

## Hurry Up and Wait?

### You Can Finish the Paperwork Shortly After a Product Is Manufactured

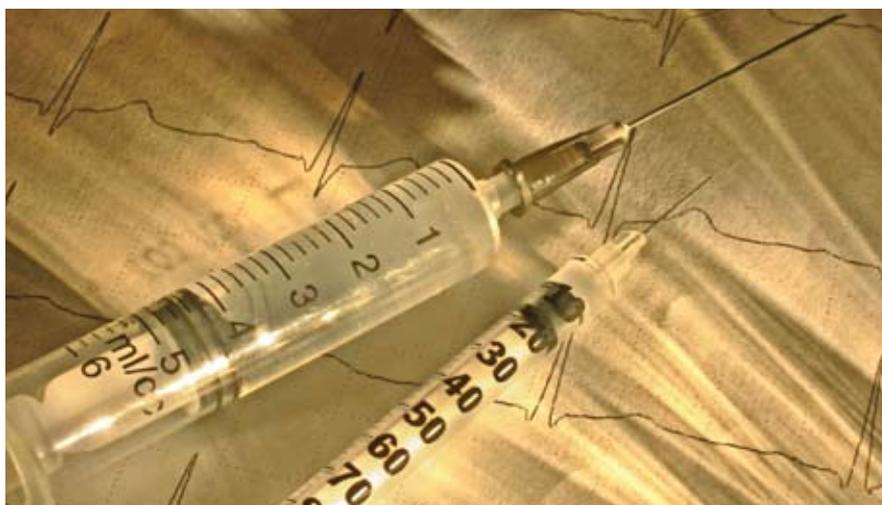
by Michalle Adkins

Reprinted with permission from *BioProcess International* 8(1) (January 2010)

From time to time we each experience the hurry to get somewhere, only to end up waiting for someone or something else. Today's air travel seems to be nothing but "hurry-up-and-wait": After you race to the airport two hours before your flight time, the plane ends up departing two hours late. Businesses suffer from the same disorder. For example, in the biopharmaceutical industry, this phenomenon is often evident in all the documentation that must be completed before a product can be released for shipment. Most of us seldom give it much thought, but delaying the shipment of a drug (especially a blockbuster) can cause business executives to become quite agitated. "Delayed shipments of our blockbuster drug could mean another 'beating' from Wall Street analysts and our shareholders," an executive might bemoan, "more warehousing costs associated with quarantined product, and making more concessions to retain our customers. It just seems like we are always hurrying up and then waiting."

Amazingly, when we stop, look, and listen to what is causing these daily battles — in both our personal and company lives — we can often identify not only the root cause of the problem, but also ways and means to improve the situation.

When the US Food and Drug Administration (FDA) announced its "Operational Excellence: Quality by



EGOR MOPANKO (WWW.ISTOCKPHOTO.COM)

Design" initiative in 2002, a major inclusion focused on quality systems:

Best practices in quality management methods, particularly in other high-tech industries, have undergone significant progress since 1978 when the CGMP regulations were last updated. The FDA wants to ensure that its regulatory practices encourage similar progress in the pharmaceutical industry. The draft guidance for industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice describes a comprehensive quality systems model that manufacturers could use and highlights the model's consistency with the CGMP regulations for manufacturing human and veterinary drugs, including biological products. The guidance explains how

manufacturers implementing such a comprehensive quality system can ensure that they comply fully with the CGMP regulations (21 CFR parts 210–211 and 600–680). This guidance is intended to serve as a bridge between the 1978 regulations and our current understanding of quality systems. (1)

Within the biopharmaceutical industry, the term *operational excellence* (OpEx) has become popular for describing the big-picture vision. This vision is one everybody is striving to achieve, but the picture too frequently becomes clouded by daily battles to meet product delivery commitments. Among the many challenges that often affect a company's ability to efficiently deliver product is successful manufacturing coupled with all the associated documentation required.

