

Outsourcing Cytotoxics & Highly Potent Parenterals

The economics of choosing a CMO are changing

By **Burkhard Wichert, M.D., Mike Borlet** and **Raul Soikes**
Baxter Healthcare Corp.

DRUG MAKERS PURSUING THE CLINICAL development of novel cancer therapeutics — as well as of high-potency prostaglandins, opiates and hormones — are finding they must balance the therapeutic promise of these agents with new fiscal challenges.

The cancer drug pipeline in particular is bursting with hundreds of new therapeutic entities,¹ many of them molecular-targeted therapeutics that use a greater understanding of the genetic basis of cancer to block the growth and spread of malignancy with greater precision than do current chemotherapeutic mainstays.² These highly potent molecules promise to dramatically change cancer treatment: industry analysts predict that, in the next five to 10 years, most oncology patients will receive drugs designed to attack specific tumors.¹

At the same time, companies are facing vastly different economic landscapes than did makers of “blockbuster” chemotherapy drugs that broadly suppress cell division and are used for multiple tumor types. For large pharmaceutical companies and smaller drug operations alike, marketing these niche molecules could mean narrower profit.

Consequently, companies are considering new approaches to the production of molecular-targeted cytotoxic drugs in order to balance sales from smaller patient populations with the cost of complex manufacturing processes, significant safety precautions, and stringent regulatory requirements.

Economics of Outsourcing

Our company estimates that about 60% of investigational cytotoxics will be outsourced to contract manufacturing organizations (CMOs), compared with just 30% of non-cytotoxic products. A number of factors are behind this trend, including the costs associated with building and maintaining high-potency molecule containment facilities, the potential market size for these agents, and the economic risks associated with cytotoxic drug development.

1: Complex Manufacturing Operations

Many pipeline cancer drugs will be produced in parenteral formulations, which require specially designed containment systems in order to assure the safety of the manufacturing facility’s employees and mitigate risks that high-potency pharmaceutical ingredients pose to operators and the general environment.

As a consequence, the capital investment required for the infrastructure to safely produce these high-potency molecules in injectable formulations exceeds that for other parenteral

Burkhard Wichert, M.D., is vice president Manufacturing Oncology. He can be reached at burkhard_wichert@baxter.com.

Mike Borlet is director of marketing. He can be reached at michael_borlet@baxter.com. **Raul Soikes** is director, R&D Program Management. He can be reached at raul_soikes@baxter.com.

drugs and is a significant financial barrier for many companies.

Multiple validated processes are necessary for the production of all parenteral products, regardless of whether or not they are highly potent, to ensure the highest levels of purity, quality and safety throughout the fill/finish processes. Parenteral cytotoxic agents are among the most highly sensitive drugs to handle and produce, because long-term exposure to even trace amounts of cytotoxics has the potential to cause cancer or mutagenesis.

When cytotoxics are dispensed as liquids or powders, it is possible to generate dust or aerosols containing minute particles that, although not visible, can be inhaled and absorbed through the lung, ingested, or absorbed via the skin or mucosal membranes. Consequently, strict separation protocols have to be in place, with special air-handling and water systems, waste treatment and barrier isolators to protect workers and prevent cross-contamination of other products or product classes.

Manufacturing safety requirements for high-potency parenteral drugs are trending toward a product separation standard that is similar to what is required for the manufacture of penicillin-based products. Current good manufacturing practices (cGMP) stipulated by the FDA for penicillin products requires their isolation from non-penicillin products during processing, either by locating the operation in a separate building or installing a separate "building within a building" for the production process.³

For the FDA, separation means more than just walls. Every aspect of the operation must be distinct, including air-handling systems and processing equipment. Personnel and equipment from the penicillin operation cannot enter the non-penicillin portion of the facility, and the entire separation process has to be audited, validated, and monitored.³

Cost of the infrastructure required to meet such stringent safety rules for cytotoxics is leading many smaller pharmaceutical companies — and those just entering the oncology market — to outsource manufacturing, a move that allows them to devote more of their limited financial resources to their core competencies. At the same time, some established pharmaceutical companies are eschewing in-house manufacturing facilities because of the difficulty in keeping pace with increasing regulatory requirements for risk mitigation in manufacturing and waste disposal.

2: Limited Return on Investment

Even for companies with the technical expertise to produce parenteral cytotoxics in-house, a second barrier to constructing a dedicated manufacturing facility is the potential return a company is likely to earn on its initial capital investment.

Novel cancer drugs are being tailored more finely to specific tumors or tumor types and are likely to be approved for narrow indications with distinct patient populations. Consequently, production batches for these niche products will be much smaller than those for traditional chemotherapeutic drugs, and higher per-unit prices are not always a viable strategy for recouping costs. Most regulatory authorities around the globe exert some control over drug prices. Although the FDA does not, and premium pricing for molecular-targeted cancer drugs has been observed in the U.S.,¹ increased competition

within particular categories and pressure from third-party payers may limit such pricing in the future.

