This case study provides a comprehensive look at Talecris[1] Biotherapeutics' approach to PAT and automation followed by examples of PAT deployed on a bioprocess. It introduces the concept of integrated and scalable automation, provides a comparison of automation concepts, and explains how the selected automation effectively supports initiatives like PAT.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
January/February 2006, Vol. 26 No. 1

Process Analytical Technology (PAT) and Scalable Automation for Bioprocess Control and Monitoring – A Case Study

by Joydeep Ganguly and Gerrit Vogel

Introduction

Of late, there has been considerable interest and intrigue in the pharmaceutical industry with regard to the recently approved FDA guideline on PAT. In September 2004, the FDA issued their final guidance for the industry, "PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance." The guidance describes a framework for the "implementation of innovative pharmaceutical development, manufacturing, and quality assurance." The guidance extends beyond mere installation of process analyzers – it encourages the application of process control, continuous improvement, and knowledge management tools along with the vision of an exciting, new approach to pharmaceutical manufacturing and regulatory efficiency. PAT promises to deliver a "culture-change" in the industry, which has too often treated innovation and productivity as step-children to regulation and compliance. With PAT guidance in place, manufacturing companies now have the FDA's encouragement to adopt a new, risk-based regulatory framework that has its basis in scientific and engineering principles. Though as with any new initiative, questions are rife as to "how" to implement PAT, what is the best approach, and how do we optimally enforce IT and automation strategies to support the PAT framework.

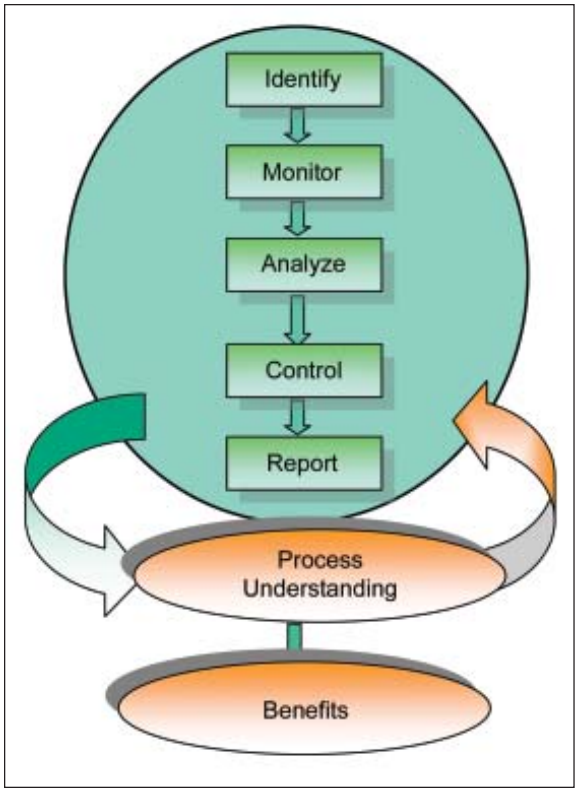

Figure 1. PAT model for the Talecris Clayton Site.

We were able to incorporate the ideas of the PAT initiative into a new biological process that our company developed and which is currently deployed at our facility in Clayton, North Carolina. Utilizing this project as a case study, this article presents the approach to PAT that we adopted at our site, along with an automation strategy that we believe enhanced our PAT effort. We will approach this article by first explaining our interpretation and the framework for PAT. We will then move on to discuss the role of automation and explain the concept of "scalable" automation. After a brief introduction to the case study, we will compare automa-

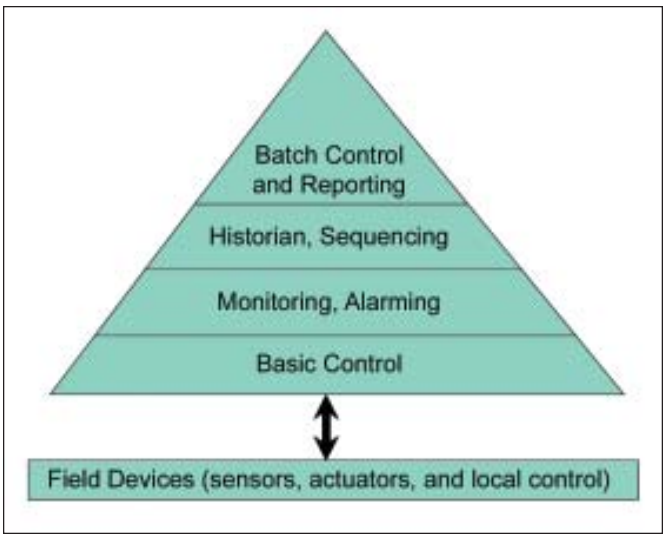

Figure 2. Automation Pyramid.

tion concepts and explain the importance of having a sufficient automation infrastructure in place to support PAT. We will then present two examples from our case study to demonstrate the benefits of deploying PAT. The first example is centered on the operation and control of our Water for Injection (WFI) systems for our processes. The second example describes a reporting application that utilizes the advantages of the automation infrastructure to provide a real-time comparison of parameters over multiple batches, also referred to as the fingerprinting of "golden batches."

The PAT Approach

The FDA guideline[1] presents a very broad interpretation of what the Agency considers PAT to be. As a site, we are in the process of developing a well-documented "master-plan" that defines our interpretation of the guideline and presents a roadmap for our company to follow while implementing PAT. The master plan defines the mission, vision, strategy, and framework of our PAT effort. It also presents a blueprint-document that all PAT projects follow to ensure consistency across various PAT initiatives. Within the master plan, the PAT framework is detailed, which explains how a PAT opportunity is initiated, executed, and evaluated. The framework is presented in Figure 1, and a detailed explanation of the proposed steps to a PAT implementation are provided in Sidebar 1.

