Outsourcing Xbox Manufacturing
Microsoft Shows the Way for Successful Outsourcing Relationships

Heather B. Hayes

Sophisticated and effective outsourcing relationships are becoming more typical in every industry. Many of the world’s leading companies such as Microsoft Corporation (Redmond, WA) and Dell Computer Corporation (Round Rock, TX) have embraced outsourcing and harnessed the expertise and capabilities of their outsourcing partners for their own success. As pharmaceutical companies confront challenges that are undermining their vertically integrated structures, they can benefit by examining how top players in the global economy have achieved outsourcing success.

At first glance, Microsoft’s recent foray into the electronic games market appears unrelated to developing and producing drugs and medical devices. Yet the case of Microsoft’s Xbox electronic game product has a lot in common with the launch of a new drug—the company must integrate the contract manufacturer into the project at an early stage of development and manage a sophisticated supply chain. The company also must manufacture and distribute globally, ramp up production as product acceptance takes hold, and ensure market supply. Finally, it must achieve very high levels of product quality and dependability. Microsoft’s decision to outsource the Xbox manufacturing illustrates just how sophisticated and effective partnering with outside contractors can be in the twenty-first century, no matter what the industry or product.

Microsoft achieved the position of world leader in software development by relying on no one but itself. But when Microsoft officials decided that they had a new kind of future in the Xbox—a piece of hardware—they also recognized that they faced several serious roadblocks to success. The software company had no factories, no real experience building things, and no stomach for the risks associated with a sudden plunge into the manufacturing business. Very quickly, officials realized that the company needed a partner to help with the heavy lifting.

Although Microsoft had relied on outside vendors to manufacture simpler items such as mouses, keyboards, and joysticks, the Xbox venture was considerably more complex and ambitious. Microsoft officials worried openly about losing control of the process, not being apprised of major and minor problems until it was too late, and not being able to find a company that could deliver the initial 800,000 units re-
The partnership approach is critical in an environment with short product delivery times and keen competition.

Microsoft’s ultimate partnership with the Singapore-based electronics manufacturing services (EMS) provider, Flextronics, almost didn’t happen. Microsoft had often employed the company to assemble mice and other small PC-related gadgets, but it had not actively considered Flextronics for the Xbox project. Flextronics management contacted Microsoft and offered new ways of thinking about outsourcing challenges and supply-chain management. The discussion quickly alleviated any fears Microsoft officials had about turning over the manufacture of the Xbox to a third-party contractor.

“One of the keys to this partnership was our ability to bring experience and knowledge to this,” said Sacherman. “We walked the Microsoft team through the entire assembly process, explaining our quality assurance system, labor, and inventory management. We showed them how Flextronics would be able to handle the manufacture of the Xbox.”

As a result, the relationship quickly became a successful hybrid of the two most traditional outsourcing arrangements: Microsoft never turned over complete responsibility to Flextronics or passively waited to hear about progress. Neither did it act as a typical employer, dictating tasks and keeping Flextronics in the dark about its long-term plans for the product. Instead, the two companies worked together collaboratively from the beginning. For example, Flextronics was hired to build the product at its industrial parks in Mexico and Hungary, but it worked closely with Microsoft to also design, engineer, and test the Xbox. In another division of labor, Flextronics handled inventory matters, purchased commodity items, and planned shipment schedules for components while Microsoft took responsibility for overseeing the management of 40 key suppliers.

Collaborate and collaborate. To make the most of the differing expertise in each company and to keep each other apprised of changes and problems, the two companies collocated their engineers. For example, Flextronics engineers attended update meetings at Microsoft headquarters and Microsoft engineers worked on the line to help Flextronics employees confront any mechanical problems that arose during production.

Pharmaceutical companies typically do not make this extra effort, but Sacherman noted that it holds huge benefits for any industry. “Quite simply, it makes projects go smoother and work better,” he said. “The sponsor company understands the issues that our engineering team encounters, and we understand their issues. We can gain that understanding in an up-close-and-personal way that an e-mail message or a telephone conversation just can’t convey. When you really need to work to a schedule, this is the only way to work.”

The new rules of outsourcing

In the face of continuing challenges to traditional outsourcing firms, outsourcing firms have changed their business models to look less like an employee–employer relationship and more like a partnership. This change has been so dramatic that “the term outsourcing no longer really applies,” according to Elad Yoran, vice-president of global business development for Symantec Corporation, which provides network security services. For this new type of partnership to work, both parties must feel comfortable with a more team-oriented approach. The following guidelines can help implement this approach:

- Define. A contract, or even a more detailed service-level agreement, should describe the responsibilities of both the outsourcing firm and the hiring firm.
- Communicate. Rather than simply hand off responsibility to an outsourcing firm, the hiring company should stay in constant contact with the outsourcing partner. For example, the client may want to appoint a liaison to communicate any and all needs, concerns, and viewpoints from one company to the other.
- Collaborate. Egos should be left at the door so each company can use its obvious strengths and capacities for the betterment of the project.
ics collects as many as 40 pieces of shop-floor data for each unit produced, and it produces 100,000 units per week.

