Operations and Quality Systems

Building in Success

by S. Anne Montgomery

To begin by stating the obvious: All the work you've read about in the previous chapters has to happen somewhere—in some sort of building. And because the marketable products that emerge from biotechnological manufacturing processes must not harm patients, that "somewhere" must be built according to stringent criteria governing contamination control, separation of manufacturing activities, environmental systems, appropriate work/personnel flow patterns, and specification of utility systems—among many other factors. Like other elements of the bio process, these also require validation and/or qualification. That entails millions of dollars, sometimes years of work with architecture and engineering (A&E) firms (**1**), and knowledge of local ordinances, conversations with concerned members of the public—and eventually inspection by the FDA. A company hopes that undergoing those activities (and devoting all that money and time) will be rewarded by the commissioning and operation of its new manufacturing plant (**2**).

Facility design is not just a matter of creating an attractive building. It must incorporate

• knowledge of critical operating systems, which requires qualification of equipment and related calibration SOPs

• qualification/validation of automated systems for process control, monitoring, and documentation

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• acquiring water-for-injection or other levels of purified/pharmaceutical-grade water (or arranging to produce them on site)

• acquiring process gases and assuring their safe handling and use, and specifying air-handling systems and other environmental controls . . .

. . . all in compliance with CGMPs. Even when all those things (and more) have happened, and even after a facility has been commissioned and is occupied by dedicated technicians and scientists happily creating their company's products, this type of work is never really completed. Quality Assurance and Control (QA/QC) personnel must continually monitor the facility's state of compliance throughout all departments, working with Regulatory Affairs professionals to ready all systems for FDA inspections and to ensure that products can safely remain in production and on the market (**3**).

The following is only a brief sketch of some issues that go into building a facility and developing its quality systems. But a wealth of literature details years of biotechnology facility design projects—in an industry that's now well over a quarter-century old. The development (for example) of modular cleanrooms and isolators—and availability of modular units/aseptic "building blocks" for speeding facility construction—have all contributed to a plethora of options and experiences to draw from (**4**). Additionally, as more and more A&E firms now have experience in design and retrofitting facilities for biotechnology companies, biotech project managers can search out those firms that offer experience with projects similar to their own.

Facilitating the Process

An Interdisciplinary Endeavor: Up to this point, you may have gotten the impression that biotechnology drug development, production, and processing is the realm mainly of microbiologists and other scientists and technicians, intellectual property lawyers and marketing experts, as well as vendors of raw materials and equipment (see the "Other Important Participants" box). But creating the appropriate work environment and operating systems for them are engineers, vendors of utility systems

and processing equipment, administrators and support staff, architects, and computer programmers—not all of whom historically have been brought up-to-speed on the longer-term (or bigger-picture) needs of facilities and systems they are developing. This is having an impact especially on IT personnel (as discussed further below).

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Process Understanding Determines Design Criteria

Once a company has decided to build its own CGMP-compliant facility (rather than outsource future manufacturing needs), it will be guided by design requirements and regulations specific to the nature of its product and production process. Decision makers will need to determine what manufacturing scale will suit their current needs as well as whether (and what) future expansions might be necessary. They will need to have realistic expectations about the timelines involved in such projects—that is, the time it will take before products can be manufactured in the new building. That depends on the stage of development a facility is intended to support (e.g., pilot or commercial scale, phase 1 or phase 2–3 clinical trials) and the complexity (rigor) of related validation procedures: A clinical pilot facility will not be subject to the same licensing procedures as a full-scale manufacturing facility, whereas a multiuse facility will need to allow for proper segregation of product and materials throughout campaigned manufacturing (including product changeover). If the company is building or moving to a different geographical site from where its R&D laboratories have been located, it must appoint a company representative or project manager to undertake a process of due diligence toward assessing the best location (5).