## CALCULATING ROIC

*Return on invested capital* (ROIC) is a measure of how effectively a company uses the money (borrowed or owned) it has invested in its operations. ROIC is calculated by dividing company's (or unit's) net income after taxes by its total assets, not counting excess cash or non-interest-bearing liabilities.

Making a product according to its predefined specifications — and doing it as efficiently as possible — is a battle that can often be won predominantly by replacing as many manual processing steps with instrumentation and automation as possible. Simultaneously producing the necessary documentation that proves a drug or biologic was manufactured in accordance with its predefined specifications is a battle that can be won through organizational commitment and the proper design and use of automation and manufacturing execution systems (MES).

The ultimate goal is to produce both the product and its accompanying documentation correctly the first time, and to do so minutes after the drug or biologic is manufactured. We realistically understand that attaining this ultimate goal is a stretch. But ways and means are available that have repeatedly demonstrated how possible it is to move companies closer to achieving “right-the-first-time” every time (RTFT-ET).

### DAILY SKIRMISHES

Overcoming the daily skirmishes to achieve RTFT-ET products and documentation requires owning up to the fact that such skirmishes actually exist within a company. This admission is sometimes difficult for people to accept. But think about your own experiences. Have you ever delayed the release of a product or contemplated the inefficient use of resources in your organization for document-related issues because of . . .

- Missing and/or illegible data entries?
- Missing and/or illegible signatures?
- Numbers being transposed (e.g., 1,243 instead of 1,234)?

- Equipment log book entries made improperly?

If your production and documentation processes are mostly manual, then you are very likely nodding your head in the affirmative. Here are some common excuses describing why lot progress, document review, or lot release is delayed. If your production and documentation processes are mostly manual, it is likely that these and/or similar issues occur:

- “Changes to the master batch record were not implemented and approved on time, so we need to mark up the existing record and log a deviation or open a change request to use it.”
- “Some materials we needed were in the wrong location, so it took extra time to find them.”
- “After materials were staged in the production area, a quarantine was issued; however, we did not catch that before using those materials on the production floor.”
- “We needed X amount of materials, but only Y amount was actually available.”
- “We did not notice that procedure pages were stuck together (or were out of order or missing) so we added ingredient A and B before adjusting the pH or temperature, or we missed a step in the batch record.”
- “We did not realize that the equipment (or transfer path) ‘clean hold or dirty hold’ time had expired, or we miscalculated the expiration time.”
- “We were distracted during manual addition and overshot the target.”
- “We did not realize that an instrument needed to be calibrated before we began to add material.”

Some biopharmaceutical companies can honestly report that they have almost completely overcome many of those sorts of daily documentation and product-release “skirmishes.” Do such companies have their own daily skirmishes to overcome? Of course they do, but theirs are new rather than recurrent. They no longer allow a skirmish to morph into a “that’s just the way it is” excuse. They are winning the battle by focusing on each and every skirmish.

What those winning companies have learned to use is a proven methodology that defines, measures, analyzes, and institutes permanent controls that help them win the RTFT-ET battle. This methodology is called *lean six sigma* (LSS), and it is based on conducting real-time, in-depth analysis of business problems.

A 2007 *Business Week* article implied that six sigma was “dead” (2). But consider that we need to recognize when an approach is being adopted as a “religion” rather than merely a tool. Six sigma, lean manufacturing, footprint rationalization, premier resource management, and similar other quality and efficiency improvement methodologies are tools that can be used at the right time, in the right way, by experienced professionals to identify and “repair” problems.

### BEGIN WITH THE END IN MIND

Stephen R. Covey (author of *Principle-Centered Leadership* and *The Seven Habits of Highly Effective People*) suggests that acquiring management support and “beginning with the end in mind” are important first steps (3). Consistent with that advice, 22 senior executives from 15 companies attending the September 2006 FutureBio 2016 forum in Boston identified 22 gaps that need to be closed for the biopharmaceutical industry to improve its operational performance (4). In a 2007 article, author Marc Puich summarized the key themes of that forum and then identified four key initiatives the biopharmaceutical companies must embrace to close those gaps: engaging company leadership, assembling capabilities, working together, and leveraging vendors (4).