To give Microsoft officials access to that data and to eliminate lag time in the supply-chain information flow, Flextronics developed a Web-based portal powered by a Cognos cube. This advanced database tool enables users to manipulate data in various ways. Now Microsoft officials and Xbox suppliers can log onto the portal and view the current product yields on every production line in real time, or they can develop their own customized queries. The portal also affords a centralized location for general information such as Xbox contact lists, the latest news about the project, and live pictures of the manufacturing process.

As a practical matter, the portal helps the entire team stay informed about problems that may arise. If the yield in one part of the operation suddenly drops, team members do not have to send a string of e-mails to get to the heart of the problem. Everyone can log onto the portal, see the relevant data, know what is happening, and devise a solution collaboratively.

But on an emotional level, the portal adds to the overall sense of teamwork and frankness. “It really gives clients a feeling that they have a manufacturer that isn’t going to hide anything from them and isn’t going to keep secrets,” Sacherman said. “We’re more or less saying, ‘Here’s everything. You can see it at any time you want,’ which makes for a very open manufacturing relationship.”

**Take advantage of the latest technologies.** To speed the manufacturing process, communicate more effectively, and keep production as cost efficient as possible, Flextronics and Microsoft used several state-of-the-art tools. Among them were automated forecast tools, e-rooms for easy communication and collaboration, and technologies to instantaneously communicate design releases and engineering change orders to the 200 suppliers involved in Xbox design and production.

**Have a contingency plan.** “Part of what makes a good partnership is when both parties understand that not everything is going to go perfectly,” Sacherman said. Because Microsoft and Flextronics were realistic about the process, they made sure that contingency plans were created up-front to handle expected and unexpected problems.

If a component supplier delivers late or if a production line produces below the expected yield levels, fallback plans should be detailed in a working paper with regularly updated flowcharts so team members can adjust accordingly. “If you’re not prepared for things to go wrong, then when they do go wrong, it takes a lot longer to solve the problem,” Sacherman explained. “And in this business, time means everything.”

The Microsoft–Flextronics Xbox project is a perfect example of how successful an outsourcing relationship can be when companies work together as a team rather than as two separate entities. For pharmaceutical companies looking to augment their own strengths with the expertise of outside firms and to become more efficient and effective in a competitive marketplace, the lessons provided by this venture should give them plenty to think about.
Gloom and doom seemed to pervade this year’s CPhI trade show, held 1–3 October in Paris, France. Manufacturers of pharmaceutical intermediates and active ingredients continue to suffer from lean demand and excess manufacturing capacity.

Big Pharma demand for contract chemical manufacturing seems to have dropped off sharply, according to show participants. This declining interest reflects the dearth of new product candidates receiving FDA approval or reaching Phase III clinical trials. The bonanza of new pharmaceutical products that analysts were forecasting has not come to pass and seems further off than ever. The weak demand also relates to the fact that as products go off-patent or reach the later stages of their life cycle, many companies have substantial manufacturing capacity to fill. Rather than shut down that capacity, most pharmaceutical companies prefer to keep work in-house, requiring them to outsource less.

An additional factor is growing competition from Asian producers, especially those in India and China. Although intellectual property and regulatory quality concerns continue to limit Asian companies’ role in the supply chain, they are being sought for their starting materials and non-GMP intermediates and for their process development expertise. Increasing pressure to reduce drug prices will continue to make the cost advantages of Asian suppliers difficult to resist. Chinese pavilions were situated in each of the three major CPhI exhibit halls, which is an indication of the strong thrust that Chinese companies are making in the global market.

Some of the leading active pharmaceutical ingredient (API) producers have been expecting the production of monoclonal antibodies and recombinant proteins to drive their growth during the next five years, but that biomanufacturing boom does not seem to be happening either. With many high-profile candidates failing in late-stage clinical trials, several of the major contract biomanufacturers are very tentative about building new capacity. The contract biomanufacturers that have committed to build capacity have begun prospecting for new business again after several years of acquiring clients just by answering telephone calls. Commitment fees are also becoming a thing of the past as API companies face a continued period of difficulty.

