essential for early development of products by companies of all sizes, and it plays an important role in later production and testing. Product development is a complex process requiring manufacturing, optimization, and testing of candidate drugs, devices, combination products, and biologicals even before they ever reach the clinic. Contract manufacturing organizations (CMOs) provide services ranging from early product development and lead-candidate screening to process development, product manufacture, and testing.

Outsourcing of development, manufacturing, testing, preclinical, and clinical activities has sharply increased since the 1990s (**1**). The number and variety of such activities has changed, as well as the types of organizations that use contracted efforts. Gone are the days where only necessity (e.g., lack of equipment and skilled personnel for a given task) drove companies to outsource activities. Contracting of development and testing has proven to be cost effective even for companies that could perform the relevant activities in-house (**2–4**).

Contracting of pharmaceutical services spans a product lifecycle: from screening of potential candidate substances to postapproval activities. Early development is often outsourced to contract research organizations (CROs). Subcontracting such work often allows companies to take advantage of discovery platforms that are not available in-house. Some CROs offer molecular biological expertise for development of



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expression constructs (whether plasmid or viral) that sponsors may not maintain. Once a product candidate has been chosen, CMOs are often used to produce the relatively small amount of material required for proof-of-concept or preclinical studies. Many established manufacturers are unwilling to adapt their large-scale operations to produce the smaller quantities needed for early characterization and preclinical studies (**3, 5, 6**).

CROs that specialize in preclinical research can be useful for testing candidates in compliance with good laboratory practices (GLPs) (**7**). Such facilities provide services ranging from experimental design and project management to in vivo testing and data analysis.

Once a candidate compound has been demonstrated to be effective in animals and on the laboratory benchtop, in the United States an investigational new drug (IND) or investigational device exemption (IDE) application can be filed. Once that has been cleared by the US FDA, clinical testing can commence. Many sponsors turn to CMOs next to produce the larger amounts of compound needed to conduct clinical trials, from early safety and exploratory studies (phases 1 and 2) through pivotal efficacy studies (phase 3). Clinical research organizations often provide the infrastructure to run these trials, providing oversight and monitoring for compliance with good clinical practice (GCP).

Even after market approval, the role of contract organizations can continue. They're used not only for outsourced development of approved products, but also (for example) contract testing laboratories may be involved in release testing throughout a product life-cycle.

Importance to the Industry

Types of Outsourced Activities: Contract organizations fill a number of roles in the pharmaceutical community. There are many niche specialties as well, and the "CMO Specialties" box lists some (**5**).

The capabilities and number of contract facility specialties has grown over time to serve industry requirements. This list, though not comprehensive, will continue to grow as the number and variety of products increases (**9**).

Trends in Outsourcing: Spending on contract services has increased steadily since 2002 (**1**), and it is expected to increase 33% by 2011 for a compound annual growth rate of 6–8% from 2004 to 2011 (**10**). Some experts estimate a compound annual growth

rate as high as 14.9% (**11**). Even with the recent global economic downturn, pharmaceutical sales are predicted to grow annually by 3–6% through 2012 (**9**). To serve this burgeoning need, the number of facilities providing contact services has increased worldwide (**12**). The "Number of Contract Manufacturers" box surveys the numbers and location of manufacturing facilities based on a list of contract organizations compiled by HighTech Business Decisions (**13**).

A survey published in 2007 by *Contract Pharma* magazine demonstrated changing trends in outsourcing. Of the >200 respondents, four in 10 said their rationale for outsourcing was "to focus on core competencies." Only 27% said their reason to outsource was that their companies were virtual and by definition must contract out all manufacturing services. Over 75% of respondents indicated that their spending on outsourcing would grow over the next year. These results indicate that increased spending will be driven both by virtual companies and those with in-house production and research capabilities (**2**). A need for large pharmaceutical companies to adopt more agile manufacturing schemes, which often include contracting out traditional supply chains, is being driven by large fluctuations in product demand, higher expectations for product innovation, and new guidance from regulatory agencies (**14**).