3: Risk of Getting to Market

A third reason companies shy away from constructing their own facilities is the risk they face simply in getting their products to market. Only about 8% of cancer drugs make it through clinical development and regulatory review,⁴ with approximately half of all research failures occurring during Phase II clinical trials.⁵

The risk of tying up capital in a manufacturing plant while a product is in clinical trials was demonstrated clearly in the 1990s, during the emergence of the biotechnology industry, when small companies were simultaneously developing complicated therapeutics and building new manufacturing plants. A perfect example is Synergen, a biotech company in Boulder, CO, that in July 1994 had a sepsis drug in Phase III trials, a completed manufacturing plant, and \$111 million in venture capital.^{6,7} When an interim analysis of Phase III data showed a lack of efficacy for sepsis, the financial blow was too much for Synergen to handle. By December 1994, it had agreed to be acquired by Amgen, which now markets the molecule for the treatment of rheumatoid arthritis as Anakinra.

Making the Right Choice

Even if the decision to outsource is clear, the choice of a CMO partner can be a make-or-break move for many pharmaceutical companies. A CMO's record of compliance with global regulatory and safety standards, and its experience and capacity for producing cytotoxics, are good indicators of whether the CMO will be able to bring a molecule to market expeditiously and maintain supply of the therapeutic over time. It's critical, therefore, for clients to assess the CMO's infrastructure and global experience.

1. Infrastructure

The sensitive nature of cytotoxics requires a facility designed specifically for high-potency molecules and staffed by technicians with the expertise to handle the assignment. In general, the facility has to feature flexible containment systems to handle multiple assignments safely, effectively, and reliably. When touring a CMO's facilities, the pharmaceutical company should examine the facility's design, equipment, safety processes, and personnel.

Dedicated Production Facility: Choosing a facility designed specifically for high-potency production and validated to meet regulatory requirements around the globe will help accelerate a cytotoxic product's move toward commercialization. Monitoring systems should be in place throughout the facility to safeguard the product's quality while meeting stringent safety requirements and standards for quality control.

Fully Integrated Production: Automated manufacturing equipment that is fully integrated throughout production suites reduces the likelihood for any variability in the production process, accelerates turn-around times, and increases the batch yield.

Containment: Quality containment systems (e.g. isolators,

RABS, etc.) must form a reliable barrier between technicians or operators and toxic substances to ensure their safety and minimize any risk of contamination. State-of-the-art containment enables closed-system manufacturing and helps to ensure products are produced under precisely controlled temperature, relative humidity, and pressure conditions, while in a clean-room Class 100 environment.

Lyophilizers: Lyophilization chambers for freeze-drying cancer therapies should optimize product quality, maintain the integrity of the molecule, and comply with standards for employee and environmental safety. Look for technologies that minimize risk for human contamination and eliminate variability in the manufacturing process. Systems featuring mobile transfer carts, constant level loading and unloading, and computer-controlled in-process quality analysis technologies are considered to be state-of-the-art.

Vial Decontamination: Health care providers want the assurance that vials containing chemotherapeutic drugs are free of any external cytotoxic residue, because even trace amounts of cytotoxics could be hazardous to their health. Consequently, pharmaceutical companies should determine whether the CMO has adequate steps in place to eliminate external surface contamination, either through vial washing processes or other proven decontamination methods.

Air-Handling Systems: When cytotoxic molecules are produced in powder or liquid form, there is always a chance for minute particles to become airborne. Therefore, it's critical that the facility have safeguards in place that protect workers and the environment. To this end, air-lock systems maintain the sterility of the clean room. Separate HVAC systems should be in place for the cytotoxic facility, and HEPA filtration systems are needed to filter effluent air and remove all traces of high-potency pharmaceutical products.

Waste Handling: Regulatory and environmental authorities require CMOs to take steps to ensure high-potency molecules do not leave the confines of the facility in water or solid waste. CMO customers should ensure the manufac-

turer has written procedures for handling and disposal of liquid and solid waste products and that the CMO's environmental management system is certified by the International Organization for Certification (ISO). ISO 14001 is the international standard for environmental management systems.

As part of its waste-handling procedures, a CMO should collect 100% of water used in formulation and finishing operations; for example, all equipment would be attached to a separate piping system (eventually even running on negative pressure) and fed into a water treatment plant that cleans and removes cytotoxins. Similarly, all solid waste would be collected and sealed in bins and then incinerated to destroy all cytotoxins.

Training: Beyond cGMP training and having the appropriate equipment and facility design, CMO personnel should have a high level of awareness of the potential risks associated with cytotoxic drug manufacturing and know the strategies necessary for managing them. It's important, therefore, to assess the level of ongoing training technicians receive. It also helps to tour the CMO facilities and speak with technicians to evaluate their knowledge and awareness.

2. Global Compliance and Experience

Makers of molecular-targeted cancer therapies, with narrow indications and small market share, would benefit from partnering with a CMO that has the experience to help streamline the product's global availability. At a minimum, the CMO should be compliant with regulatory requirements of authorities in the U.S., Europe, and Japan. Beyond that, companies with extensive global experience are likely to have a thorough understanding of global regulatory issues concerning the production, packaging, and distribution of cytotoxic therapeutics, a working knowledge of multiple countries and their regulators, and experience in the regulatory review and approval process.