M&A update
Acquisition activity heated up the past few months following the usual summer slowdown. One of the most interesting developments was the acquisition of Atlantic Pharmaceutical Services (Owings Mills, MD) from Niro Inc., by Shire Pharmaceuticals Group (Basingstoke, UK). Shire will use the facility for manufacturing its proprietary products and will no longer offer contract manufacturing services. Atlantic was established by Niro in 1996 and offered specialty processing services, including spray-drying, using Niro and Fielder equipment. Shire paid $17 million for the facility.

Covance expanded its central laboratory services franchise with the acquisition of Virtual Central Laboratory b.v. (VCL, The Netherlands). VCL’s proprietary methodology can harmonize laboratory data acquired from local laboratories used for analyzing patient samples. Covance views VCL’s capabilities as especially valuable for providing services for trials conducted in remote regions of the world where getting samples to a central lab is not feasible. Covance’s central laboratory business leads the industry with an annual revenue of approximately $250 million.

Finally, Charles River Laboratories Inc. (Wilmington, MA), acquired Springborn Laboratories, Inc. (Spencerville, OH), for $27 million. Springborn is a provider of preclinical toxicology services and had revenues of $15 million for the 12 months preceding the acquisition. Charles River has maintained a sharp focus on preclinical services in its outsourcing business, with services that include traditional toxicology testing services and operation of animal facilities on a client’s site.
IBM’s new outsourcing venture is another confirmation of the validity and appeal of the outsourcing model.

IBM sets an example

IBM (Armonk, NY) announced the establishment of a major new outsourcing venture, IBM Engineering and Technology Services, which will help other companies design new electronics products. The venture is a vehicle for generating revenue from IBM’s product- and component-design expertise, but it is also a means to sell IBM-made components and to license IBM’s intellectual property. One of its first customers is medical-device manufacturer Medtronic.

The venture’s relevance to the pharmaceutical industry is twofold. For one, it is another confirmation of the validity and appeal of the outsourcing model—when one of the largest corporations in the world commits to the outsourcing business, it gives the business a cloak of legitimacy and compels executives in all industries to seriously consider the outsourcing strategy.

It is also relevant because the business model, which seeks to sell expertise and also gain long-term returns for licensing intellectual property, has appeal in the pharmaceutical industry. Contractors that provide chemistry and formulation services have increasingly tried to incorporate an intellectual-property component into their business offerings through proprietary drug delivery systems and process technologies. One of the highest-profile examples is Cardinal Health (Somerset, NJ), which has been accumulating a portfolio of drug delivery technologies. Cardinal Health has built a new development facility whose services will include helping sponsors develop products by incorporating its technologies. Cardinal Health also acquired Magellan Laboratories, a company that knows how to run a development operation. Albany Molecular Research (Albany, NY) has pursued a similar strategy on the chemistry side.

As the pharmaceutical industry adjusts to an increasingly difficult business environment, we expect to see pharma companies adopt the outsourcing models used successfully in other industries.
Quality in Pharmacovigilance

Brian Edwards* and Jeffrey Priem

A core activity in pharmacovigilance is the management of individual case safety reports (ICSR). A quality system program for ICSR helps improve effectiveness and integrates different functions and processes, thus reducing the risk of compliance deviations that may compromise product safety.

In today’s business environment, where corporate responsibility and compliance are riding high on the political and social agendas, many pharmaceutical organizations face the challenge of implementing their pharmacovigilance obligations. Pharmacovigilance is defined as a company’s statutory obligation to monitor the benefits and risks of its product(s) and then take the appropriate actions to ensure that a product maintains the quality, safety, and efficacy that are compatible with its approved status.

Pharmacovigilance is an increasingly important part of drug development. Inspired by interaction with other companies and the need to process individual case safety reports (ICSR) more cost efficiently to stay competitive, certain CROs have developed effective pharmacovigilance processes. Thus, outsourcing pharmacovigilance is a feasible option, although companies must understand what they can outsource, what pitfalls they may encounter, and how a CRO views business risk and liability so that a successful program can be established.

The main sources of data for pharmacovigilance activities are postmarketing spontaneous reports of adverse reactions and clinical trial adverse events, which are collectively referred to as ICSR. Thus, maintaining the quality and consistency of each case report is essential if a company wishes to portray its product’s safety profile as accurately as possible. To achieve this, a company should increase its level of efficiency by improving its use of human resources. For example, a company can reduce the number of ICSR handovers between different team members, integrate standard operating procedures (SOPs) (which can surreptitiously increase in number unnecessarily), and ensure that all relevant business units are interacting appropriately so that data are assessed at a central point. Implementing pharmacovigilance basically means getting the right...
information to the right people at the right time.

