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SPECIAL REPORT ON BIOPHARMA AUTOMATION

# Transformation through Training

Biopharmaceutical manufacturing is poised to enter a more efficient and robust phase. New technologies, particularly in the area of automation, are enabling operations that are faster and better understood than in the past. If biomanufacturers are to keep up with, and leverage, technological advances, they must provide effective training for their key personnel. This special PDF—with additional links to web-based resources—looks at the importance of automation technical training and how it can provide biopharma manufacturers with clear competitive advantages.

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# Workforce Training: EMBRACING THE *NECESSARY EVIL*

As FDA probes the connection between workforce training and quality, drug manufacturers must do the same.

*By Paul Thomas, Senior Editor*

In a warning letter sent in 2010 to a maker of over-the-counter skin-care products, FDA wrote: "You failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or combination thereof, to enable that person to perform their assigned functions."

The letter continues: "For example, your 'QC/ R&D Chemist' has not been trained to perform specific tasks such as microbial limits testing . . . Your response is inadequate because you have not established completion dates and training programs for current good manufacturing practices and SOPs."

The admonition is not unlike many found in warning letters of late. Better get used to it, experts say. Employee training—and the documentation of it—is on FDA's radar.

FDA "is trying to get to the root cause of a lot of the problems they're finding" during investigations, says consultant Michael Gregor, president of Compliance Gurus, Inc. Whether these problems lie in Quality Control or elsewhere, the Agency wants to know whether manufacturers have the right people doing the right jobs, and that they can prove it. Meanwhile, Gregor says, FDA is intensifying scrutiny of issues related to 21 CFR Part 11—including training records and electronic signature authorizations—and sending dedicated Part 11 investigators on inspection visits.

Bill Ciambrone, senior VP for technical operations at Shire Human Genetic Therapies, has also noticed the Agency's change. "They recognize that there are so many deviations that are related to training," he says. "I would venture to say that in many instances, manufacturing failure is oftentimes due to a failure to properly train personnel. It's one thing that comes up when we look at deviations and investigations—have our people been appropriately trained so they can perform their functions adequately?"

Another issue of consequence is the effectiveness of training. In its August 30, 2010, letter to Bristol-Myers Squibb regarding its Manati, Puerto Rico facility, the Agency wrote: "Please provide a plan that evaluates your training program, specifically the program's effectiveness and your assurances of personnel compliance to aseptic processes prior to certification to work in an aseptic area."

The upshot: Manufacturers, like it or not, need to reevaluate the training records of their employees, how they manage and monitor training, and whether or not it produces its intended consequences.

### NOT A GOOD TIME

FDA's renewed emphasis comes at a time when manufacturers are struggling to manage their workforces and ensure that the right people are doing the right jobs. With mergers and acquisitions rampant, and manufacturers cutting costs and "leaning" their operations (i.e., fewer people doing the same amount of work), maintaining a consistently competent workforce is a challenge.

Nowhere is this better exemplified than at J&J's McNeil division, whose quality control and personnel problems have been well documented. Many of them derive from the fact that products in question were brought over in the purchase of Pfizer's consumer health care division, and their production transferred, on the cheap, to McNeil's now notorious Fort Washington, Pennsylvania facility.

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## HOW LEADING MANUFACTURERS TRAIN

According to the American Society for Training & Development, companies who excel in training:

- have formal processes to align business strategies with learning initiatives and priorities
- map learning resources to competencies, individual development plans, roles, and corporate goals
- have visible support from senior executives and involve leaders as teachers
- maximize the efficiency of the learning function by balancing centralized and decentralized aspects of the learning function, internal process improvement, use of technology, and strategic outsourcing
- maximize the effectiveness of learning by aligning learning activities with business needs and providing timely access to relevant learning opportunities.
- spend more, but many spend less than the norm
- provide a broad range of internal and external formal and work-based learning opportunities, including knowledge-sharing systems, coaching, and the ability to attend conferences
- demonstrate effectiveness by monitoring individual and organizational performance indicators and linking changes in performance to learning and nontraining performance improvement activities
- demonstrate the efficiency of the learning organization by monitoring time, usage, and cost indicators, and linking decreases in these to changes in the processes and practices of the learning function
- devote a large portion of their resources to nontraining performance improvement activities, particularly organizational development, process improvement, and job-specific resources.