The process of identifying, monitoring, analyzing, controlling, and reporting combined from the PAT approach. Once these discrete steps have been deployed, we expect to achieve the final goal of most PAT initiatives – process understanding. Understanding the process well, with critical points identified and controlled, and all sources of variability under check, we can then reap the benefits of the PAT model. These benefits include, but are not limited to:

- real-time quality assurance
- right first-time and enhanced root cause analysis tools
- reduced cycle times
- yield improvement opportunities
- faster time to market potential
- decreased burden of final product testing
- reduced manual testing

Role of Automation

The model in Figure 1 underlines the importance of having automation in place, which can support the monitoring, modeling, controlling, and reporting of the Critical Quality Attributes (CQAs) for any PAT effort. To implement PAT effectively, automation needs to support the effort of continuously and automatically collecting data not just from the sensors directly associated with the process, but from all of the other factors that could influence the results. In other words, close integration with the control system becomes very desirable if decisions are being made on the basis of online measurements, while deviation handling capabilities are necessary to ensure process control. The control concept is based on the model of the so-called automation pyramid - Figure 2. The pyramid describes the layers and functions of automation beginning with the plant floor or field instrumentation and actuators. It can extend all the way up to the Manufacturing Execution System, (MES) and Enterprise Resource Planning, (ERP) level.

The idea behind the applied concept of "scalable" automation is to put the basic infrastructure and functions for automation in place with every new project. This allows for higher levels of automation, including PAT functions, to be added later on in the project or even during the operational phase of the facility. The application of today's "New Generation" control system technology makes this control concept flexible, affordable, and it allows for quick implementation. The "New Generation" control system technology is based on open interfaces, modular configuration, qualification, as well as scalability. So, automating the process would start at the basic control level and then the described PAT principles would be applied - Figure 1, Sidebar 1. The more we understand our process, the more we can increase the level of automation to support the increased understanding. Automating a full batch process to start the project, it was felt would result in a lot of re-work as the project progressed and process idiosyncrasies were better understood.

The Case Study

Figure 3, shows at a very high-level, the process flow for a newly implemented process at our facility. This process is the basis of our case study on PAT and scalable automation. The process flow is typical of biotherapeutics facilities and consists of numerous discrete steps, including dissolution, filtration, chromatography, ultrafiltration/diafiltration (UF/DF), nanofiltration, followed by formulation, filling, and freeze drying (not shown). The chromatography and UF/DF skids comprise the heart of our process. In addition, there are numerous vessels, tanks, pH adjustment carts, and Temperature Control Modules (TCMs) that we combined in the "balance of process" environment. Two other vital components in the process are the CIP system and the WFI system. The CIP system, like chromatography and the UF/DF, is

typically a skid-based system. The WFI system is probably the most crucial ancillary system in the process. WFI is utilized approximately 50 percent of the time in the overall production process.

During normal production, data is collected at each step in the process, and the results of each step are critical for normal sequential processing of the product. The chromatography and UF/DF skids (as with the CIP skids) are all typically automated in their operation and are controlled locally with local operator interfaces. The conventional approach until now, in the industry, has been to buy chromatography, UF/DF, and CIP skids from different vendors usually with proprietary and differently configured/documented control systems installed on each skid. Besides lending itself to arduous data collection, communication (also referred to as "handshaking") between the skids for optimal operation and process control is a huge and often costly challenge. Furthermore, understanding and reducing variability in the overall process became very difficult with so many different control platforms controlling the same process. In addition, the installation of skids from different vendors with individual control solutions would result in multiple, different operator interfaces (graphics design, color codes, alarm handling/messages, commands, and logins). We consider this a serious challenge for our production operators who have to operate multiple skids, control the non-skid related "balance of process" environment, and interact with the utilities systems. Different operator interfaces not only cause inefficiencies, but can develop into a main source of operator errors.

Comparison of Automation Concepts

When we were tasked to develop the automation concept for our case study, we used the model of the Automation Pyramid to assess the different approaches available to us. For this article the two most extreme approaches to bioprocess automation will be discussed. As described before, pharmaceutical and bioprocess facilities usually consist of an assembly of skids from different vendors set in a process environment that supplies utilities, process aids, storage, and cleaning. In Figure 4, automation concepts for the same process utilizing skids from different manufacturers that are set in a process environment are compared. In the "**islands of automation**" concept **on the left** of Figure 4, the option of having individual automation solutions for the skids and the environment is analyzed. The skids are not interfaced with each other and have individual operator interfaces. The **scalable automation** concept **on the right** of Figure 4**,** presents the solution we selected for our case study. We worked with our skid manufacturers and system integrators to implement their automation and expertise on the same "new generation" control system platform. Thanks to inherent scalability, modular approach, and ease of configuration, these control solutions are also attractive to the skid manufacturers. In this concept, we have individual skids that can be developed and tested stand-alone. Later on they can be applied to the process and play in concert with each other (imagine the "plug and play concept" from your home and office computer world). Skid manufactures and integrators are required to utilize standardized and pre-qualified configuration modules, as well as to adhere to the same configuration rules (such as graphic standards).

Figure 4 uses the automation pyramid to compare both solutions layer by layer.

Automation Concepts and PAT

Based on the comparison in Figure 4, the advantages of automating the entire process on one scalable control system platform became apparent to us. Not only for one skid, but across the entire process, **scalable automation:**

- fulfills the need to effectively access all sources of variability
- provides a method to monitor the CQA's in a common format
- provides a clear relation of data to the batch and process step information
- allows for handshaking and interlocking between skids as well as common process and utilities systems
- These characteristics are imperative to enhance the PAT effort.