This article focuses on one key aspect of pharmacovigilance: the quality of ICSR management. **Quality** is the combination of attributes and culture that defines an organization’s commitment to its regulatory obligations. The chief executive officer, board of directors, and senior managers can shape their company’s attitude toward pharmacovigilance by emphasizing its importance to the long-term success of products and customer service. Incorporating a quality system program for ICSR management depends on top managers’ positive attitude toward and commitment to the system combined with a disciplined approach.

**Features of ICSR management**

To effectively implement an ICSR management program, one should consider a quality system composed of the following six activities:

- capturing postmarketing spontaneous reports of adverse reactions or clinical trial serious adverse events
- assessing, classifying, and prioritizing ICSR
- recording results into the ICSR system (i.e., databases)
- reporting to the appropriate parties such as regulatory authorities and the medical community
- closing the ICSR after follow-up when appropriate
- monitoring the ICSR process, its implementation, and its results (i.e., trending).

These common activities of ICSR management must be considered along with factors such as

- internal business pressures: keeping costs down and increasing efficiency
- desirable medical outcomes: scientifically accurate ICSR that are classified and recorded to acceptable standards
- requirements for feedback from patients and prescribers: transparency with accurate and comprehensible information
- demands for compliance by regulatory authorities: All serious and unexpected adverse reactions must be submitted within 15 days. All Council for International Organizations of Medical Sciences (CIOMS) I form boxes must be completed at the time of submission. (CIOMS I is the standard form for international ICSR reporting, whereas the MedWatch 3500A form is used for US domestic reporting.)
- the need for electronic reporting of ICSR, which may be required as early as 2003.

The previously described activities influence and drive the work flow of the ICSR process, which determines compliance with regulatory requirements. These activities vary by company and by product within the same company. Because of the procedures’ variability, managers should consistently question the effectiveness of ICSR management and how long it will continue to remain effective even if it is adequate at the moment.

**The nature of variation within pharmacovigilance**

In pharmacovigilance as a whole, the concern of effective ICSR management is set against a constantly changing background. The risks and benefits of a product change (even if no new data on that product are produced) as other products and therapies are introduced in the market and as society’s attitudes and expectations toward a disease or its treatment changes. Although these external factors are particular to pharmacovigilance, variation is a feature of any system, especially as processes tend to adapt to the most comfortable, but not necessarily the most effective, route.

To avoid the appearance of complacency, one strives to mitigate the effects of variation on the process. To do so, the potential sources of variation in the process must be identified and addressed. In the context of pharmacovigilance, variation results from the way personnel interact with the process, the corresponding procedures that are used, the physical environment in which a process is performed, and the measurement activities and technology that are used for a process. Examples of the types of variation that can occur in ICSR management are listed in the sidebar, “Variation in ICSR management.”

By mitigating potential sources of variation, one hopes to eliminate deviations or errors that occur within the quality system program. Thus, one aim of a quality system program should be variation mitigation with zero tolerance toward key deviations and errors, which threaten regulatory compliance and ultimately may compromise patient safety. Changes or deviations may be permissible within agreed limits without being considered errors if they do not compromise compliance; however, when evaluating the effect of variation on a process, one must also con-
When evaluating variation within the process, one should ask the following questions:

- Has the process been properly defined with correct specifications?
- Are the process procedures sufficient?
- Are all other process components (e.g. materials, equipment, facilities, personnel) sufficient?
- What can management do to ensure that procedures are followed?
- Is this solely a performance issue?

In addition, a quality system program should focus on specific areas, which should be targeted for assessment particularly if they are likely to be sources of variation such as:

- uncertainties and inaccuracies about the science of the product
- errors in executing the spontaneous report process
- lack of specifications about acceptable normal limits of variation, which may lead to unreasonable expectations
- adequacy of the monitoring and oversight of the process
- adequacy of the controls in place, especially at weak points
- the interface with other quality systems or systems that manage product complaints

The complexity of the process itself.

Examining these issues may be complicated by varied individual or company understanding of and experience with pharmacovigilance regulations and internal or external pressures concerning certain products, adequacy of resources, and length of timelines.

Even if one acknowledges the weak points in the process, the question remains, “How do we start to address this variation?” It is important that all personnel involved in managing ICSR understand the scientific and public health rationale of ICSR management if they are to grasp fully what is expected of them. Managers should be trained in the principles of pharmacovigilance to help improve their understanding of the entire process, not just their part. Of course, more-specific reasons exist that indicate why a process might fail; for example, employees not understanding the underlying process or their job or interference with someone’s ability to do the job. A lack of control measurements at key points can be another factor.