Source: ASTD, 2009 State of the Industry Report

"There were no wholesale layoffs in quality control," wrote Mina Kimes in a recent *Fortune* article. "Instead experienced staffers were repeatedly laid off and replaced with newbies who mostly lacked technical pharmaceutical experience. By 2008 the analytical laboratory, formerly staffed almost entirely by full-time scientists, was half-full of contract workers, according to a former manager there."

"Those product handoffs are expensive and difficult," says regulatory consultant John English. "And when you move, you lose the collective memory or oral history" that production personnel have of a product.

Add to that the fact that a lot of the industry's expertise is retiring (or being forced to do so), and you're left with fewer plant-floor operators and other professionals who really know what they're doing. Meanwhile, training and travel budgets have been slashed. No longer can manufacturers afford to take personnel off the lines for a week or two of seminars and certification programs.

Most warning letters of late reference poor or inadequate training, English has noticed. "The tea leaves would say it's an issue," he adds. "It's always been an issue, but backwards. If there were problems at a manufacturer, the company would say that they'll train their workers [to address the problems]. But I always ask, how good were their training systems in the first place?" And it appears FDA has this interest, too, he says.

### THE NECESSARY EVIL

Management buy-in is at the core of successful employee training (see "How Leading Manufacturers Train," Box). And yet at many drug manufacturers, training is at best a "cost center" and at worst a "necessary evil." Kimes' article chronicles how training and personnel development were far from the top of J&J management's priority list.

## SIGNS THAT SOMETHING'S AWRY

Common indicators that manufacturing employees may need more or better training, courtesy of Bill Sicari, General Manager of Festo Didactic:

1. **Frequent production downtime.** A poorly trained workforce may have difficulty properly troubleshooting a problem in a production process, and therefore misdiagnose frequent interruptions of the production line.
2. **Increased maintenance costs.** Employees who have not received sufficient training to perform their job assignments properly will often replace system components that are functioning properly, or take an inordinate amount of time to locate a problem component or failed sub-system.
3. **Product quality problems.** While the process design can be flawed, it is usually that improperly trained operators or technicians are unable to isolate and detect process variations that lead to products that do not meet product design specifications.
4. **High employee turnover.** Companies that invest in their employees usually enjoy low relative turnover rates of their staffs. Employees appreciate the employer that is willing to invest in their future in the company, and their success on the job.

FDA has signaled that it will begin to hold executives accountable for what happens at their facilities, and those of contract partners as well—"you are ultimately responsible for the quality of your products" regardless of who manufactures them, the Agency has repeatedly said of late. This position is bound to get management's attention.

Shire's Ciambrone has heard the "necessary evil" tune before. "Most companies spend an awful lot of money on plant facilities," he says. "I find it bizarre to not also invest in training, as if somehow you're naturally going to get qualified employees off the street. You can't rely on the old, "follow me around for a couple days and we'll do on-the-job training." That's what you would see in factories 20 years ago. These products are highly complex, the processes highly automated, there's lots of computer interface. People are a key resource that we invest in, and it's only good business to make sure that they're adequately trained."

"Good training is a literal cornerstone of good GMP," he continues. "Not just because it's required by the regs, but because we are relying upon the employees to execute a function. In our case, our product is extraordinarily expensive."

Ciambrone is encouraged by what he sees as a "wave" of renewed interest in training. "Best practice should change," he says. "That's the whole idea. So as people get better at [training], as the bar gets raised, so will performance. It's not going to happen overnight, but will happen with inspection cycles and as the technology is there to institute a robust training program."