#### Engage Company Leadership:

Certainly it is possible to improve without the support of company leadership, but it is not easy or as much fun to do so. With management support, it is far easier to address cross-department and cross-facility issues. When management is an active participant, not only can astounding results be achieved, but also hurdles disappear and funding appears, cooperation and consistency abound,

## SURVEYS SAY...

According to 22 senior executives attending the September 2006 FutureBio 2016 conference in Boston, MA (3):

- The biopharmaceutical industry has been focused on better overall performance for several years, a key measure of that being the ability to move high-quality products through the supply chain quickly. Companies still struggle to minimize cycle times, primarily because of quality issues throughout production. Activities that focus on reducing process variability and improving processes need to be developed.
- The biopharmaceutical industry is less operationally sophisticated than other industries in many areas of its operating business.
- Results of a 2006 operational excellence survey reported that 94% of respondents said reducing cycle time is a key focus area within their companies (6).
- A 2003 survey of pharmaceutical companies conducted by Ken Morris (Purdue University) and Sam Venugopal and Michael Eckstut (Conformia Software, Inc.) focused on drug research, but it is fairly safe to assume that companies that have trouble tracking data and decision-making progress during product development are likely to experience similar difficulties during drug manufacturing as well (7). The study revealed that most respondents were dissatisfied with the ability of their existing IT systems to capture and manage drug development information. It discovered that specialists were spending an average of five hours each week looking for data and about two-thirds of respondents reported that they could not find 10–20% of the data they needed. Whether in development or manufacturing, it is virtually impossible to achieve “right the first time” status in such a working environment.

trials and tribulations are far less devastating, and successes are celebrated. In short, when company leadership is fully engaged, the entire effort is simply better for everyone.

**Assemble Capabilities:** Years ago, most companies offered their employees two separate career paths: a management track and a technical track. Then along came “right-sizing,” and the technical track all but

disappeared. Although the consequences were not immediately apparent, today it is becoming increasingly obvious that staff cuts may have gone too deep.

Some biopharmaceutical companies have begun to rebuild their internal capabilities by resurrecting their technical career tracks. They also are acutely aware that some of the best sources of current best practices and 21st-century technology reside with consultants who already have experience overcoming some of the very same gaps in the biopharmaceutical industry (as well as other industries). Assembling the capabilities needed is most efficiently accomplished when internal company staff who are intimately knowledgeable about the production processes and unique company procedures are joined by experienced industry experts and highly focused vendor teams.

**Work Together:** At first this seems obvious. What the executives attending FutureBio 2016 talked about is that there are industry-wide gaps in such areas as regulatory policies that would be best addressed through a unified industry effort such as the BioPharmaceutical Operations Excellence Consortium ([www.tefen.com/bio](http://www.tefen.com/bio)).

**Leverage Vendors:** Several gaps identified by FutureBio 2016 participants require extensive knowledge about currently available technologies, including instrumentation and automation. The five major benefits of closing these gaps are rapid process improvements, short lab-to-commercialization timelines, flexible multiproduct facilities, reduced cost of goods sold (COGS), and improved overall cycle times.

So how do we actually start closing those gaps to reap the benefits of reducing cost-of-goods-sold (COGS) and overall cycle times? Is it even possible to achieve a state of operational excellence?