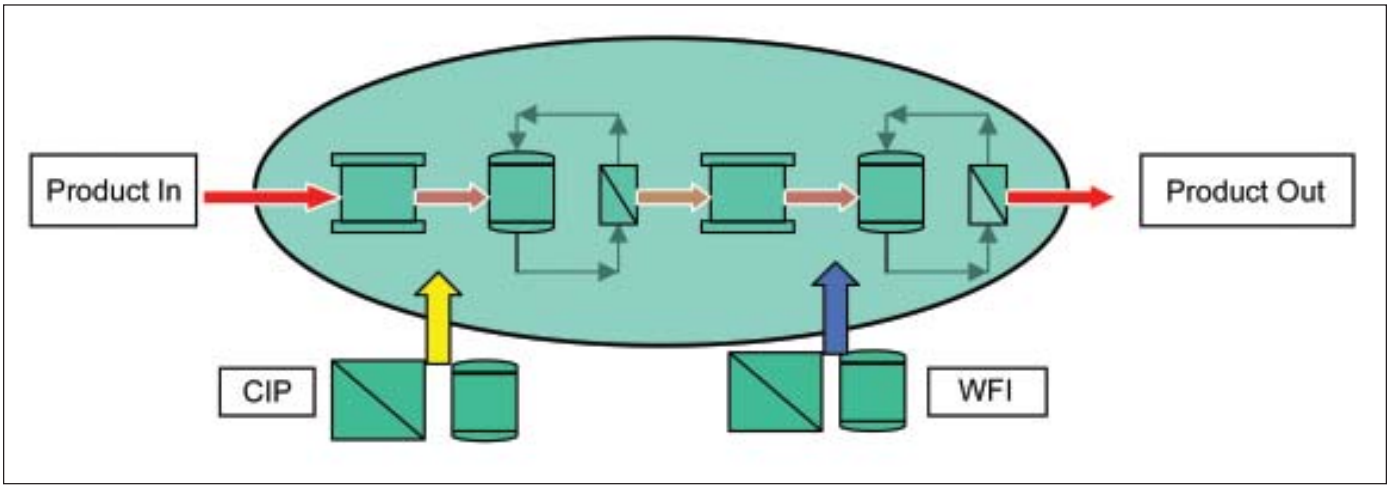

Figure 3. Process flow for new biological process.

The "**islands of automation**" method of control system infrastructure (as depicted on the left in Figure 4) makes each one of the characteristics listed above complex on many accounts. It is difficult to collect and exchange data from five skids and supporting infrastructure systems. Once available, correlation of data becomes a huge challenge. Batch data are usually unavailable for the entire process, and the bottom line is that control is still being done with individual and non-interfaced control systems. So the final element of PAT, being control, based on real-time measurements to provide real time quality assurance, becomes difficult to implement.

Trending across an entire batch becomes possible if a centralized historian for data collection is added, but philosophies like model predictive control are difficult to realize since the effects of one process step can rarely be correlated with another process step down the line.

After all these considerations including a total cost of ownership analysis, it was decided to implement the centralized and scalable automation approach. This lends itself very effectively to the PAT concept. Having installed all skids, the production equipment, and the critical utilities systems on the same control system platform, we are able to:

- obtain all the process relevant data via one common interface
- collect multiple pieces of real-time data to develop reports and even models
- report on multiple batches using one common reporting engine
- handle deviations from the process specifications in a timely manner

The last facet is achieved due to the fact that skids across the process have all the relevant information with regard to the entire process, as opposed to just operating with information regarding their own skid. With all systems on one common automation platform, we were truly able to lay the framework for deploying the entire breadth of PAT and begin to understand our process from a holistic standpoint.

Implementing the concept of scalable automation enabled us to install the framework for automation and PAT. This framework best provides information and tools to increase our process understanding. Since the expectation was to use data from the control system for process decisions and release of product, we ensured that the control system met all requisite Part 11 requirements.

With the scalable automation concept in place, we parsed our process into smaller more manageable sub-systems, and deployed PAT principles on sub-systems when the opportunity presented itself. One such sub-system which benefited from the centralized automation concept and PAT principles was the WFI sub-system.

WFI Example

Our site uses WFI as a solvent in processing its products, as a solvent in equipment and system cleaning processes, and as a significant component of many of its products (the product being considered for our case study is roughly 90 percent

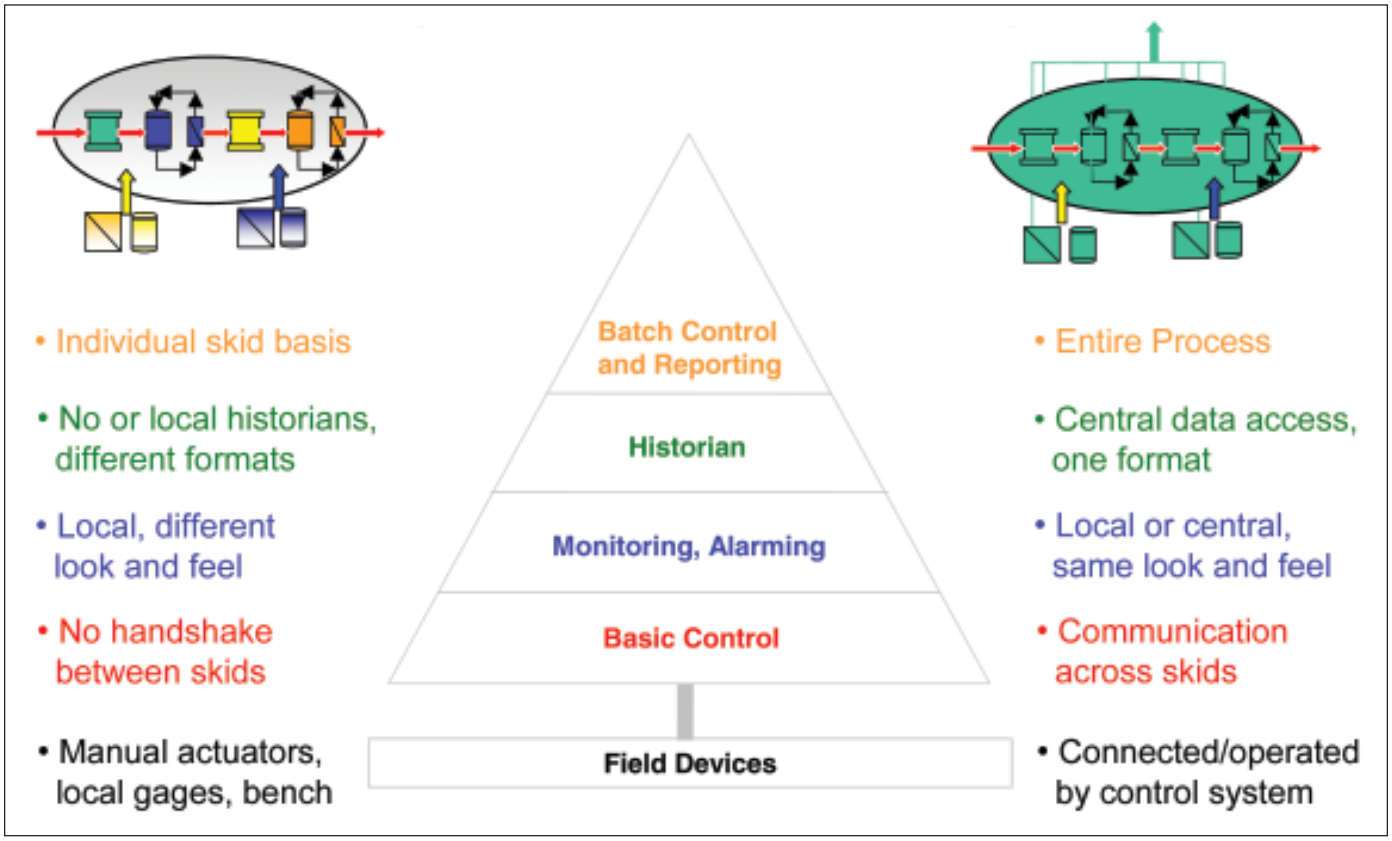

Figure 4. Comparison of automation concepts for new process.

