

Edward R. Arling, Ralph Dillon, and Joseph Noferi

Bringing a drug product to market requires that all parts of the manufacturing and validation puzzle comply with an increasing number of regulations. Managing the quality aspects for far-flung organizations can be a colossal assignment. A quality assurance unit may be the answer you need, along with finding capable, competent people and ensuring that they have the right communication tools.

Corresponding author **Edward R. Arling** is senior director of QA, **Ralph Dillon** is director of quality engineering, and **Joseph Noferi, Esq.** is director of AQ compliance and validation at Pharmacia GS API Biopharma, global supply, 5200 Old Orchard Road, Skokie, IL 60077, 847.581.6590, fax 847.581.6590, edward.r.arling@pharmacia.com, www.pharmacia.com.

Creating Effective Biopharmaceutical QA/QC Organizations

Your People Are the Key

Roughly 90% of what we know in biology, genetics, and pharmaceuticals has been discovered in the past 30 years. Our ability to process and store data doubles every 18 months, yet our regulatory enforcement environment is understaffed, under pressure, and facing a devastating workload. Nowhere is that more acute than in today's biopharmaceutical and biotechnology industries. We live in exciting times.

Pharmacia Corporation was created in April 2000 through the merger of Pharmacia and Upjohn with the Monsanto Company and its G.D. Searle unit. Following that merger, a new biopharma organization was created to meld the existing manufacturing operations of Pharmacia and the research operations of Searle. Our task was to create a new quality assurance unit (QAU) linking different philosophies, diverse product lines, and multinational operations to position our company for growth and success. Here we share thoughts and experiences from that endeavor.

A New Landscape

Traditionally, manufacturing plants produced goods for their local markets, performing all operations (or at least completing all operations) for active pharmaceutical ingredients (API) or drug products. That was, and to a large extent still is, the model on which small molecule pharmaceutical businesses are based.

Now the environment looks much different, especially for API biopharma operations. Only rarely are all production and testing operations carried out in a single facility. Biopharma supply chains typically have cell bank production and storage in multiple locations, fermentation and isolation at one contractor, and downstream processing operations at another. Analytical support often involves multiple laboratory sites, and drug production and release occurs

in yet other locations. These operations are often located in different countries and on different continents, and they are owned by different entities. Each possesses unique cultural company and country identities. Managing all the quality assurance (QA) requirements into a single, homogeneous product flow is the challenge facing biopharma QAUs today.

Capacity and personnel crunch. The biopharmaceutical industry is experiencing a documented shortage in production capacity. Also in short supply are experienced manufacturing and QA personnel and employees with the expertise to navigate an intense regulatory environment. Regulators and internal QAUs are incapable of spreading their staff's contributions and talents to the many sites and departments that require the depth and expertise demanded by today's development and production environments.

Compliance requirements, which are continually increasing, demand expertise to support rigorous computer and plant automation systems, electronic records and signatures (Part 11), and complex cleaning and processing validations. Meeting those requirements places a growing demand on quality systems, training, and documentation.

Most of today's Quality leaders possess a life science background, began their careers with laboratory experience, and eventually made their way to management. Few degrees are offered in QA. By building on their scientific knowledge, common sense, and work experience, QA departments have become confident and knowledgeable in managing and leading QAUs.

The Quality Requirements

Whether your company is big pharma, a start-up, or somewhere in between, regulatory compliance must be the number one priority. Quality and compliance are

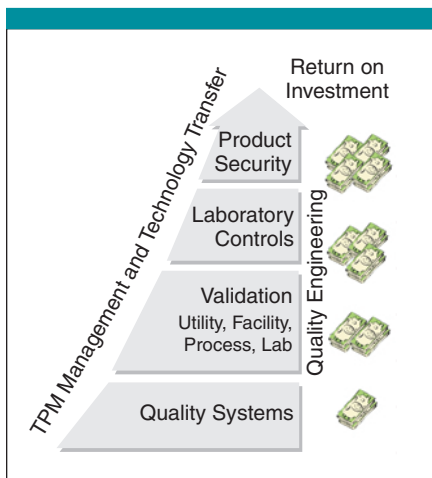


Figure 1. The foundation of a biopharma QAU begins with quality systems. The return on quality investments (ROQI) increases with robust supporting systems. (Figure by Daniel Gandor, Pharmacia GS API Biopharma; “TPM” stand for third-party manufacturing).

inextricably linked in this industry and often confused for each other. QAUs include critical elements of both. They lead the effort that allows an enterprise to operate (compliance) and maintain high customer satisfaction (quality) — while optimizing costs. Designing both regulatory compliance elements and QA leadership into a QAU is essential for long-term business success.

Robust QA leadership matrices include functions supporting process improvements, quality engineering, automation, and security. As the cost of biopharma production continues to rise and product values increase, so do the number of incidents of product counterfeiting and tampering. Incorporating elements beyond compliance brings balance to QAUs and provides the basis for cost savings, process improvements, and value-added activities and programs (Figure 1). Such programs can be capitalized on to multiply the return on initial resource investment. Maintaining improvement matrices reinforces management decisions to provide the QAU with resources.