Considerations typically include availability of trained workers/technicians (perhaps from a nearby university or technical institute), proximity to vendors or similar companies, attractiveness of local/regional tax and other financial incentives, access to utilities,

Other Important Participants in the Bio Process(es)

As you may realize by now, the business of developing a biotechnology drug or therapeutic is a hugely interdisciplinary endeavor, and there are other participants in the process whose essential efforts may not always be appreciated.

As construction contracts are drawn up and future plans are discussed, among the vital groups supporting the bio process is a **company's legal counsel or department.** Biotechnology patent protection is an increasingly complex enterprise with direct impact, for good or for ill, on the success of eventual marketing efforts and a company's bottom line. This has become an increasing area of specialty also: Many biotechnology attorneys themselves offer backgrounds in pharmaceutical and biotechnology science (and even manufacturing).

Another group with an increasing voice in the industry are **bioethicists**. In fact, some companies are now including them in initial product development discussions, especially regarding marketing products (vaccines especially) to areas of the developing world where strong markets may not exist. Ethicists figure strongly in debates over stem-cell research and clinical studies—and many of those who specialize in bioethics also have solid scientific industry experience.

This small sample of web sites focusing on bioethics also contains links to similar resources:

- *The American Journal of Bioethics*: www.bioethics.net
- Biotechnology Industry Organization: www.bio.org/bioethics
- National Institutes of Health, Bioethics on the Web: www.nih.gov/sigs/bioethics
- Markkula Center for Applied Ethics, Santa Clara University (California): www.scu.edu/ethics
- University of Pennsylvania, Center for Bioethics: www.bioethics.upenn.edu.

Although most people expect **marketing and public relations groups** to build awareness of a company's products and services, those groups play an especially critical role in biotechnology companies. Marketing representatives must demonstrate solid understanding both of their companies' products and a client's equipment and process needs — including related safety, documentation, and training issues. They must understand issues of scale and know what equipment is appropriate for different applications. They must be able to prove that they will consistently provide the raw materials and/or components essential to a client's product and process—throughout the lifetime of that product.

Marketing consultants from vendor companies sometimes work with their clients to optimize processes. It should therefore come as no surprise that many people working in biotech marketing have come out of biotechnology or microbiology research, production, or manufacturing. Sometimes they themselves have developed the product or method they are promoting.

Aided by market research provided by the public relations staff, these groups help to create their company's image and assure its credibility in the industry. All these groups contribute to promoting public awareness of biotechnology, supporting its conferences and educational programs, and helping to build community acceptance of new facilities in their areas.

Critical Utility Systems (18)

Based on the level of contamination control needed for aseptic processing needs, facility design includes making early decisions about the following:

Backup Systems: How might a major power outage affect the stability of your product, especially that in storage? Millions of dollars' worth of vaccines were lost in New York from lack of refrigeration during the August 2003 blackout, for example (**1**).

Disposal, Drainage (Waste Management): Does facility waste need to be treated, or can it safely go into the sewer system? Is there adequate protection against backflushing that could contaminate your system? What other provisions need to be made for safe disposal of other materials? What do local ordinances mandate?

Environmental Controls: Facility design must incorporate equipment that maintains control over air pressure, dust, microorganisms, humidity, and temperature; production areas may require prefilters and particulate air filters; dust must not be allowed to recirculate from production areas; exhaust systems must adequately control contaminants; even lighting might have a negative affect on the stability of some products in storage.

Gases: Will the company draw up a contract with a vendor for its process gases, or will it manufacture what it needs on site? Gases that are dangerous to transport and handle (such as chlorine dioxide, for example, used in some sterilization processes) may need to be manufactured on-site.

Water: Where in the facility can local (tap) water be used, and where will pharmaceutical-grade water be required? Plumbing standards are set by the EPA in 40 CFR part 141 and must be met.