The length of time a company has been in the business of producing high-potency parenteral products is a good indicator of its experience, as is the CMO's audit history with regulators and

the number of countries to which it is qualified to ship cytotoxic products.

3. Corporate Culture

When a pharmaceutical company entrusts its molecule to a CMO for the first time, the choice of a manufacturing operation often is based on the CMO's capabilities, qualifications, capacity, and experience. The second time the company assigns a molecule to the same manufacturing operation, the CMO's corporate culture probably had a major influence on the decision.

Too often, a pharmaceutical company discovers whether it can work effectively with a CMO after the contract manufacturer has begun the process of bringing the company's molecule to market. But there are several basic indicators that can help a company choose the right CMO the first time.

Key to the choice is finding a CMO that can document the level and quality of service it will provide, including the key point of contact and decision-maker throughout formulation, fill, and finishing phases, the internal processes that will be involved, and the escalation plan. The CMO also should provide potential customers with access to the individuals who will be responsible for production of the molecule, such as quality and technical service teams. Moreover, the CMO should be willing and able to document and agree to every aspect of the process, including score cards, metrics, batch release times, and exception times — before the manufacturing process has begun. CMOs that are able to document the level of service a company can expect are service organizations that have the best interests of their customers and healthcare consumers at heart.

High-potency agents — cytotoxic drugs, as well as prostaglandins, opiates, and certain hormones — comprise approximately 25% of all pipeline therapeutics,⁸ and innovations in cancer drugs are thought to be a considerable force behind the growth in this category.

As a variety of molecular-targeted cancer therapeutics move through clinical development, the drug industry is witnessing a trend toward outsourcing the manufacturing of these complex

agents, and more CMOs are entering the high-potency market as a consequence.⁹

With more CMOs producing cytotoxics, drug manufacturers have greater choices and options. Thorough examination of a CMO's experience is critical, however, because the choice of a cytotoxic manufacturing partner can have a direct impact on a company's bottom line.

Production of cytotoxic molecules formulated for parenteral delivery is extremely complex, and requires multiple controls to ensure product quality, maintain the product's aseptic state, and comply with standards for occupational and environmental safety. To this end, the manufacturer must ensure separation of the molecule from its employees and take multiple precautions to protect communities surrounding the manufacturing facility, healthcare workers who administer therapeutics in hospitals and clinics, and patients whose health and lives depend on a reliable supply of the drugs.

CMOs with experience in cytotoxics should have appropriate infrastructure in place and extensive technical and regulatory experience to comply with global standards for product quality and sterility, as well as occupational and environmental safety.

When evaluating a CMO partner, a pharmaceutical company will be able to evaluate a manufacturer's capabilities and capacity for production of cytotoxic parenteral products, its safety record and its experience with global regulatory authorities. These are basic indicators of whether the company is committed to staying in the cytotoxic manufacturing business and keeping pace with changing requirements.

For extra measure, however, it pays to tour a CMO's facilities and speak with the operators at the plant. Do they seem willing to go the extra mile to get a customer's product to market safely and on time? The quality of employees on the front line of a manufacturing facility is a good meter of whether the CMO has a strong service culture, will maintain quality and safety standards, avoid production shutdowns, and assure continual supplies of life-saving drugs to cancer patients.

A CMO whose employees are committed to service is one that will help assure the financial survival of its customers. And they'll do that by keeping patients — the ultimate customers — top of mind. ■

References

1. *Therapeutic Categories Outlook*. Boston: Cowen and Company; October 2007.
2. Targeted Cancer Therapies: Questions and Answers. June 13, 2006; <http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted>. Accessed March 12, 2008.
3. Rutledge CR. Human Drug CGMP Notes. March; <http://www.fda.gov/cder/hdn/cnotes0300.htm>. Accessed March 12, 2008.
4. Despite more cancer drugs in R&D, overall U.S. approval rate is 8%. News release]. September 5; <http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=83>. Accessed March 3, 2007.
5. Dimasi JA. Risks in new drug development: approval success rates for investigational drugs. *Clin Pharmacol Ther*. May 2001;69(5):297-307.
6. Herrman M. When products fail. *Nature Biotechnology Supplement*. June 2001;19(6):BE37-BE38.
7. Amgen Boulder Inc · 10-Q · For 9/30/94. Securities and Exchange Commission. <http://www.secinfo.com/dM97p.bj.htm>. Accessed March 17, 2008.
8. Van Arnum P. Investing in high-potency manufacturing: market demand for cytotoxic drugs is leading CMOs to expand their API manufacturing and formulation services. *Pharmaceutical Technology*. Vol 31 2007:54-59.
9. Van Arnum P. Contract manufacturing organizations expand in high-potency manufacturing. *Pharmaceutical Technology*. Vol 30; 2006:62-66.