water). A WFI system at our site is structured so that there is a centralized WFI generation with main distribution tanks, which then feed intermediate production, sub-distribution tanks. The intermediate production, sub-distribution tanks store WFI until production actually requires it. At that time, the main distribution loop starts re-feeding the intermediate sub-distribution tanks.

The requirements for WFI systems are set forth in the major pharmacopoeias: United States Pharmacopeia (USP), European Pharmacopoeia (EP), and Japanese Pharmacopoeia (JP). Figure 5 shows a still and a main distribution tank, which feed a utilities sub-distribution tank, which in turn feeds a production intermediate, sub-distribution tank. Production at our site uses water by opening and closing the valves into the main process. For the sake of illustration, we have just concentrated on one chromatography system and a UF/DF system, but the same process applies to most of the skids in the process.

WFI Example – "Non-PAT" Approach

Before we illustrate PAT and scalable automation applied to the WFI systems using centralized automation, we will take a look at the operation of the WFI systems without the application of PAT utilizing the "islands of automation" concept (WFI control system different from the skid control system). When production wants WFI, the production operator would have to confirm with the utilities operator whether WFI is available for use or not. Electronic requests via serial links or hardwired signals back and forth are options; however, both are susceptible to failure and costly in a validated environment.

Upon receiving a request for WFI, the utilities operator would ensure that the critical parameters were within specifications, and return production's request, allowing them to use WFI. Production would then open the valve and use WFI for processing.

Among the major problems with this approach, a few in particular standout – (1) The major problem is that if any Critical Quality Attributes go out of specification during production usage, there is no way of the production control system taking action, until the operator manually stops the WFI flow into the process. In essence, there is no real time quality assurance. (2) Secondly, since the other skids are oblivious to the interactions of this skid with the utilities, there is no room for any sort of predictive control to occur.

WFI Example with PAT and Automation Concept in Place

Revisiting the WFI example from a PAT perspective, we started the deployment of the bandwidth of PAT at the first level, the identification of the CQAs. In the case of WFI, we utilized USP standards for chemistry, and determined TOC, conductivity, and return temperature as critical attributes that we needed to monitor. The next step was identifying where these measurements needed to be made to ensure sufficient WFI monitoring. Considering line sizes, system dynamics, etc.; we placed online analyzers (TOC and conductivity) at the returns of all tanks and loops. Figure 6 shows the placement of the analyzers.

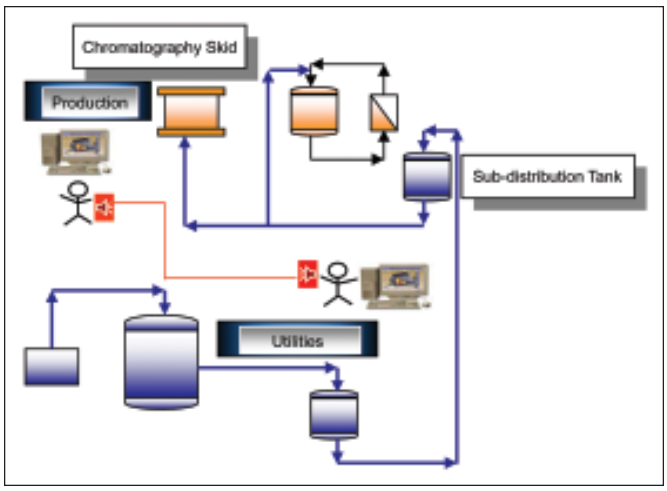

Figure 5. WFI system on site without PAT.

The next step was to monitor the analyzers. Signals from the TOC and conductivity analyzers were sent back to the utilities controller (note that the utilities and production DCS are now on the same platform). The signals in this example were 4-20 mA signals; however, the control system is compatible with all of the latest bus (i.e., fieldbus, profibus, etc.) technologies that could have been deployed. Alarm limits were set in the control system at values at or below the "out of tolerance" limits. The alarms were identified as "GMP critical alarms," and any out of tolerance alarm was reported in an integrated reporting package. Here, it is important to note that we relied on at least two years of operating experience with these online analyzers (particularly TOC), before we began to completely rely on them for process decisions (e.g., automated interlocks and reduced sampling).

When production needed WFI, a recipe parameter requests it from the utilities controller. Once the controller determines that conductivity, TOC, and return temperature (the CQAs for the utilities systems) are within acceptable limits, it returns another recipe parameter to the production controller allowing it to open the valve and the production valve opens.

For example, if TOC exceeds the acceptable limits, interlocks automatically close the production valves and prevent production from using WFI. Real-time quality assurance of WFI is maintained throughout the entire production process. In addition, the other skids can take mitigative action to account for any deviations from the standard values.

The centralized automation concept also supports the generation of QA relevant reports, ad-hoc reports and offline analyses for the entire WFI system. This achieves the final aspect of the PAT idea – wherein we identify, monitor, control, and report the CQAs.

The benefits of this approach of the WFI example in our case include:

- real-time quality assurance with the constant monitoring of the CQAs.