Reference

1 Ryan US. How Effective Has the US Government Been in Supporting the Development of a Biodefense Industry? *Phacilitate Vaccine Forum* Fall 2003, 17–20 November, Boston, MA.

acceptable options for waste management, local acceptance of biotechnology, perhaps access to transportation and shipping resources, even quality-of-life issues for employee retention—and so on (**5**). A number of US companies these days are finding good incentives to build manufacturing plants outside the United States, in Ireland or The Netherlands for example, or on Puerto Rico. In such cases, cultural and language differences may factor into the decision as well as unfamiliar regulatory requirements.

Once a location is chosen, an architecture firm must be found. Project managers will look for one with experience in designing similar facilities. They will make their decision based on both reliability in meeting deadlines and willingness to work closely with company representatives (ideally from several major departments/functions) to design for specific product and process needs (**6–8**).

Whether a company is retrofitting an older facility, building a new one from scratch for its own production needs, or even building a facility for contracting work, the same general criteria must be incorporated into this process. Very few modern facilities are built to manufacture a single product alone. Designers must therefore protect one product from cross-contamination with another and prevent personnel moving between those areas from

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bringing contaminants in from one process to another. So in addition to validating equipment, systems, and manufacturing processes, operators of such facilities must validate the effectiveness of their procedures for cleaning nondedicated equipment and supplies during product changeover (**9**).

Design Features: To facilitate cleaning, a building's floors, walls, and ceilings must be smooth, and equipment must be impervious to sanitizing agents and resistant to deterioration, with sealed joints, coved corners (where vertical and horizontal surfaces join in a concave curve), and no exposed piping. Connections and pipes must minimize "deadleg" areas that could be missed during cleaning and sterilization procedures and thus trap contamination (**9, 10**). Before a facility can be cleared for operation, its cleaning/sterilization systems and aseptic connections must be validated. The "Critical Utility Systems" box lists other general considerations.

Equipment Needs and Qualification: Equipment and instrumentation installed in a new facility (or added at any later point) must be identified by a unique number or code and qualified based on its intended use according to performance, operation, and design specifications. Materials of construction and other substances used by that equipment (lubricants, for example) must be verified not to contact product and/or react with it to affect quality. SOPs must be in place for regular maintenance and calibration (**9**). For example, how will maintenance personnel make repairs in aseptic suites? Many facilities have "walkable" ceiling designs that allow maintenance of utility systems (and some process monitoring) to happen outside the most heavily isolated areas.

A New Facility Design Option

Cost analyses of facility design are complex studies involving calculation of future equipment and capacity needs (**11**). Will a company want to leave room for future expansion, for example? One major consideration these days is whether a manufacturing process will make use of disposable (single-use) equipment and/or components, and if so at what stages and how.

As introduced in Chapter Three of this supplement, disposable technologies may present a safe, economical alternative to certain stainless steel "hardware." Adoption of single-use options ranging from stand-

alone components and devices to multicomponent systems that are designed for unit operations may eliminate the need for some cleaning, sterilization, and aseptic assembly. They can improve process safety and quality by lowering the risks of cross contamination (especially valuable in multiuse/multiproduct facilities and for contract manufacturers) and human error by reducing cleaning requirements and the number of aseptic connections needed. And because they are less expensive than large, stainless steel processing equipment—and they eliminate the time and materials costs for cleaning, cleaning validation, and steam sterilization validation—their use also reduces initial capital costs and can thus have a dramatic impact on facility-design decisions (**12**).

Disposable technologies for upstream processing include benchtop devices for cell culture operations (temperature, oxygen, and pH monitoring) and filtration, and equipment such as tank liners, culture media preparation bags, tubing, and disposable bioreactors. Downstream processing applications include direct-flow filtration (DFF) filters, tangential-flow filtration (TFF) cassettes, membrane chromatography capsules, lenticular depth filters, filling equipment, aseptic connections devices, tubing, adaptors, clamps, and storage bags:

> Disposables technology represents a fundamental change in processing approach and facility design. As a closed-loop system, it prevents the need to disassemble, transport, clean, validate, and reassemble components in classified cleanroom environment. In many cases, disposable products are supplied presterilized to eliminate the need for steam-in-place (SIP) or autoclaving. . . . The result is not only labor savings, but also a shift in facility design toward fewer cleanrooms and reduced environmental monitoring requirements.
>
> With single-use operations, applications no longer need to be physically segregated. Instead, they can be performed side by side as closed-loop systems. This makes more efficient use of facility space, especially for CMOs and biotech start-ups. Even as disposable systems seal off processes from contamination, their translucency provides operators with convenient visibility into manufacturing operations. Users can observe flow and fluid levels as well as spot fluid discoloration and air pockets immediately. Single-use processes also allow for a high degree of modularity in that capacity can be built out gradually in phases as demand increases. Within conventional facilities, not only do hard-piped systems need to be factored into the initial facility design, but also oversized large utility systems. (**13**)

Some biotech start-ups can benefit from single-use technology to manufacture products in house without having to endure the capital costs of building a facility or even of outsourcing their work—especially at early clinical stages in which product failure is still a high risk. So they have potentially greater flexibility and control over their costs of development and production, which will make their "angel" and venture-capitalist investors happy. The FDA is a major proponent of disposables technology. "Considering that validation accounts for 10–20% of the cost of a new plant, disposables suppliers share the agency's sentiment to provide industry with practical solutions to alleviate the challenges and costs associated with cleaning operations " (**13, 14**).

Decision-makers, however, must keep in mind that potential cost savings in designs that incorporate disposables must be weighed against the ongoing costs for purchase of such components as well as monitoring/auditing supplier validation practices, whatever necessary qualification the materials require

A Few Terms Used in This Chapter

commissioning: A process that can take six to 12 months, it is an activity in which functional subsystems are examined to determine that a facility is functioning properly within defined operating conditions and any necessary remedial actions are undertaken before the site can be occupied. It involves verification, validation, and/or qualification testing of HVAC (heating, ventilation, and air-conditioning) systems and electrical, plumbing, and other systems to assure proper functioning and adherence to design criteria. Verification and validation tests are performed on complete systems.

due diligence: A process of systematically evaluating information to identify attractiveness and key risks relating to a proposed transaction; it starts on initial inspection of an opportunity and may continue throughout a project.

isolators: Disposable units for filtration, separation, and capture operations in bioprocessing unit operations, they protect operators from hazardous/potent processes, or protect processes from people or detrimental external environments (or both). *Closed isolators* do not exchange unfiltered air or contaminants with adjacent environments. *Open isolators* are designed to allow for continuous or semicontinuous egress of materials during operation, while maintaining a level of protection over the internal environment.

qualification: A documented determination that a product (and its associated software), component, packaging, or labeling, meets all prescribed design and performance requirements.

XML (extensible markup language): A flexible way to create common information formats and share both the format and the data on the Worldwide Web, intranets, and elsewhere; users can define (markup) "tags" that identify data and specify appearance of material on display, facilitating searching and display.

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Water, Water Everywhere . . .

Even the types of water used in biopharmaceutical processing are subject to strict quality guidelines. The *United States Pharmacopeia* (www.usp.org) contains monographs that define criteria and tests for "bulk waters" suitable for pharmaceuticals.

Each kind of water for pharmaceutical purposes starts with a source water. In the United States, the requirements for source water are those from the national primary drinking water regulations issued by the Environmental Protection Agency (EPA, www.epa.gov); in the *European Pharmacopoeia,* the source water requirements are for drinking water as prescribed by the European Union; in the *Japanese Pharmacopoeia* the drinking water requirements are those for source water and are prescribed by the Japanese Ministry of Health, Labor, and Welfare.

Purified water is water produced using a suitable process from source water that complies with EPA drinking water regulations or comparable regulations of the European Union or Japan. It contains no added substances, indicating that chlorine levels should be neutralized before it can be used for purified water. It cannot be used for preparations intended for injections or parenteral use. However, it can be used as an ingredient for nonsterile dosage forms (other than injections) if it is sterilized and protected from microbial contamination during storage.