## COMPETITIVE ADVANTAGE

Is training a competitive advantage for vendor companies? Absolutely, says Bill Sicari, Manager of Festo Corp.'s Didactic group, a separate profit-making arm of the automation company. Didactic offers general technical training for the process industries. Like Siemers, Sicari says manufacturers just can't afford to send their top workers offsite for days or weeks to get the skills they need. As such, Didactic conducts web-based assessments, factory-based seminars, and even has a 53-foot tractor trailer that it drives around and uses to train up to 20 people at a time.

How to convince manufacturers that the training is needed? It's not just a matter of having skilled personnel, Sicari says. It's also getting the most bang for their buck in terms of exploiting the products and technologies that they have purchased. "Training closes the loop in automation technology," he says.

The optimal solution to the "training issue," of course, is to be proactive and ensure that the value of training is part of a company's culture. Shire, for example, has recently contracted with an outside company to do focused quality training, to improve quality leadership and groom leaders of the future. The program is module-based, notes Ciambrone, covering specific quality-related aspects of pharmaceutical chemistry, formulation, analytics, microbiology, and more. After three years of training, "students" are eligible for a master's degree.

It's a win-win, says Ciambrone. The individuals get the career development they need and desire, and the company gets increasingly competent leaders who do not have to go outside the organization for their training and development.

**At many drug manufacturers, training is at best a *cost center* and at worst a *necessary evil.***

# Building a Culture of Training:
# BEST PRACTICES FROM SHIRE HGT

A discussion with Bill Ciambrone, Senior Vice President of Technical Operations for Shire Human Genetic Therapies, about critical issues in workforce training today.

*By Paul Thomas, Senior Editor*

**PhM:** You've had an increased focus on training within your company, and we're seeing it within FDA and the industry in general. What explains it?

**Ciambrone:** We have always focused a lot on training. And that has to do with the industry we're in. In the biotech sector especially, you're talking about fairly complex processes. In order to keep your costs where you want them to be, you certainly can't hire PhD scientists to execute manufacturing all the time.

And as much as you try to make the processes either automated or fairly foolproof, the fact is that some of them require a really well-trained workforce. So for sound business reasons, we've always focused on the training of our employees.

What you say about focus from the Agency is true as well. They recognize that there are so many deviations that are related to training. I would venture to say that in many instances, manufacturing failure is oftentimes due to a failure to properly train personnel. It's one thing that comes up when we look at deviations and investigations—have our people been appropriately trained so they can perform their functions adequately?

**PhM:** Is it your sense that the deeper that FDA digs into this, the more they'll find that manufacturers are not training their staffs comprehensively?

**Ciambrone:** My guess would be that they have already seen a lot of these things. They will find, perhaps, that there are a lot of ways to skin a cat. There are different ways of training. So they'll probably focus on what the fundamental goals in training programs are.

My sense is that most pharmaceutical companies have what they consider a well-documented training program. The problem is not can you properly document what people are trained on, but do you have a way of assuring that what they're trained on is what they need to know? They need to develop a curriculum of baseline things workers need to know, and develop training that is programmatic.

And most importantly, how do you verify that training is effective? This is what companies really struggle with. It's so hard to demonstrate.

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**PhM:** How do you measure that your training is effective, and how has that changed over the years?

**Ciambrone:** We've taken the approach where the simple documentation of training to an SOP is really only the first step. We've follow that with a proficiency assessment that includes having a supervisor verify or validate the practical training.  So that in order to perform an operation, it's certainly not just familiarity with the SOP that's required of you, but actually practical training on the floor, witnessed by supervisors and signed off on by the appropriate level of management, so that there's accountability that the person is trained.

Training is really the responsibility of the management, but the employee as well. It's important to have that dual responsibility, a system of checks and balances.