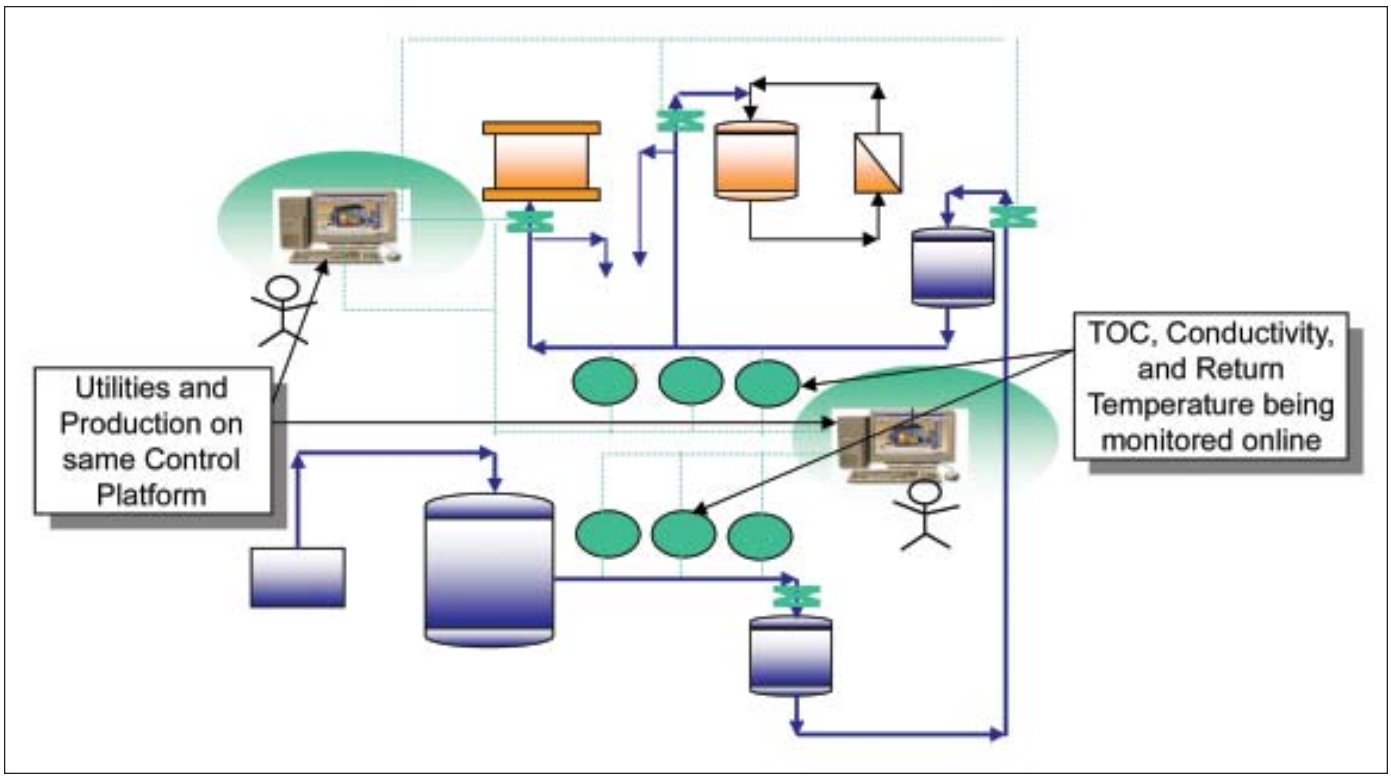

Figure 6. WFI example with PAT in place.

- WFI management is electronic. Online totalizers allow utilities to send WFI to its most critical users with advanced predictive information on how much will be needed for that phase of the recipe.
- Strong reporting components allow for multivariate analysis.
- Reduced manual testing. TOC and conductivity needs to no longer be tested daily due to constant monitoring of the centralized control system. This also eliminates the possibility of manual errors that occur during the processing of laboratory samples.

The described online WFI monitoring and control provide the highest degree of assurance that WFI contamination does not impact production. In addition, we were able to cut our QC costs by replacing conductivity and TOC related manual chemistry testing.

The centralized and scalable automation concept provides the required infrastructure for the PAT based paradigm shift of our WFI utilization philosophy. All the I/O in the centralized automation approach is wired directly to the new generation control systems with an integrated historian and reporting packages. All systems work in a virtual, shared network in such a way that data from all skids is available on a common platform. The centralized control system controls the entire process, and facilitates the comparison of critical data from all skid-based systems on one platform. So now, all the skid information is available, and if a critical parameter for WFI would trend toward an unacceptable limit, valves could be proactively shut off to mitigate the risk of contamination.

Another benefit of this approach was that using this example, we were able to implement PAT into the site in a phased manner with a quick-win, and thereby build management confidence. Other opportunities like rapid micro and real-time endotoxin analyzers are under evaluation that would further improve the quality assurance of WFI. The important point here is that as analyzer technology proves itself on site, we add it onto the centralized control system – thereby quality critical data is available on one control system, which facilitates easier deployment of the "control" aspect of PAT.

Fingerprinting of Golden Batches

Within the scope of our case study, we were able to deploy an online reporting tool that provides a real-time comparison of parameters over multiple batches, also referred to as the fingerprinting of "golden batches." It allows us to compare data with respect to time, process step or batch-ID over multiple batches, which greatly facilitates process monitoring and understanding. This reporting application fully utilizes the centralized automation infrastructure we discussed before.

Our interpretation of a "golden batch" is no different than the one shared by the rest of the industry – we considered a golden batch to be one that performs ideally with respect to cycle times, yield, and quality. Our goal is to identify characteristics of this golden batch, and control the parameters of interest so they fit the values of the golden batch. To truly understand all the dynamics of our process, we need to compare parameters over time, from batch to batch, and then correlate these parameters with other parameters to analyze the various interactions in our process. Having a centralized

automation concept gives us a strategic advantage in achieving this goal; in that we have information regarding all the parameters in one repository, the centralized historian. What we needed to do was find an effective way to utilize the data to help us understand the causes of variability in our process.

The tool we deployed sits on top of the historian and has access to all the batch and continuous data. The tool is a user-configurable tool that allows a user with appropriate privileges to select the points or the CQAs that the user wants to trend and compare. After navigating a few setup screens, it allows the user to select the batches of interest for comparison.

The user can drill down to the phase and unit level granularity if a particular CQA needs to be compared from one phase to the next phase - *Figure 7*. The net result is that a user can now obtain trends for that particular CQA across various batches/phases/units. The user can then compare this CQA with other CQAs to determine statistical correlations and obtain a greater understanding of the process. Once the process is better understood, the process can be automated to be controlled at the characteristics of the golden or ideal batch. Using this tool and the fact that all the data can be overlaid via one reporting engine, sources of variability can be understood and PAT implementation is further enhanced.