Purified water sterilized contains no antimicrobial agents, and it must not be used for parenteral preparations. It is tested for acceptable ranges of pH, ammonia, calcium, carbon dioxide, chloride, sulfate, and oxidizable substances.

Water for injection (WFI) is water purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms. It meets the same requirements as purified water or sterilized purified water if it is produced on-site or if purchased in bulk containers, respectively. In addition, WFI must not contain more than 0.25 USP endotoxin units per mL.

Water for hemodialysis is bulk pharmaceutical water that is used extensively in hemodialysis. It complies with the US EPA requirements for drinking water and then is subjected to further treatment using a suitable process to reduce chemical and microbiological components. It is produced and used on-site in dialysis centers under the direction of qualified personnel, and it contains no added antimicrobials and is not intended for injection. It is the only subject of a water monograph in USP that has a microbial limit requirement (not more than 100 cfu/mL). It also has a bacterial endotoxins requirement (not more than 2 USP endotoxin units/mL), a conductivity requirement, and an oxidizable substances requirement.

Source: Dabbah R. USP Pharmaceutical Waters, Part 1: Bulk Waters. *BioProcess International* 4(3) 2006, in press.

when they arrive on site, and possible costs of any resulting downtime should there be an interruption in a vendor's supply (this is part of due-diligence risk analysis). Formulations scientists must be involved in certain decisions to the extent that disposable materials of construction may interact detrimentally with a product under development. For example, will the company need to ensure a supply of animal-component–free plastics, for example? Additionally, many in the industry warn that use of disposable bags still introduces limitations of scale, given that very large bags are heavy and hard to lift safely. Will the company be able to scale up such systems to meet future production needs?

Secure Designs

Security is an important issue for any biotechnology facility. Visitors to a site (even on guided group tours) are usually required to sign in and receive badges, and they are authorized to move through the facility (and usually just parts of it) only as escorted. Sometimes visitors don special gowns, gloves, slippers, and head and face coverings to tour certain areas of a plant—and they still won't see the very critical areas up close. Many modern biotechnology facilities, therefore, have designed wide hallways to enable visitors to safely view critical operations through windows into cleanroom or even fill-and-finish suites.

Security of data and product-related records is just as important. Until recently, those working in IT departments were considered fairly interchangeable from industry to industry. But as the FDA and other agencies urge greater reliance on electronic submissions, computer systems designers and administrators—especially those involved in monitoring/control systems and the documentation generated from them—now need to know more about ways their data will actually be used throughout GMP-regulated process development, about which groups need to access that information, and about protecting it to ensure its longterm security and reliability (**15–17**).

Biopharmaceutical IT systems also must comply with requirements outlined in Title 21 of the *Code of Federal Regulations* (**18**). Computer-systems validation processes must demonstrate that software operates as intended and that only authorized personal may enter data or make changes to production and control records. Backup systems must be reliable. The "electronic signatures rule" (Electronic Records, Electronic Signatures; 21 CFR Part 11) is currently being reevaluated (**19**), but what has not changed—and one aspect that will not change—is the need to assure that only authorized personnel can sign off on a batch record or other important step. Laboratory notebooks must be kept in secure locations and checked out only by authorized personnel. If they are electronic notebooks, their data must be protected from alteration (**20**).

Following issuance of Part 11 in 1997, many proprietary software systems were developed for compliant management of a company's data. As the attention of regulators turns toward recommending greater reliance on monitoring and documenting process control throughout manufacturing—that is, assuring product quality through ongoing testing, with less reliance on final

lot-release testing—IT departments are being brought up-to-speed on "GxPs" to facilitate the exchange and continuing integrity of data across departmental and developmental stages.