I don't know that we or anyone else has the back end of that worked out completely yet. Now that a person's qualified and someone has signed off on that, how do you follow up on the effectiveness? Are you monitoring that performance over time, employee by employee? That's the next generation for most companies.

**PhM:** A lot of companies say training is a necessary evil. How do you get a culture in which good training is really something that everybody wants and demands?

**Ciambrone:** To be honest, I would be afraid of a company that took the attitude you talked about. Good training is a literal cornerstone of good GMP. Not just because it's required by the regs, but because we are relying upon the employees to execute a function. In our case, our product is extraordinarily expensive, and we spend a lot of money on equipment and facilities.

Most companies spend an awful lot of money on plant and facilities. I find it bizarre to not also invest in training, as if somehow you're naturally going to get qualified employees off the street. You can't rely on the old, "follow me around for a couple days and we'll do on-the-job training." That's what you would see in factories 20 years ago. These products are highly complex, the processes highly automated, there's lots of computer interface. People are a key resource that we invest in, and it's only good business to make sure that they're adequately trained.

**PhM:** Is it also a competitive advantage when you're trying to lure top people to your company?

**Ciambrone:** We think so. People want to be successful when they join a company. Giving them good training and all the tools they need, you can attract better employees and keep them more motivated because you're telling them, you're a critical resource. If you put them on the factory floor and don't adequately train them, I don't think they'll feel like they're as important as the equipment that you so lovingly maintain.

"Most companies spend an awful lot of money on plant facilities. I find it bizarre to not also invest in training, as if somehow you're naturally going to get qualified employees off the street."

— Bill Ciambrone, Shire HGT

# BIOMANUFACTURING MORPHS

In biopharma, budgets are returning and manufacturers are focusing on productivity by "retooling" and training existing staff resources.

*By Eric S. Langer, President, BioPlan Associates, Inc.*

Biopharmaceutical manufacturers are now defying many of the overall trends seen in the pharmaceutical and other mature industries. Namely, they are already showing strong signs of recovery from recent worldwide economic problems. As it matures, the industry continues its shift toward improved productivity and quality, all the while controlling costs.

These trends are documented in our 8th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production [1]. In 2011 we find that company budgets are clearly recovering from recent economic belt tightening. However, manufacturers are maintaining their conservative approach to production, and keeping their focus on cost reduction and quality improvements. In this year's study (see Figure 1), the shift in the focus to production quality was particularly apparent. Here, we saw an 11 percentage point increase, to 57.1%, of global respondents indicating they are seeing operational changes toward production quality.

This trend is affecting company budgets linked to these factors. The largest budget increases this year were in areas associated with productivity and quality. This was a change from previous years when most budgets had simply been slashed. Responses indicate that companies are expanding budgets, but are doing so cautiously, with expenditures being critically evaluated. Overall, spending in virtually all budget areas is up in 2011, between 1% and 6%.

This year, "New technologies to improve efficiencies/costs for downstream production" leads the pack with a 6.4% average spending increase. This budget increase comes on top of last year's budget-leading 4+% increase. This is a result of funding for activities that reduce capacity constraints due to bottlenecks from downstream operations. Funding of new technology in upstream processing is nearly as substantial as downstream funding. Integrating "New technologies to improve efficiencies/costs for upstream" saw budget increases of 6.2% (Figure 2). Upstream manufacturing's greatly increased yields in recent years keep it competitive from both productivity and performance standpoints.

In this year's study, responses from 352 global biomanufacturers/CMOs in 31 countries, and 186 vendors to the industry, show that the top spending projections are going toward internal investments into new technology (upstream and downstream) and personnel and process development and optimization.

Companies are focusing on productivity by "retooling" and training existing staff resources. In fact, "Operations staff training to improve efficiency" ranked 4th this year, which suggests that funding for on-going process improvements is likely to continue. Similarly, the survey shows respondents attributing "Better process development" and "Overall better control of process" as the number 1 and number 3 factors, respectively, in creating " 'Significant' or 'Some' Improvement in Biomanufacturing Performance."