CMO Specialties

API Manufacture

Small-Molecule Synthesis: preclinical, phase 1–3, commercial

Biosynthesis: preclinical, phase 1–3, commercial

Analytical: characterization, release testing, method development, stability

Formulation: topical, parenteral, oral, and others

Other Services and Product Types

Drug Product Fill and Finish: packaging, labeling; vials, ampules, syringes, tablets, suspensions

Medical Devices: class I, II, and III

As spending on CMOs increases, such organizations have gained more bargaining power to limit product-sponsors' demands on them. This has included reductions in the amount of historical data revealed and the number and scope of allowable audits.

Deciding to Outsource

The decision to outsource manufacturing or development is complex. Many factors come into play: internal capacities (including the in-house availability of relevant skilled and experienced personnel), financial constraints (e.g., costs for building capabilities or expanding existing facilities), and strategic concerns (e.g., concentrating on core strengths and maintaining flexibility) (**3, 5, 6, 15, 16**). Additional considerations when deciding whether to outsource internationally include time and cultural differences, travel costs, and communication barriers. Locating a CMO can be complex when international sites are involved. Although abundant information is available online, personal recommendations or networking within the pharmaceutical community should be key tools in locating and choosing a CMO. Such contacts can be used to gain accurate information on a given CMO's capabilities as well as serve to verify the accuracy of information obtained elsewhere.

Choosing a CMO

When choosing a CMO, sponsors should consider not only their own needs and what contractors have to offer, but also be aware of constraints (e.g., legal or regulatory issues) that might complicate their choice (**17**). When outsourcing internationally, sponsors should be aware of the interactions that may occur between laws of different countries as well as the impact of domestic and foreign regulatory requirements (e.g., import/export). Due-diligence auditing will be necessary to thoroughly evaluate these characteristics.

Characteristics of a Successful CMO: Certain characteristics are universal in choosing a CMO successfully (**18**). The "Characteristics to Look for" box lists areas that should be examined during this decision-making process.

The first four characteristics listed are inherent qualities that should be examined in all contractors considered to support pharmaceutical development or production. The remaining two are historical information that would be useful to characterize a contractor's past successes or failures. Often such information will not be freely provided, but even indirect answers to such questions can be informative.

Other Considerations: Many other considerations gain a higher level of importance when a foreign CMO is chosen. These include laws and regulations that may differ between a sponsor's location and the contractor's (and potentially differing in the target marketing location) and long-term considerations of sponsor needs compared with the CMO's capabilities and capacities throughout a product life-cycle (**17, 18**). The "Considerations" box lists questions to ask.

Number of Contract Manufacturers By Region*

North America	**98**
Europe	**60**
Asia	**33**
Central and South America	**16**
Australia	**13**
Africa	**10**

* Number of companies with facilities on each continent

Managing Interactions

Central elements that both contractors and sponsors consider key to managing successful contracting relationships are well-defined goals and responsibilities (**4, 17**). Communication and well-defined expectations are also critical (**4**). All of these elements can be spelled out through a series of technology transfer agreements that will be useful in specifying the goals of the relationship between two companies and their respective responsibilities (**19**).

Technology Transfer Agreements: There are four major categories of technology transfer or manufacturing

Characteristics to Look for in a CMO: Questions to Ask

Capacity: Can it manufacture your product in the necessary time frame?

Experience: Does it have experience in manufacturing the same or similar products? If not, what will be the delay in implementation?

Facilities (Environmental Monitoring and Capabilities): Does the CMO have appropriate facilities to not only produce your product, but also to produce it to the required standards (e.g., cGMP). Does it have the correct systems to provide evidence that those standards are observed?

Quality Systems: Is an adequate quality system in place?

Regulatory Track Record: Has the contractor already manufactured products that have been approved by regulatory agencies, either domestic or foreign? Does it have experience with the regulatory agencies? Which ones?