Electronic regulatory submissions require regulators to be able to access accompanying data in a format that each agency specifies. For example, as of 31 October 2005, the FDA requires product labeling to be submitted using "Structured Product Labeling" or SPL, a pharmaceutical community XML standard that facilitates communication of drug information among various groups—the FDA, hospitals, prescribing organization, doctors, and the general public (**17**).

Risk Management: Although it is not the scope of this special issue, any discussion these days of facility design and quality systems (and other manufacturing systems) inevitably falls under agency-wide regulatory emphasis on increasing sophistication of in-process controls and other tools for risk assessment and management (**21**). Certainly advance planning for disaster contingencies is just good business these days (see the "Disaster" box). But as biotechnology project managers, CEOs, and CFOs begin to design their projects, they also need to develop familiarity with a number of acronyms that were once more familiar to other industries and even other FDA division (devices, primarily). Such terms are becoming industry-wide mantras—HACCP (hazard analysis critical control point) and FMEA (failure mode and effect analysis) methods, for example **(22–26)**. As another example, industry advisors are urging their biotherapeutics clients to devote greater attention to establishing CAPA systems (systems for corrective and preventive actions, which were introduced into the device GMPs in 1996) (**27**).

The FDA's emphasis on incorporating process analytical technologies (PAT) as tools predictive of a product's success at early stages of development is intended to lessen a company's financial risk should a product fail in clinical trials, to perhaps speed a successful product to market by reducing the need for lot-release testing, and to prevent the occurrence of adverse events and (therefore) product recalls—all in the service of ensuring and protecting the public health (**28–30**). The industry's embrace of single-use components and systems serves to lessen capital expenditures and increase flexibility (as discussed in more detail below), and sophisticated economic models are being developed to help companies lessen risks incurred in making decisions to build or remodel facilities (**11**).

Those initiatives and the biotechnology industry's responses to them will be the subject of an upcoming 2006 supplement to *BioProcess International*.

Quality Systems and Trends in System-Based Inspections

> Quality control considerations must be given to raw materials and reagents used throughout a process because material quality significantly affects process consistency and even product quality. Documentation is paramount and includes laboratory notebooks, batch records, and analytical methods and results. Timely completion of development reports and raw data archiving are necessary. We can never overstate the importance of documentation in biotechnology. (**31**)

Finally, given the complex interconnected processes that have been described throughout this special issue, it of course must fall on someone to see that everything comes together as it should so that regulatory reviews and facility inspections can succeed. When validation occurs and when equipment and computer systems are qualified, when batches are released for clinical trials or for further processing and scale-up, when raw materials are quarantined upon delivery, when product is labeled and segregated as required, when personnel training is conducted according to GMP directions—in short, anywhere in a biotechnology facility that SOPs are created and expected to be followed, QA/QC professionals are tasked with seeing that all procedures are followed and documented, as specified by the regulations and GMPs.

> There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible to approving or rejecting drug products manufactured, processed, packed, or held under contract by another company. (**32**)

Disaster Contingencies

Beginning at the due diligence phase of site selection, project managers must take into account their company's potential ability to respond to possible disruptions in their processes and production efforts—from many angles. Aside from designing their production and processing suites and data systems with an eye toward mitigating risk, they may need to weigh the advantages of one site against an infrastructure of another that might help them respond more quickly to such events as

- cyber attacks
- equipment failures (including hardware and software)
- geographical restrictions due to potential chemical contamination
- natural disasters such as floods, earthquakes, and tornados
- power failures
- supplier disruptions
- telecommunications failure
- workforce shortages
- workplace violence

Although no one can truly predict when such emergencies might occur, a company must have backup systems and SOPs in place to ensure (to the best its ability!) that it will be able to operate, remain in compliance, and keep its products safe.

Source: Fiscus PW. Would Your Company Survive Disastor? BioProcess International 2(8) 2004: 16–20.