Senior leadership involvement. Convincing management to approve additional personnel requires arguments with sound reasoning and justification. Business leaders realize that a company’s “Right to Operate” depends on compliance. They are routinely reminded by FDA through consent decrees, delayed approvals, and other regulatory

actions that “there is no production without compliance.” Recent FDA frustration with company attitudes and inability to comply with regulations has resulted in increasing enforcement actions, such as Abbott’s \$100 million fine and consent decree and Wyeth’s \$30 million disgorgement-of-profit penalty. FDA inspection and reinspection of Eli Lilly and Company resulted in delayed approvals and reduced earning forecasts. Manufacturing problems at several Schering-Plough Corporation facilities led to a delay of FDA approval and loss of bonuses for top executives. Some FDA regulators believe the industry “still doesn’t get it,” even after all the warning signs the agency has given.

Specific regulations and guidelines for companies manufacturing or importing into the United States are numerous. They are available on Web sites such as those listed in the “Regulations” box.

FDA recently instituted a program for their inspections: the Quality Systems Inspection Technique (QSIT). QSIT directs inspectors to look at a minimum of two and possibly all six systems they expect to find compliant at each facility. The systems FDA staff might inspect at their next visit to your company are quality systems, facilities and equipment, materials, production, packaging and labeling, and laboratory controls.

Although industry has some concerns about QSIT, FDA is pursuing it and other initiatives designed to maximize efficient use of scarce resources. Many companies now use QSIT as a model for reshaping their own GMP assessment procedures. Remember, “the right to operate” implies that “quality is compliance.”

The Resource Challenge

Two challenges can prevent a company from building an effective QAU, one internal and the other external. The internal challenge is obtaining management approval to hire additional personnel. The external challenge is identifying and recruiting staff with appropriate talent, expertise, and personality to support the growing technical demands being placed on the industry.

To receive approval to hire, we recommend that QAUs evaluate the company’s mission critical needs, assess its current ability to meet those needs, and then prepare a gap analysis that describes what is required. If there is genuine need based on compliance,

a gap analysis makes the urgency clear to management. Before finalizing the analysis, create a plan that outlines the proposed strategy and tactics that will deliver the results that the analysis pointed out. Such a plan can be used to secure management approval to hire.

We successfully demonstrated our resource needs by using a tool we developed called a *resource map*. The resource map provides management with a clear delineation of identified gaps that cannot be remedied with current resources. By outlining the compliance gaps and risks, a compelling argument can be made for additional talent.

Recruiting talent is a significant undertaking requiring time and focus. This should not be underestimated. Planning for that time, energy, and focus up front should pay huge dividends later when productive talent is on board contributing to your efforts. Such a commitment requires suspending ongoing work to focus on the recruitment process, a required trade-off if progress is to be expected.

When seeking talent, focus on three areas: identifying candidates with the talent and expertise needed to fill the gaps, finding the right personality and cultural fit to support the existing organization, and ensuring that the candidate has the ability to work in a team-based, knowledge-sharing environment.

A QAU is required by regulation and internal expectation to have expertise and knowledge that is broader in scope and depth than any other technical department in the company. It needs expertise in providing guidance, review, and approval and in maintaining ethical practices in all technical areas of the business. Expertise is required in research, development, scale-up, manufacturing, and technology transfer, and QAUs need to be aware of all current regulatory compliance requirements. QAUs must work effectively with those involved in the production process both inside and outside of the organization, helping them maintain compliance. QAU staff are also expected to have team-based leadership skills and several years of experience, and you want them to be a cultural fit, affordable, and willing to travel to all locations required by the job.

There is a shortage of talent to support the QAUs in biopharma today. The personnel

shortfall is based not on lack of education (personnel recruited for the biotech area are some of the best educated in the pharmaceutical industry) but on a shortage of experience in an industry where regulatory experience makes a difference. The solution to this challenge is to find talent that has most of the core attributes needed to deliver the results and then to help those people develop their full potential. Find individuals who possess core capabilities, are willing to learn and address weaknesses, and who can fit into your company culture. Ensure that your recruiting provides a balance of staff with different skills who can communicate well, rely on each other's strengths, and ultimately provide the foundation needed to meet business demands through teamwork, cooperation, and sharing knowledge and expertise.

Recruiting top talent with experience is difficult.

Good candidates know they are in demand. The better talent is already well placed and well compensated. Securing top talent that can lead and mentor less experienced yet capable staff provides a competitive advantage that should be exploited. An alternative to finding the best talent is finding the best people with specific skills to make up the organization, and then to coach, mentor, and lead them to work together and, ultimately, to develop into the leaders needed for progress in our industry.

Previously, the rule-of-thumb used to determine the ratio of QA personnel to plant operation staff for a small molecule manufacturing site was one in 10 to one in 15. Today's biopharma API plant ratio is closer to three-and-a-half to five QA staff members for every 10 plant personnel. That higher resource demand, coupled with the limited experienced talent available exacerbates recruiting difficulties.