### FOLLOW THE LEADERS

We should agree on a definition for *operational excellence* (OpEx), a holistic

approach that integrates operations and management methodologies (e.g., lean manufacturing and six sigma) with change management to optimize people, equipment, and processes. OpEx is all about increasing the return on invested capital (ROIC) while meeting or exceeding customer expectations. It's not just something the biopharmaceutical industry is pursuing; efforts to achieve an OpEx state are aggressively under way in other industries including petroleum refining, specialty chemicals, and foods/beverages. In fact, like the FDA in its 2002 announcement, the executives attending FutureBio 2016 encouraged their industry to avoid “reinventing the wheel” and to look at how others are addressing and solving some of these very same problems.

Organizations pursuing OpEx report that different business functions (e.g., maintenance, production, and R&D) almost always require different forms of assistance, skills, tools, and methodologies to achieve a sustainable level of success. Several report that they struggle with questions about which methodology to use (only six sigma or only lean manufacturing, or a mix of the two). It seems that each has so many different tools available, so which tools are most applicable for a given issue? What if certification is required? How will an organization manage each certification? What about training? How do companies know which and how much data to collect about a specific gap they want to close? Rather than agonizing over these and similar questions, companies can actually save money and time by engaging consultants with domain wisdom and experience.

When investigating consultants, look for those with hefty credentials and portfolios that include flexible methodologies that they can enthusiastically tailor to fit your unique organizational needs. Although that need may not be immediately apparent, you will eventually come to appreciate that flexibility when you can tailor and retaylor a methodology to accommodate changing business conditions long after the consultant has moved on.

Much of biopharmaceutical production is carried out using batch processing, which is a well-orchestrated combination of regulatory process control (blend, mix, flow, temperature, level, and so on) and discrete manufacturing (start/stop, open/close, fill/empty, clean, transfer, and so on). If we think of batch control as an orchestration of process and discrete control, the reason why the most popular and successful OpEx batch control projects are combining six sigma and lean manufacturing for LSS (also called S4 for *smarter six sigma solutions*) becomes clearer.

### USING LEAN SIX SIGMA

LSS is actually an adaptation of traditional six sigma's DMAIC methodology combined with efficiency-improvement methods popularized by lean manufacturing. Among the associated tools an experienced LSS consultant will apply are kaizen, failure mode and effects analysis (FMEA), value-stream mapping (VSM), collaborative diagrams, design of experiments (DoE), business process mapping, quality systems, fishbone diagrams, and quality function deployment, among others.

Like every endeavor to improve quality and efficiency, you begin with things that will be easiest and fastest to improve. These are often referred to as "low-hanging fruit." Even though most companies know such improvement opportunities exist, for many reasons, most simply have not been able to permanently improve them. OpEx is about increasing ROIC while meeting or exceeding your customers' expectations, so companies should express measurable, quantifiable results, such as increasing profitability by 5%, exceeding 10% ROIC, increasing RTFT from 95% to 99.99% while improving customer satisfaction.

Regardless of the industry, shortening batch-cycle times (including the time required to complete documentation) produces significant positive ROIC impact in production, sales and service, and warehousing and distribution. To illustrate an application of the

DMAIC methodology to reduce batch-cycle times, what follows is a fictitious case study using details from multiple, real-world case histories.

**Define (Assessment):** Two questions need to be answered when assessing ways to reduce the batch cycle time of a production facility: Of the many improvement opportunities you can identify, which should you work on first? And what quantifiable business results will this opportunity improve? You already know that once you begin an assessment, your list of improvement opportunities is likely to become quite long. Like a seasoned detective examining a crime scene, an experienced consultant can help you examine the evidence and identify one or two "leads" that you need to work on first.

The example goal is a 10% reduction of time and effort required to release a finished product to shipment. Discussions that led us to establishing this particular goal included several points: There is a tremendous amount of paperwork required to release a product, tracking all the associated paper is cumbersome, inventory of work in process (WIP) or finished goods is increasing, islands of automation produce islands of data, inconsistency of applications abound, and manual brute-force efforts are often used to get product released.

Some of those items very obviously fit the goal; others are less obvious. For example, increasing inventory is likely to be the "cushion" that a sales or planning department has determined is necessary to overcome the inability to release finished product on time.