An organization's quality professionals may represent a broad range of skills and experience, from analytical scientists in a QC laboratory to documentation/GMP specialists to entry-level technicians. They are the ones who make sure that all documentation is in place and that personnel are trained to know what to do when FDA comes to inspect—and how to document what was done before that:

> Faced with long, complicated and sometimes ambiguous legal requirements for how their business must be conducted, monitored and documented, companies turn to the quality unit as their guiding light. Quality professionals are expected to make sure that after products make it through the long journey of development, testing and approval and into the marketplace, they stay on the market. At the same time, the regulators look to each company's quality unit to provide objective oversight and the independence, honesty and integrity to make the concept of self-policing a reasonable protection of the public health. (**3**)

Given that biotechnology processes involve personnel from varying disciplines, all with different areas of specialized expertise and priorities and different approaches to validating their work, the quality staff must have both an intimate knowledge of applicable regulations and a very broad understanding of operations in their facility. They must make sure that personnel in all departments understand the importance of creating and following SOPs and demonstrating and documenting that their processes are under control at all times. They must make sure that employees also understand the necessity of documenting any changes to their processes and systematically evaluating the effect of those changes upon product quality and consistency.

Systems-Based Inspections: A company's quality control unit is part of its quality system, one of six manufacturing systems in a facility that are subject to inspection by the FDA:

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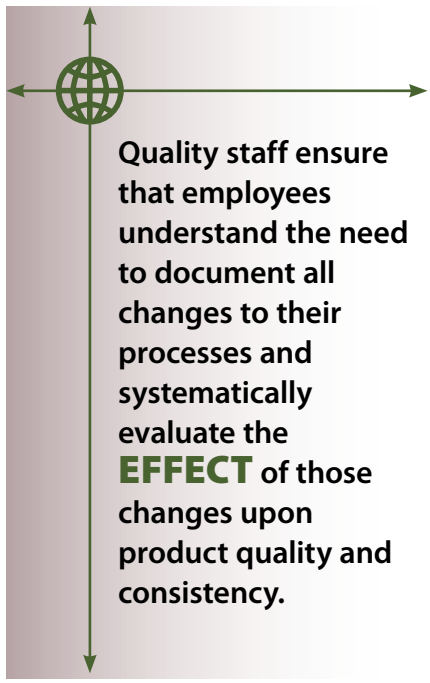

- Quality System
- Facilities and Equipment
- Materials
- Production
- Packaging and Labeling
- Laboratory Control

As of 2002, the agency is inspecting two or more of those systems along with the quality system (which is mandatory) (**33**). This "systems-based" approach was implemented in part because FDA was stretched beyond its resources and funding (and personnel) to keep up with mandated inspection schedules (**34, 35**). The rationale is that if a manufacturing system is in compliance, then all products dealt with as part of that system should be under the same degree of compliance. If SOPs exist for one product class, then they can be assumed to exist for others within that system and thereby reflect "the state of control in that system for every profile class." This then leaves to each investigator's discretion whether to examine any element unique to a specific product's requirements. A number of documents are available to explain the FDA's current rationale and approaches to quality-systems inspections—issues still very much in the process of debate and redefinition among industry groups (**36–44**).

Is Your Process in Control?

Whatever the shape of the biotechnology industry and its governing regulations across the globe in years to come, the need for documenting compliance with those regulations and ensuring that all processes are under control are unlikely to change fundamentally. Increasing emphasis on risk-based approaches, if handled as intended, will help companies be selective in choosing safeguards; if overinterpreted, risk-averse practices may slow development to a crawl.

Such changes in agency guidances and expectations are not the first—and will not be the last. Coinciding as they are with the transfer of certain products from CBER to CDER, they have caused some confusion (along with adding some more acronyms) and even controversy within the industry. But it is important to view these changes as part of the inevitable, continuing evolution of an industry characterized from its start by an inventive and entrepreneurial spirit—an industry that survived its lean years by creating new business models for itself. And whatever forms the industry and its regulatory policies take in the coming years, its goal will always be to create safe and effective treatments for some of humankind's most devasting diseases and medical conditions.

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