The QAU Plan

Each QAU serves unique business needs and should be custom-designed to do so. With all the regulatory requirements and disparate supply chains prevalent in the industry today, robust QAUs should include elements of compliance and validation, quality systems, analytical laboratory compliance, and quality engineering, as well as a unit to address technology transfers and third-party manufacturing (TPM) issues. The QAU must be able to manage quality both internally and with outside services and contractors. Its organization must be based on an assessment of critical business and regulatory needs and be organized for successful integration of product line and staff functions.

Compliance and validation. The process is the product in biopharma. Regulatory scrutiny continues to increase — and products will succeed or fail — based on the quality of a company's process, cleaning, facility, and utility validations and on its conformance to standards. The compliance and validation unit of QAUs must also address the new requirements for computer validation and the security of electronic signatures as well.

Quality systems. FDA QSIT inspection guidelines require that effective systems be in place for training, contractual relationships and responsibilities, change controls, deviation handling, documentation, annual product reviews, and archiving of developmental reports and other critical supporting documentation.

Analytical laboratory compliance. Laboratory controls, methods validations, technology transfer protocols, reporting processes, and compliance documentation are the basis from which all manufacturing decisions are made. Biopharma expertise and good laboratory practices (GLPs) are needed to

Manufacturing and Importing Regulations

Specific regulations and guidelines for companies that manufacture or bring product into the United States are numerous. Many, however, can be found on the Web sites of FDA (www.fda.gov), the **International Society of Pharmaceutical Engineers** (www.ispe.org), and the **International Conference on Harmonisation** (www.ifpma.org). Key regulations in the United States are in the *Code of Federal Regulations*, Title 21, Parts 210, 211, 310, 312, and 600

(available at www.access.gpo.gov/nara/cfr/cfr-table-search.html). Also important is the September 1999 **Guidance for Industry** (as well as other guidances from both CDER and CBER (available at www.fda.gov/cder/guidance/guidance.htm)). FDA recently approved new **ICH Guidelines (Q7A)** for API, which specifically address biopharma issues for development and commercial products (www.ifpma.org/ich5q.html).

support product development and commercial activities.

Quality engineering. Process improvements; equipment, utility, and facility selections; and most recently product tracking, security, and assurance are supported by this group. Recent requirements require more detailed control and documentation of plant automation systems as well.

Technology transfer and third-parties. This unit specializes in bioscience, scale-up technology transfers, and working with outside TPMs. Eventually, commercial production will be remotely controlled assuring compliance to quality principles. This section of the QAU needs to participate in project teams from early-stage development through commercialization and life-cycle product management.

If these five elements are part of your QAU, they become the foundation that improves your compliance and quality efforts. The regulatory bodies that govern our industry require QA (compliance) focus on documented proof of safety, consistency, and adherence to regulations. Process

efficiency and cost-effective production are not regulatory concerns. A well-designed QAU has regulatory compliance as part of its design, but it also integrates quality engineering to optimize the potential financial return inherent in all existing processes.

Executing the Plan

To execute your QAU plan, hire the best talent. Because your employees are essential to executing your QA plan, use recruiters, print advertisements, Internet job sites, and trade journals; they cast a wide net. When recruiting for several positions, wide-net strategies work well. An applicant may not be the best fit for the position applied for but might fill a different void in the organization. Such tactics need to be part of your overall strategy. Networking through known associates can produce superior results when targeting candidates for specific positions. References received through known sources can provide insight into the applicant's capability and willingness and into the culture he or she is

used to working in. Knowing that background can accelerate the process of filling gaps in your QAU.

While recruiting, seek candidates that possess as many job-related skills as possible, meeting at least 70% of your well-written, specific job description. Include key attributes you are looking for such as team-based working and communication skills, an essential attribute for the cross-functional support needed within the QAU. Failure is imminent for companies staffed by employees that are unable to share information or that lack expertise, experience, and knowledge of industry issues and how to effectively deal with them.

Hold "super days," when all potential, prescreened candidates for a particular position can be brought together at one time for personal interviewing. This gives all stakeholders involved with the interview process an opportunity to compare candidates. Such days help focus the interviews and the discussions that result.

A new paradigm and unique challenges confront the QA biopharma world. Biopharmaceutical production is unlike other pharmaceutical businesses, in which talent, infrastructure, systems, and expertise are well established and maintenance modes of operations can be counted on.

Our specific challenges include complex supply chains, limited experience in an emerging industry, limited talent pools, and increased scrutiny and action from regulatory agencies. Enormous pressure is on our industry because organizations are dealing with changes in their own QA infrastructure as well as those same changes required of their suppliers, partners, and contractors. Those changes affect the way we think about and approach our business.

Building a successful QAU means finding capable, competent people, designing mechanisms that ensure that the organizational puzzle fits together with all the required pieces, and making sure that the teams communicate. The right attitude is essential in filling the gap in our industry that doesn't yet have all the answers. After a robust QAU is in place, vigilant leveraging of staff strengths and managing organizational gaps are the challenge our leaders must face to be successful. **BP**