Examining each topic in greater detail reveals that each item is a significant contributor to the overall goal of reducing the amount of time and effort it takes to release a finished product for shipment. To illustrate the findings, collaborative diagrams are developed that indicate the sources of batch-end data, the data flow paths including each time a human physically handles various pieces of paper, the frequency of data back-tracking that resulted from incomplete

### A LITTLE ABOUT SIX SIGMA

*Wikipedia* says six sigma ( $6\sigma$ ) is a continuous improvement methodology used to identify, manage, and reduce or eliminate process variations that cause defects in products and services ([http://en.wikipedia.org/wiki/six\\_sigma](http://en.wikipedia.org/wiki/six_sigma)).

Six sigma has two key methodologies:

- DMAIC (define, measure, analyze, improve, control)
- DMADV (define, measure, analyze, design, verify).

DMAIC is used to improve an existing business process, whereas DMADV (also referred to as design-for-six-sigma, DFSS) is used to create a new product or process design in such a way that it performs more predictably, maturely, and defect free. Sometimes a DMAIC project may turn into a DMADV project if a process needs to be completely redesigned to bring about desired improvements.

or missing data, and so on. The resultant mosaic reveals several tortuous paths (and individual yet coordinated activities) necessary in resolving batch discrepancies, getting appropriate sign-offs, and being able to finally release the finished product for shipment. The next step is to determine what constitutes a reasonable reduction for each identified project.

**Measure (Study):** Projects seldom get approved without solid, quantified results. Different industries and companies use different terminology and metrics. However, having a goal of reducing batch cycle times and documentation review efforts by 10% is well understood by every company in every industry.

Examining the batch-record paperwork for 100 or so batches reveals that the time required to complete document review and release the finished product for shipment ranges from 60 to 80 days. Using cause and effect (fishbone) and VSM diagrams, the root causes, number of occurrences, and potential for improvement are pictorially documented as items that can delay or inefficiently use resources during document review and product release. These root causes include missing and ambiguous entries;

**Table 1:** Calculated savings

Category of Savings	Single-Product Facility	Multiproduct Facility
Increase throughput	\$425,000	\$3,859,000
Eliminate paper batch record processing	\$102,000	\$948,000
Reduce manpower for batch record execution and approval	\$488,000	\$610,000
Reduce the number of deviations	\$150,000	\$1,021,000
Reduce/eliminate paper log books	\$25,000	\$100,000
<b>Total Savings</b>	<b>\$1,190,000</b>	<b>\$6,588,000</b>

\* These results were based on multiple projects.

## A LITTLE ABOUT LEAN MANUFACTURING

Lean manufacturing is more than a tool-set. *Wikipedia* calls it a holistic, comprehensive, enterprise-wide program designed to be integrated into an organization's core strategy ([http://en.wikipedia.org/wiki/lean\\_manufacturing](http://en.wikipedia.org/wiki/lean_manufacturing)). Lean manufacturing focuses on the reduction of seven production waste streams: overproduction, waiting time, transportation, processing, inventory, motion, and scrap in manufactured products.

"Lean" is all about getting the right things to the right place at the right time in the right quantity while minimizing waste and being flexible and open to change.

incorrect entries and those in the wrong places; clarifications required, such as illegible handwriting and crossed-out entries; calculation and rounding errors; deviations outside defined control limits and those due to human errors or document-related issues; testing-related difficulties; finding and evaluating appropriate data; and miscellaneous questions. But is the potential for improvement as good as it can be?