Quality system programs identify and address potential areas of variation with the assumption that these variations are a normal part of any total process. A quality system program, when applied to pharmacovigilance, is a view of the system from top to bottom. Here, the entire process is viewed as a package and not on a site-by-site or procedure-by-procedure basis. This thorough evaluation helps identify process failures and the mechanisms that can mitigate the potential program variation as a whole and not simply at one point. In addition, typical questions that are asked during regulatory inspections are about the quality system program design. Some examples of these questions are

- Does the company have a quality system program?
- How well does this quality system pro-
program work (i.e., do failures or deviations exist within the process)?
- How well does this quality system interface with other systems (i.e., is this the same process for multiple products, and how will ancillary quality systems such as nonconformance handling processes become engaged)?

A quality system program approach to pharmacovigilance will answer these regulatory questions as well as focus the scrutiny on the technical content components of the pharmacovigilance process outcomes and not necessarily its pharmacovigilance process applications.

**Setting up a pharmacovigilance quality system**

When evaluating the design of any quality system, the following fundamental components should be considered:
- major process identification: the way that an ICSR process is managed within a company, which includes all possible portals for data entry as well as various types of data
- subprocess identification: a part of the major process that accomplishes a specific objective such as handling spontaneous reports using the central pharmacovigilance unit of a company
- ancillary activities identification: a part of the subprocess such as classifying a spontaneous report
- key tasks identification: individual elements of an activity such as determination of the seriousness and expectedness of an adverse reaction as a part of the classification ancillary activity.

Developing a pharmacovigilance quality system program should result in several key outcomes. Figure 1 shows these outcomes, which serve as the foundation of all pharmacovigilance processes and quality system programs.

In a pharmacovigilance quality system program, activities occur as several discrete phases, which include the process design, assessment, revision, implementation, and continuous improvement activities. A process flow diagram can be a useful tool to conceptualize the process phases of ICSR management. As an example, Figure 2 outlines these phases and the key steps and elements that support the pharmacovigilance process.

A process map also can be a beneficial tool to communicate the design of a particular system or process. For example, Figure 3 is a graphical representation of the management of spontaneous reports of suspected adverse reactions. This visual approach to a process’s design can be supplemented by a checklist that addresses issues such as known obstacles, the definition and factors of success or failure, and the areas where variation might occur; all of which reflect personnel, technology, and intrinsic features in methodology and mode of measurement. On the basis of these checklisted items, a process design map can be created consisting of:
- key inputs such as SOPs, the raw data of a spontaneous report, and procedure templates such as international or national pharmacovigilance regulations and CIOMS I forms
- a process flow diagram indicating each department involved such as company affiliates and comarketing partners
- outputs from the process flow such as the completed CIOMS I form or line listings for a periodic safety update report
- interfaces with other systems
- performance measures such as a 15-day time limit for expedited spontaneous reports
- process outcomes such as satisfactory regulatory compliance and adequate regulatory safety information.

In this design, performance measures are distilled into metrics to monitor the process performance. Some common performance metrics include measures of efficiency that are related to consumed re-
A company that is motivated to invest in the quality of data and systems must set priorities.

Applying the quality system approach to pharmacovigilance standardizes the ICSR process and includes the following attributes:

- Key responsibilities are defined.
- Requirements and assumptions are identified.
- A common lexicon of definitions is established (i.e., coding).
- Processes and subprocesses are standardized (i.e., classification process).
- Preplanned corrective actions are established to address process failures and problems (e.g., crisis management).
- The performance monitoring mechanism is defined, which can create cross-functional feedback through audits and regulatory inspections and internal pharmacovigilance system feedback.

Adopting the quality approach

Ideally, all companies that manage spontaneous reports should develop and implement a quality systems program. However, in reality, a company that is motivated to invest in the quality of data and systems must set priorities. For instance, a company may have products of major commercial importance that may have generated considerable regulatory activity because of safety concerns.

With the quality system program approach to pharmacovigilance, the right information should get to the right people at the right time, thereby resulting in obtaining predictable data from pharmacovigilance systems in terms of the product, process, and regulatory requirements. The approach described in this article can help establish preplanned corrective actions for failures in the process and how to react to a crisis. It also provides practical guidance about implementing and maintaining some of the core systems for pharmacovigilance. Because pharmacovigilance involves the entire organization, a defined system is necessary to ensure regulatory compliance and to be aware of business concerns such as value for money. Failure to understand the scope of pharmacovigilance can lead to several difficulties both in complying with regulatory requirements and in effectively controlling product risk minimization and benefit maximization, which are the ultimate goals of pharmacovigilance.