483s and Other Action Letters: Has the contractor undergone inspection, and what is its track record? Has it experienced recalls, and if so, what were the root causes?

Quality Agreements: Core Elements

Defining roles and responsibilities

Audit frequency and duration

Interaction of sponsor and CMO quality systems

Reporting on out-of-specification results

Interaction with regulatory agencies

agreements (**20**): business contracts, quality agreements (required by regulatory agencies), technical or manufacturing agreements, and technical task agreements.

Business agreements include contracts for the financial interactions between a contractor and product sponsor. Specific goals and responsibilities may be mapped out within such a document, or they may cross-reference other agreements. This document maps out the business terms for a contractual relationship including payments, payment schedules, materials delivery, timelines, and exclusivity requirements (e.g., is a contractor allowed to manufacture product for a direct competitor?) (**21**). The business contract is sometimes referred to as a *supply agreement* (**4**).

Quality agreements are required by many regulatory agencies for all contracting arrangements. As the "Quality Agreements" box shows, they contain many elements critical to the successful quality and regulatory management of a contracted product.

A good quality agreement defines the roles and responsibilities not only of contractor and sponsor, but also of specific team members. A sponsor audits the contractor to determine and maintain both contractual and regulatory compliance, and a well-defined quality agreement defines the scope, frequency, and duration of such audits.

Defining the interactions of a sponsor's and contractor's quality systems is very important. It encompasses a wide range of issues including management and approval of documents, deviations, and change control within a process (**22**). In particular, the handling of out-of-specification (OOS) results should be well defined: e.g., how soon the sponsor will be informed and what the decision-making process will be for resolving OOS issues.

Finally, the quality agreement should map out interactions with regulatory agencies. This includes documents a contractor will be required to produce for regulatory filings (e.g., relevant master files to reference) and the process for handling regulatory inspections. For example, will a sponsor representative be present for an inspection, what role will he or she play, and for how long will he or she participate?

A **manufacturing agreement** includes a description of specific manufacturing tasks that will be performed by a contractor with the specifications and requirements (e.g., yield) for successful manufacture and the respective responsibilities of sponsor and manufacturer in executing or changing the process (**5**). This should also include agreements on contingencies such as failures or recalls (**21**).

When contract organizations perform testing or specific technical tasks, a technical agreement spells out the scope and requirements for success. Additionally, it may map out responsibilities and consequences (both fiscal and scientific) for failing to meet those requirements delineated in the agreement. This agreement will also map out responsibilities and timelines for technology transfer activities, including comparability and necessary validation.

A **technical task agreement** is used when a contracted scientific project is more limited in its scope and goal. This type of agreement defines that specific goal and the methodology that will be used to achieve it. For instance, a company considering a switch in raw material might contract out an analytical comparison of old and putative new raw materials to a contract laboratory.

Regulatory Requirements: Ultimately, regulatory agencies define the minimum requirements that must be spelled out in contracting agreements. They expect a sponsor to conduct proper quality oversight of all contract manufacturers (**23**). They expect a written quality agreement and other documents to clearly

Considerations for Choosing a Foreign CMO: More Questions

Long-Term Prospects (Product Life Cycle): Will your choice of CMO satisfy strategic requirements over both the long and short terms (e.g., at other stages in the product lifecycle)?

Laws: Will legal barriers complicate the product strategy (e.g., imports/exports) or the sponsor–CMO relationship (e.g., requirements for materials sourcing)?

Regulations: Will differences among regulatory bodies governing the CMO location and target markets change product requirements?

Financial Aspects: Does using a foreign contractor lead to any additional financial constraints (e.g., exchange rate) or considerations (e.g., travel costs)?

Intellectual Property: Are there intellectual property complications?

identify the responsibilities of each party as well as the lines of communication and reporting. And they expect planned transition and demonstration of comparability for both process and product when a process is established at a new contractor. These requirements make sound financial sense in that they reduce risk for a product sponsor. Only when a full picture of requirements, constraints, and advantages is generated can financial decisions on cost of good sold (CoGS) and return on investment (RoI) be calculated accurately and a sound financial contract drafted.