Determining what constitutes "good" requires benchmarking: knowing where you are relative to others in the same or a similar industry. Industry benchmarking provides comparisons among "like" companies, but even the very best in one industry might fall short when compared with companies in other industries doing similar things. For example, a 2004 survey revealed that most pharmaceutical companies achieve about 85–95% (2.5 $\sigma$ –3.1 $\sigma$ ) RTFT to quality review, with the best of them achieving ~96% (3.3 $\sigma$ ). The same survey also revealed that world-class

manufacturing and processing facilities across multiple industries were achieving a 99.4% (4.0 $\sigma$ ) RTFT to quality review (5). So even the best pharmaceutical companies were experiencing more than three times as many defects per million opportunities as comparable companies in other industries (19,500 defects compared with 6,000).

You cannot possibly know where you're going or when you get there if you don't know where you began. LSS is a robust, proven methodology that not only reveals where you are but where you can go.

**Explore Possibilities:** Picking individual pieces of "low-hanging fruit" will produce some immediate improvements, but that is not what using LSS should help an organization accomplish. It is certainly not the way for a company to achieve a state of OpEx.

In the example case history, two solutions are developed. The first forms a "temporary state" for a small single-product facility. Efforts focus on improving procedures and practices of master and executed batch record approval work flow, thus eliminating paper batch records. The goal is to provide immediate financial benefits while establishing a solid foundation on which to continue building. The second solution — for a large multiproduct facility — is to apply document management and electronic work instructions software that creates a "paperless" product review and approval process. Documentation is thus produced nearly simultaneously with products and includes additional interfaces with other systems used in those processes.

Table 1 provides calculated savings for those two product facility types. Projected savings claims are frequently negotiated, but the documentation

produced using LSS tools reveal a compelling enough future state that, without exception, each of the real case histories that contribute to this fictional case study received executive management approval.

Delaying the shipment of any drug, especially a blockbuster, can cause business executives to become quite agitated. They understand that although stockholders and Wall Street analysts might praise a company for being among the best within its industry, that is not what achieving a state of OpEx is about. Smart executives understand that it is really about breaking away from the daily skirmishes that cause a company to "hurry up and wait." Applying LSS is one of the best ways to achieve that.

## REFERENCES

- 1 Puich M. BioPharmaceutical Operations Roadmap. *BioPharm Int.* April 2007.
- 2 Hindo B. Six Sigma: So Yesterday? *Business Week* 11 June 2007; [www.businessweek.com/magazine/content/07\\_24/b4038409.htm](http://www.businessweek.com/magazine/content/07_24/b4038409.htm).
- 3 Covey SR. *The Seven Habits of Highly Effective People*. Free Press; Glencoe, IL, 1989; <https://www.stephencovey.com/7habits/7habits.php>.
- 4 Breyfogle FW. *Implementing Six Sigma*. Wiley Interscience: Hoboken, NJ, 2003.
- 5 Benson R, McCabe J. From Good Manufacturing Practice to Good Manufacturing Performance. *Pharmaceut. Eng.* July/August 2004: 26–34.
- 6 Shanley A. Pharma Sharpens Its Game: Results of Our First OpEx Survey. *PharmaManufact.* May 2006; [www.pharmamanufacturing.com/articles/2006/096.html?page=full](http://www.pharmamanufacturing.com/articles/2006/096.html?page=full).
- 7 Morris K, Venugopal S, Eckstut M. Making the Most of Drug Development Data. *PharmaManufact.* 4(10) 2005: 16–23. 🌐

**Michalle Adkins** is senior consultant at *Life Sciences Industry, Global Industry Solutions Emerson Process Management, 410 West Linfield Trappe Road, Suite 200, Royersford, PA 19468; 610-569-4005, fax 610-569-4001; michalle.adkins@emerson.com*.

## Key Search Words:

Batch, Benchmarking, Biological, Biopharmaceutical, Blockbuster, Capabilities, CGMP, COGS Covey, DFA, DMAIC, Drug, Excellence, High-tech, Knowledge, Lean, LSS, Management, MES Operational, OpEx, Paperless, Paperwork, pH, Product, Quality, Quarantine, Record, RTFT, Shipment Sign-offs, Stockholders, Tool, VSM, WIP