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Across all departments, budget trends are a leading indicator of how constraints have loosened, especially for expenditures that improve process performance. The annual survey documents how this industry, despite recent worldwide economic difficulties, has maintained steady growth, and continues to mature.

## OUTSOURCING IS UP

Survey data indicate that biopharmaceutical companies are increasing their outsourcing, but are doing so in areas that may reduce costs, or improve productivity. Recent increases in company budgets are often not being directed toward rebuilding in-house staff that had been reduced, or eliminated in recent years. Outsourcing of certain key tasks, such as manufacturing, is growing at a steady pace. Overall, the prospects for outsourcing by biopharmaceutical companies, including contract testing and manufacturing companies, appears promising with healthy growth expected, particularly for the more sophisticated and broadly-capable contractors.

This year's survey included evaluation of 23 key areas of biopharmaceutical outsourcing. As shown in Figure 3, when asked where costs had been successfully reduced last year through outsourcing (in addition to any prior years' cutbacks and outsourcing), the highest percentage, 13.2%, reported outsourcing of jobs in process development, and 9% outsourcing R&D, and 11.8% manufacturing, including 5.7% off-shoring manufacturing to foreign contract manufacturers (CMOs).

Essentially every biopharmaceutical company now outsources to some extent, whether for manufacture of clinical supplies, process development, R&D, assay services, validation testing, fill-finish or a wide variety of other outsourced activities. Survey results show a significant increase in the percentage of biopharmaceutical companies planning outsourcing of upstream and downstream bioprocessing within the next 24 months.

This year, 22.1% of respondents expected to significantly increase outsourcing of downstream manufacturing (e.g., purification) operations, a jump to 2nd from 6th place (14.3%) last year. Similarly, 22.1% expected to significantly increase outsourcing of upstream (active agent production) manufacturing operations, a dramatic increase from 8.6% last year. A majority (=60%) of respondents projected at least some outsourcing of manufacturing by 2015. This included 63.5% of those currently using mammalian systems reporting they expect to outsource at least some of this by 2015.

| | 2011 | 2010 |
|---|---|---|
| Increased focus on productivity | 75.8% | 72.3% |
| Increased focus on cost cutting | 70.6% | 71.0% |
| Increased focus on production quality | 57.1% | 45.9% |

Figure 1. Selected Operational Changes Due to Recent Global Economics
(% Indicating "Much Greater" or "Somewhat Greater" Impact)

| Budget Change Comparisons | 2011 | 2010 | 2009 |
|---|---|---|---|
| New technologies to improve efficiencies/costs for downstream production | +6.4% | +4.2% | +2.5% |
| New technologies to improve efficiencies/costs for upstream production | +6.2% | +3.3% | +2.4% |

Figure 2. Selected Data: Approximate Average Change in Biomanufacturers' Budgets

Companies are more aggressively incorporating outsourcing as part of their overall manufacturing strategies. Outsourcing is no long perceived as simply a convenient method of adding needed capacity or as a means to eliminate jobs and overhead costs. Companies have developed confidence in their ability to model and assess the value delivered by outsourcing, and are increasingly demanding more value from their outsourcing partners, including CMOs. As a result, companies are establishing more complex and deeper relationships and dependencies on their outsourcing partners. Outsourcing is increasingly more about doing things better and more competitively and less just about cost savings.

## SUMMARY

Trends in biologics today point toward increased growth and profitability, in contrast with some mainstream small-molecule-oriented pharmaceutical industry segments. Major trends affecting the biopharmaceutical industry include increasing company budgets; the adoption of single-use/disposable equipment and other bioprocessing advances that improve cost-savings, quality, productivity, and flexibility in manufacturing; and the advent of biosimilars increasing in the number of biopharmaceutical products and companies present in the market in coming years.