Conclusion

PAT promises to deliver a new culture to the pharmaceutical industry – a culture of innovation. Automation deployment needs to support this FDA encouraged effort by providing an infrastructure that fosters integrated data management and data analysis abilities across the entire process. This leads to improved process understanding, which in return allows for the implementation of additional automation and PAT functions where it is determined to be most beneficial for product safety and yield. The presented concept of scalable automation enables an efficient addition of these automation and PAT functions throughout the entire lifecycle of the facility.

The presented WFI example shows that the application of PAT and automation leads to increased product safety and efficiency. The "fingerprinting of golden batches" example gives an exciting outlook on what the potential of today's PAT and automation tools can provide us with.

This article not only focuses on the need to have a sufficient automation structure in place, it also emphasizes the importance of defining and following a structured PAT approach. The FDA guideline on PAT describes a broad framework that allows pharmaceutical and biotech companies to define their approach to PAT considering their product and

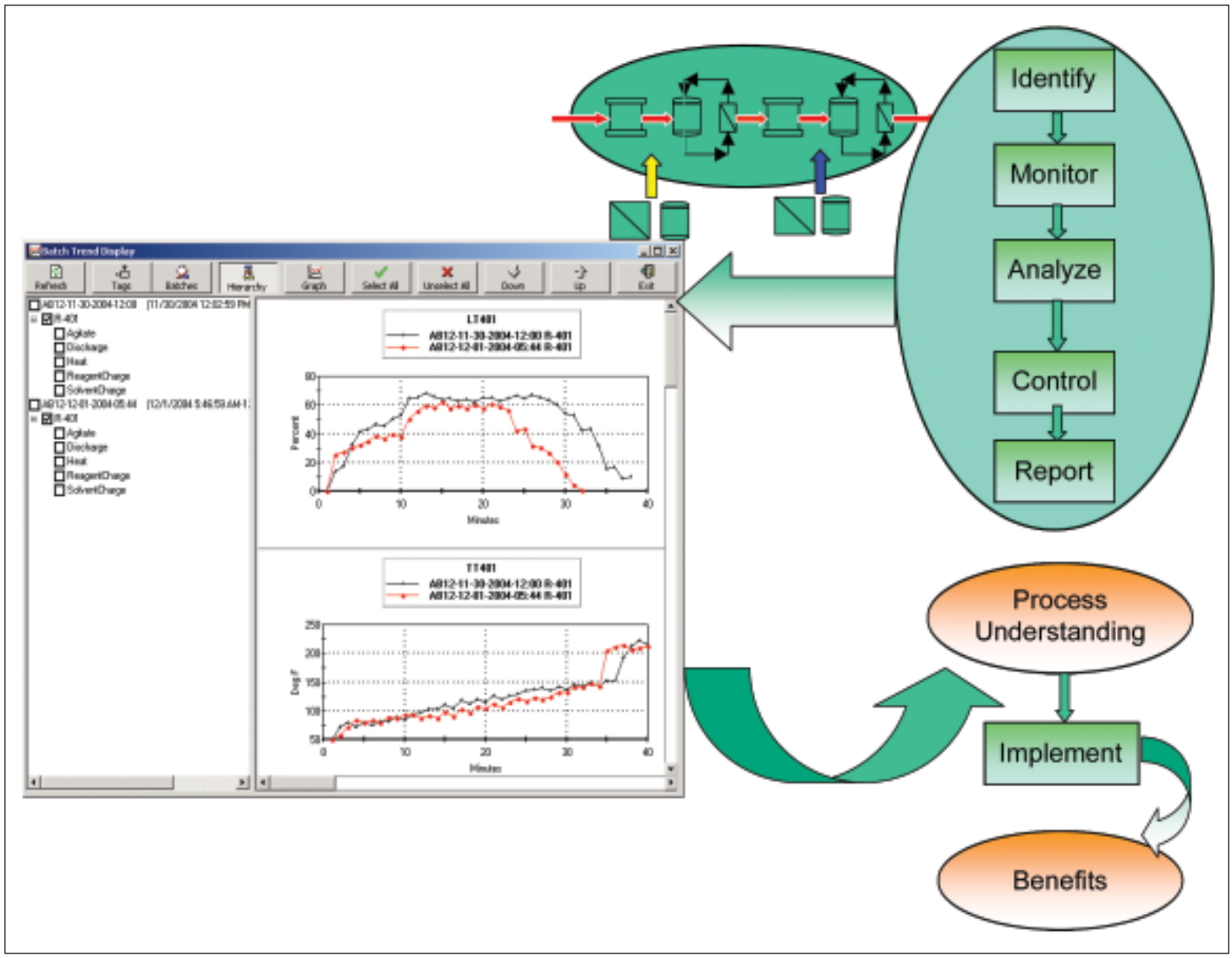

Figure 7. Fingerprinting of batches.

process characteristics, as well as their infrastructure and organization. This article is written as a case study describing approaches and examples that have worked best for our needs at Talecris. The intent of this article is to share our experiences and to contribute to an industry wide discussion on PAT. As it is true for the entire pharmaceutical and biotech industry, PAT at our company is still in the process of being defined and structured with some very encouraging and real value-adding results.

Proposed Steps to a PAT Implementation

1. Identify: this step includes the process of identifying an opportunity that would benefit from the PAT approach, as well as identifying the critical quality attributes that need to be monitored and controlled in the process. For a WFI system, that may be Total Organic Carbon (TOC) and conductivity; for a chromatography process, it may be pH. Essentially, this process details the critical control points that directly impact product efficacy or quality.

2. Monitor: the next step after identifying the critical quality attributes would be to monitor them. Monitoring is usually achieved using on-line instruments. Recent advances in on-line analytical instrumentation have encouraged more online monitoring of parameters of interest. The simple premise is that we cannot control something we cannot monitor. The monitoring step allows us to collect data for the CQA of interest and evaluate the effect of adjusting the CQA on the overall process efficacy.

3. Analyze: the analysis step ensures that once we have identified our critical quality points and monitored them, we employ statistical analysis to determine how the critical quality attribute is related to the overall process efficacy. This step includes the development, verification, and validation of any statistical models that could define the process. Experimental studies, engineering test plans, and retrospective data analysis are methods that we employ to analyze the CQA relationship to the overall process.