Team Organization: Defining the team and specific roles of its members, including project management and avenues of communication, is a key element to success in a contracting relationship (**22**) — and it's also a regulatory requirement. All participants should have defined roles and responsibilities so each relevant task has an owner. A central tracking document can be used to manage all tasks and team members. Documented assignment of specific tasks to team members becomes an even more critical issue when international organizations are involved because of language issues and time-zone differences.

Domestic or Foreign CMO?

A number of challenges are inherent to using international rather than domestic CMOs, particularly in the two fastest-growing regions for contract manufacturing: China and India (**11**). These include barriers such as language and cultural differences, time-zone differences that complicate program management, differing legal requirements (including intellectual property, IP, protection), and regulatory differences (**24**). Additional considerations include transportation, logistics (including costs of raw materials and infrastructure needs like electricity), and other hidden costs of doing business from afar (**22**). Infrastructure is a concern in both India and China as both countries attempt to keep up with demands on their utilities (**25–27**).

Cost Areas to Evaluate for Savings and Expenses

Raw Materials: Possible limitations on raw material vendors when considering international CMOs

Facilities: Square footage costs as well as necessary improvements and upkeep

Infrastructural Overhead: Electricity, water, sewage, waste management

Labor: Employee turnover and labor costs

Regulatory Costs: Additional costs of interaction with local regulatory agencies; awareness of the strategies needed for regulatory review in specific countries

IP Costs: Costs for protection of intellectual property in the manufacturing location

Due Diligence: Time spent auditing vendors

Travel Costs: Travel costs for due diligence, on-site meetings, auditing, and inspections

Communication Costs: Teleconference charges, translation charges, and/or the cost of local agents

Marketing: Limitations in marketing imposed by the manufacturing location

Legal Costs: Permits or other local regulations

Taxes: Domestic and foreign levies

Technology Transfer: Costs inherent in moving technology to a CMO that might not fall into the above categories, as well as costs of future transfer

(Adapted from Rohloff J. API Manufacturing in Asia. CBSA Biobreakfast 12 February 2008; with additional information from Ref. #22.)

Long-term concerns also need analysis. Legal and regulatory limitations exist in India and China that should be fully researched before making cost calculations. India is currently the industry leader for contract manufacture of generics, and China is more focused on APIs (**11**). This dichotomy is likely to change over the next decade, however, because China has a large unrealized capacity (estimated at 40% of its total capacity) for pharmaceutical contract manufacturing (**11**). As more companies take advantage of that capacity, sponsors should be aware of the potential effects on their future business terms. Dwindling capacity could beneficially affect infrastructure as competition increases and more companies manufacture in China and India. All of these hidden costs, as well as the advantages listed below, should be included in estimations of COGs and the cost of manufacturing when considering a foreign CMO.

Advantages to Using International CMOs: The many potential advantages to using international CMOs from upcoming markets such as China and India include reduced labor rates, a stable employment base, lower rental and land costs, reduced corporate tax rates, and the potential to negotiate tax exemptions with local governments (**27–29**).

Drastically lower labor costs and overhead may outweigh all cultural or time-zone differences. A 50–80% reduction has been estimated (**11**). These advantages could even be magnified — and disadvantages minimized — if the international location being considered is the same as a product's major potential market.

Calculating the Real Costs of Outsourcing: The costs of outsourcing domestically are already difficult to divine, and international locations add even more complication. The "Cost Areas" box lists cost areas for tallying savings compared with expenses.

Tax laws should be considered for both the sponsor's and contractor's country. Each nation has its own specific tax laws that can significantly affect a company's profits. For example, Brazil taxes outputs in ways not seen elsewhere: the Program for Social Integration (PIS) contribution, the Contribution for the Financing of Social Security (COFINS), the federal excise tax (IPI), and state value-added tax (ICMS) (**30**).