With ever-increasing knowledge, technological advances, successful products and companies, and improving manufacturing economics, biopharmaceuticals are a bright spot within the pharmaceutical industry. Biopharmaceuticals currently provide around 15% of pharmaceutical industry revenue. This will increase rapidly in coming years, with an estimated 40% of pharmaceuticals currently in development being biopharmaceuticals.

## ABOUT THE AUTHOR

Eric S. Langer is president and managing partner at BioPlan Associates, Inc., a Rockville, MD-based biotechnology and life sciences marketing research and publishing firm established in 1989. He can be reached at elanger@bioplanassociates.com or 301-921-5979.

References

1. *Langer, E., 8th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production: BioPlan Associates, April 2011, 490 pages, www.bioplanassociates.com.*

| Outsourcing Activities: "During the past 12 months, which actions has your organization taken to reduce costs at your facility?" | |
|---|---|
| Outsourced jobs in Process Development | 13.2% |
| Outsourced jobs in Manufacturing | 11.8% |
| Outsourced jobs in R&D | 9.0% |
| Outsourcing manufacturing activities to domestic service providers | 7.1% |
| Outsourcing manufacturing activities to non-domestic service providers (offshoring) | 5.7% |

Figure 3. Selected Cost Cutting Changes, Outsourced Jobs, by Segment and Geography

# PHARMA SUPPLIERS SEE TRAINING AS COMPETITIVE ADVANTAGE

As drug manufacturers struggle to train their workers, solution providers step in to help.

*By Paul Thomas, Senior Editor*

As manufacturers struggle to train their workers, expect solution providers to rush to their rescue. The economic crisis of 2008 and beyond has dramatically change the training landscape, but probably for the better, says Jim Siemers, Manager of Educational Services at Emerson Process Management. Clients "still really needed the training," he says, "but they needed a lower-cost option." Emerson set up a remote classroom in Austin, Texas, by which students anywhere in the world could view instructors via live video feeds, access PowerPoint slides, ask questions, chat with other students, take tests, and mirror the experience that they'd have were they right there in Austin. "We weren't going to do anything remote that cut into the time and skill sets that people needed to learn," Siemers says.

Economics has been the catalyst for going remote, says Siemers, but compliance is also driving training to be more web-based, where operator training can be accelerated, while also monitored and documented. Drug manufacturers are taking their training obligations much more seriously, he adds. In the past, training was seen as a "necessary evil," but now manufacturers are beginning to connect successful training with improved performance and a clear return on investment. And they know that FDA is inspecting training records more rigorously than before.

Is training a competitive advantage for vendor companies? Absolutely, says Bill Sicari, Manager of Festo Corp.'s Didactic group, a separate profit-making arm of the automation company. Didactic offers general technical training—mostly vendor-neutral, Sicari says—for the process industries, and knowing that Festo values and provides comprehensive training is a draw for many clients, he says.

Like Siemers, Sicari says manufacturers just can't afford to send their top workers offsite for days or weeks to get the skills they need. As such, Didactic conducts web-based assessments, factory-based seminars ("we ship all our equipment in," he says), and even has a 53-foot tractor trailer—its Mobile Mechatronics Lab—that it drives around to manufacturing sites and uses to train up to 20 students at a time.

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Sicari has also found that manufacturers are challenged to find skilled personnel, despite the high unemployment rates in the U.S. and elsewhere. Festo conducts holistic training, a good measure of theory in addition to hands-on, applied work. “There are so many technologies required to run a factory today, you need to teach a little bit of everything,” Sicari says. Companies are looking for “general practitioners” who know what to do 90% of the time, he says, and know to call in a specialist the other 10%.

Much of training Sicari’s group does is for high school and college faculty—that is, training the trainers. “Community colleges lost their way,” he says. “The instruction didn’t keep up with current technologies.”

How to convince manufacturers that the training more than pays for itself? It’s not just a matter of having skilled personnel, he says. It’s also getting the most bang for their buck in terms of the products and technologies that they have purchased. “Training closes the loop in automation technology,” he says.

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