4. Control: after we have analyzed the relationship between the CQA and overall process efficacy and developed any statistical models, the next step in the PAT effort would be to control the process to ensure that the CQA is within specified limits at all times. This is the most critical step of the PAT roadmap that essentially ensures that "real-time" quality assurance is met.

5. Report: the last step in the PAT implementation framework in our model is a reporting element. The reporting element encompasses any tools that aid in assuring that the process was in fact in control throughout the processing period. Reporting tools serve two purposes – they allow for data to be reported in a fashion that aids in developing process understanding, and they allow for any exceptions from the "ideal state" to be documented in the final release records.

Abbreviations

CIP	Clean-In-Place
CQA	Critical Quality Attribute
EP	European Pharmacopoeia
ERP	Enterprise Resource Planning
JP	Japanese Pharmacopoeia
MES	Manufacturing Execution System
PAT	Process Analytical Technology
TOC	Total Organic Carbon
UF/DF	Ultrafiltration/Diafiltration
USP	United States Pharmacopoeia
WFI	Water For Injection

References

1. Talecris Biotherapeutics operates one of the largest sites dedicated to products that are derived from human blood plasma.
2. FDA, "Guidance for Industry: PAT – A Framework for Innovation Pharmaceutical Development, Manufacturing and Quality Assurance," *Center of Drug Evaluation and Research, Food and Drug Administration.*
3. FDA, "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach," http://www.fda.gov/cder/gmp/index.htm.
4. Cohen, Nissan, "Validation of a Water System for the 21st Century," *Pharmaceutical Engineering*, July/August 1999.

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This article investigates the options for upgrading the containment performance of traditional pharmaceutical facilities using alternative (low cost) containment technologies.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
January/February 2006, Vol. 26 No. 1

Pharmaceutical Facility Upgrades: The Containment Issues

by Martyn Ryder

Introduction

Make no mistake, pharmaceutical sciences are passing through an exciting period of discovery and progress. New drug molecules, often with increased pharmacological potency, are being developed along with novel delivery systems, all in the hope of finding new cures for human ailments. Even though we are a few steps closer to the route to the market place, we have to accept that these new Active Pharmaceutical Ingredients (APIs) are going to pose serious challenges to our existing manufacturing facilities. Do we look to provide new facilities to address these challenges or can we refurbish existing plants? The ISPE Zurich Seminar (October 2003) discussed these issues in detail.

This article highlights the process containment aspects and provides advice on how alternative containment technologies may be used

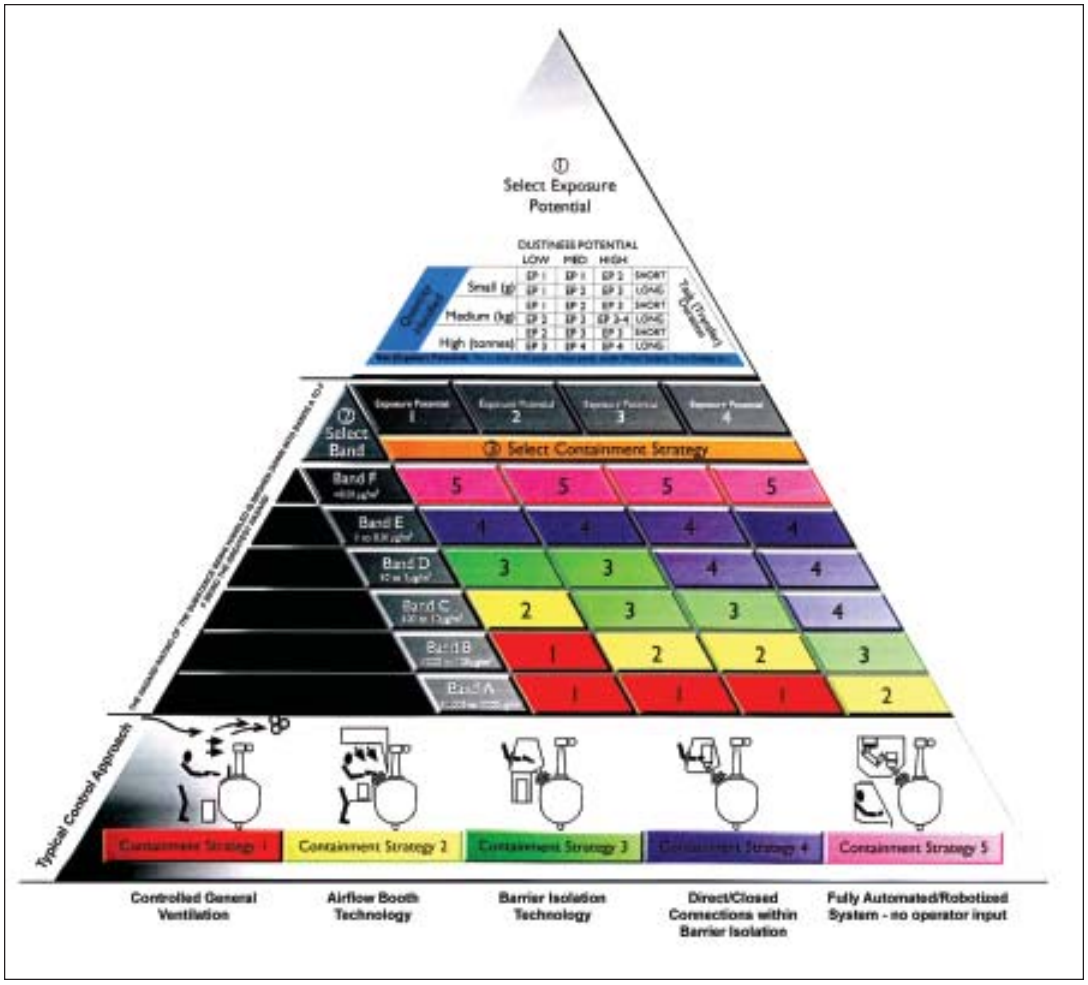

Figure 1. Containment approach selection chart.