Certain elements are key to a successful CMO relationship, whether domestic or international. These include communication and definition of expectations, the comprehensiveness of agreements in place, due diligence and sufficient information on contractors, and auditing and adequate verification.

When a company considers international sites for contract manufacturing, especially up-and-coming markets in Asia, these basic elements remain important factors for success. But the additional advantages and challenges specific to international arrangements should be thoroughly weighed when deciding on a contracting location.

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References

1 *BCC Research Report on Pharmaceutical Contract Manufacturing and Research.* BCC Research Website May 2005; www.the-infoshop.com/study/bc29685-pharmaceutical-contract.html.

2 Third Annual Outsourcing Survey. *Contract Pharma* May 2007: 50–59.

3 Fox S. Maximizing Outsourced Biopharma Production. *Contract Pharma* June 2004: 72–78.

4 Ryland J. What Makes You the Best/Worst Sponsor: Building Win–Win Relationships with CMOs. *Am. Pharmaceut. Outsourcing* 9(5) 2008: 18–24.

5 Chrai S. Outsourcing Clinical Supply Materials. *Contract Pharma* May 2004: 48–53.

6 Escobar G. Working with a Contract Manufacturer: Key Considerations. *BioPharm Int.* April 2008: S8–S15.

7 Good Laboratory Practice Regulations. Department of Health and Human Services, Food and Drug Administration. *Code of Federal Regulations* Title 21, Part 58. US Department of Health and Human Services, Food and Drug Administration, 1987.

8 Novak J. Effective Approaches for Oversight of Contract Manufacturers Worldwide. *CBSA Bio-Breakfast* 12 February 2008. Colorado BioScience Association: Denver, CO; www.cobioscience.com.

9 Barnes R. *For Pharmaceuticals: Pundits Forecast Pharma's Future.* Master Control Web Site, 2008; www.mastercontrol.com/newsletter/pharmaceutical/pharm_0508.html.

10 BCC Research press release. *World Market for Global Pharmaceutical Contract Manufacturing and CROs Expected to Increase to $185.4 Billion in 2011.* 7 November 2007; www.bccresearch.com/pressroom/RPHM043B.htm.

11 Ghosh A. CMOs: A Robust Growth Trend. *BioSpectrum* 1 March 2008; www.biospectrumasis.com/content/100308OTH5733.asp.

12 Langer E, Ranck J. Capacity Bottleneck Squeezed By Downstream Processes. *BioProcess Int.* 4(3) 2006: 14–17.

13 *Directory of Biopharmaceutical Contract Manufacturers.* High Tech Business Decisions Inc.: San Jose, CA, 2006; www.hightechdecisions.com/industry_bioman.html.

14 Cislo M. Achieving Agility in Contract Manufacturing, Criteria for Thriving in the New Era. *Contract Pharma* April 2008: 1–5.

15 Caplan P, Wu F. CMOs: A Business and Technical Perspective. *BioPharm Int.* October 2003: 15–22.

16 Horn M. Strategic Outsourcing: The Growing Trend in the Pharmaceutical Industry. *Pharmaceut. Online Newsletter* 5 August 2008; http://images.vertmarkets.com/crlive/files/Downloads/70FBD1AE-256B-4DB0-BD24-F5168A85BA3D/Horn.pdf.

17 Haslam R. The Challenges of Outsourcing Pharmaceutical Development. *Pharmaceut. Int.* 2008; www.pharmaceutical-int.com/categories/somerset-house-consultants-news/the-challenges-of-outsourcing-pharmaceutical-development.asp.

18 Wheat J. Aligning Expectations: Keys to Successful Contract Manufacturing. *BioProcess Int.* 1(3) 2003; 34–40.

19 Beaty N. Guidelines for Manufacturing Contracts. *BioPharm Int.* October 2003: 23–29.

20 Novak J. Strategies for Planning, Managing, and Implementing Seamless Method and Process Transfers. *IBC's Second International Technology Transfer for Biopharmaceuticals,* 26–27 February 2007, Carlsbad, CA. IBC Life Sciences: Westborough, MA; www.ibclifesciences.com.

21 O'Korn D. Negotiating a Manufacturing Agreement: What Do You Need to Know? *Contract Pharma* 9(2) 2007: 56–63.

22 Dastmalchi B, Vermeij R. *Manufacturing Outsourcing: Seven Common Pitfalls to Avoid.* Symphony Consulting and Arena Solutions: Sunnyvale, CA, 2007: 1–11.

23 Draft Guidance. *Guidance for Industry: Cooperative Manufacturing Arrangements for Licensed Biologics.* US Department of Health and Human Services, Food and Drug Administration, 2007; www.fda.gov/CbER/gdlns/coopmfr.pdf.

24 Rohloff J. API Manufacturing in Asia. *CBSA Bio-Breakfast* 12 February 2008. Colorado BioScience Association: Denver, CO; www.cobioscience.com.

25 Langer E. China as a Biopharmaceutical Powerhouse: Just a Matter of Time. *BioPharm Int.* 20(12) 2007: 22–27.

26 Langer E. Biopharmaceuticals in India: A New Era. *BioPharm Int.* 21(1) 2008: 26–28.

27 Singh A, Singh K, Farkhas C. *The Indian Opportunity in Pharmaceutical R&D and Manufacturing.* World Economic Forum Annual Meeting 2008, Governors Meeting for Healthcare Industries, Thursday 24 January 2008, Davos, Switzerland. World Economic Forum: Geneva, Switzerland; www.bain.com/bainweb/PDFs/cms/Public/TheIndianopportunityinpharma_WEF_March2008.pdf.

28 *Asia Pacific Access.* World Trade Center: Denver Website; www.apaccess.com, updated 10 February 2006, accessed 3 July 2008.

29 Langer E. Biologics Regulation in India. *BioPharm Int.* 21(3) 2008: 22–27.

30 Ressla DR, Da Silva S. Brazil Revises Tax Treatment of Contract Manufacturers. *LexUniversal* 3 April 2003; www.lexuniversal.com/en/articles/4950.

For Further Reading

Arnum P. Global and US Biotech Markets Show Strength. *Pharmaceut. Technol. Sourcing and Management Newsletter.* 4(6) 2008; http://pharmtech.findpharma.com/pharmtech/Article/Global-and-US-Biotech-Markets-Show-Strength/ArticleStandard/Article/detail/519117.

Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; Current Good Manufacturing Practice For Finished Pharmaceuticals. *Code of Federal Regulations* Title 21, Parts 210 and 211. US Department of Health and Human Services, Food and Drug Administration, 1996.

Protection of Human Subjects; Informed Consent; Standards for Institutional Review Boards for Clinical Investigations. *Code of Federal Regulations* Title 21, Parts 50 and 56. US Department of Health and Human Services, Food and Drug Administration, 1988.

International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use. E6(R1): Harmonized Tripartite Guidance Guideline for Good Clinical Practice. *Fed. Reg.* 62(90) 1997, 25691–25709; www.ich.org/LOB/media/MEDIA482.pdf.

Gatyas G, Longwell L. IMS Press Release: *IMS Health Reports US Prescription Sales Grew 3.8 Percent in 2007, to $286.5 Billion.* 12 March 2008; www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_83470499,00.html.

International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use. E2A: Harmonized Tripartite Guidance Clinical Safety Data Management — Definitions and Standards for Expedited Reporting. *Fed. Reg.* 60(40) 1995: 11284–11287.

Montgomery S, Rosin L, Scott C. The Many Roles of Service Providers. *BioProcess Int.* 4(8) 2006: S22–S25.

Business Monitor International. *United States Pharmaceuticals and Healthcare Report Q2 2008.* Research and Markets: Dublin, Ireland, May 2008; 110; www.researchandmarkets.com/reportinfo.asp?report_id=597811&t=d&cat_id.

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