	Small Scale Operation	Medium Scale	Large Scale	Smaller hardware investment / Larger hardware investment
Occasional Process	Consider disposable laboratory glove bag.	Consider machine top only enclosure. Zipper airlocks.	Consider full M/C enclosure tent. Bonded to facility floor. Zipper airlocks.	
Campaign Process	Very small applications. Consider acrylic mini isolator. PVC flexible isolator with rigid work platform. Zipper airlocks.	Consider machine top only enclosure. Rigid airlock with gasket seals.	Consider full M/C enclosure tent. Bonded to facility floor. RTP entry/exit.	
Continuous Process	PVC flexible isolator with rigid work platform. RTP material entry and exit.	Consider machine top only enclosure. RTP material entry/exit.	Cleanability needs suggest conventional rigid isolator may be necessary.	

Table A. Selecting the containment device according to scale of operation and process frequency.

to provide additional levels of Safety Health and Environment (SHE) and regulatory compliance (GMP) in instances where new molecules and mature facilities are combined, at least for the short term.

As with any refurbishment project, the primary issues are summarized by the four Ps:

- Product (the SHE & GMP implications of the new molecule)
- Process (identify critical activities needing containment)
- Procedures (define new SOPs and emergency procedures to ensure staff safety is not compromised by the new molecule)
- People (seek "buy in" of the operating teams to develop effective ways of handling the new molecule and its associated containment devices).

This approach is based on my "from experience" empirical formulae that attaining GMP/SHE goals split down into:

"device" + "correct operation" + "maintenance"
= Attainment of target

The Containment Issues

Product: Recognizing Risk and Hazard

A detailed review of the manufacturing process is needed to clearly identify every potent or API material handling task that places the operator at risk of exposure. Simplistically, the quantities of material being handled in "open transfer" and how dusty the compound is at this stage of the process must be understood. The pyramid chart permits risk of exposure – or – exposure potential to be evaluated according to the quantity of powder and dustiness of the powder - *Figure 1*.

The hazard associated with the new API needs the full involvement of the industrial hygiene specialists. The Operator Exposure Limit (OEL) needs to be identified. Also, is there an acceptable Short Term Exposure Limit (STEL) that permits occasional tasks to transgress the normal 8-hour time weighted average exposure?

Several pharmaceutical manufacturers are now adopting a more flexible, statistical analysis of API handling task exposure. This method uses nine or more of pumped environmental measurement filter heads to evaluate a specific task and its surroundings in detail. Often referred to as the "3x5 rule," whereby the normal Engineering Control Limit (ECL) may be transgressed by up to three times during a 30-minute task duration. The exposure of any one of the multiple samples around the task site can be exceeded by up to five times the ECL for the task duration. Any application with exposure to the API exceeding the 3x5 rule is considered "out of control" and therefore requiring further containment attention.

There are other over riding constraints, including whether or not the compound is a dermal or respiratory sensitizer. These factors may have significant implications to the risk posed to our process operator and indeed may point to a more contained approach as to how the material is handled in the facility.

A risk and hazard profiling of every open API transfer task ideally needs to be carried out – this also should consider "non production" aspects such as QA sampling of the compound in adjacent laboratories through to the risk posed to maintenance operatives.

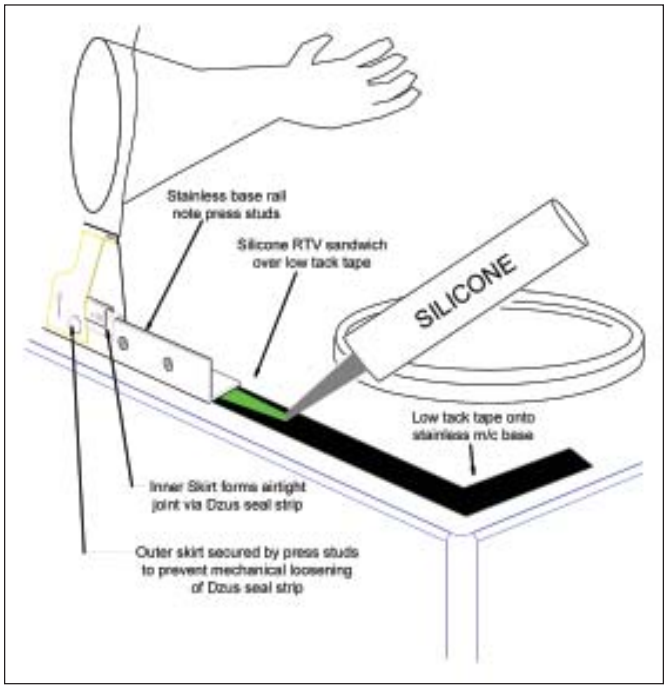

Figure 2. Attachment of flexible encloser to a stainless base rail.

Figure 3. Flexible glove bag systems.

This procedure, although lengthy, permits the correct level of process containment equipment. The next thing to consider is the equipment to process these new APIs and the tasks the operating teams are expected to perform in normal production.

Process

We have a facility to refurbish to allow new APIs to be handled. Let's ask what scale of production are we looking to contain? Smaller operations at laboratory or pilot plant scale are easier to enclose in flexible isolators than operations involving the handling of 50Kg containers. A good rule of thumb is 10Kg batch size maximum for flexible isolation – this can be stretched to 25Kg where special drum support platforms are developed as part of the design. Containers much above this size really need drum lifters/tippers and a solid interface such as a pouring hopper to ensure a repeatable and safe powder transfer system. Also at this time, while reviewing the inherited equipment, we can ascertain the best method of isolation. Some large floor standing machines such as tablet compression presses or granulators can only be effectively contained by dropping a full enclosure over the machine. Here an open base enclosure that is sealed to the floor is a good solution. For processes such as weighing and dispensing or QA sampling where operator interface is intensive, an isolated work bench type containment is probably a better solution. This planning period is the time to consider the best methodology of entry and exit of materials from the contained enclosure without loss of containment and negative pressure. Table A lists recommendations on the type of enclosure together with entry/exit methods.

With regard to full machine enclosures; these can either be equipped with an integral fully sealed PVC ground sheet floor (ideal for where the machine is light and portable), or the enclosure can be open at the base to permit its construction of the enclosure around the machine or equipment requiring containment. The latter method requires careful consideration of how to achieve an airtight/liquid tight seal to the facility floor (or machine top) without creating a permanent anchorage and damaging the machine or facility floor. One method of attachment is illustrated in Figure 2.

Procedures and People

These final two Ps are just as critical as understanding the product (new API) and the process. Indeed, because we are in a refurbishment project mode where the containment solutions are a retrofit, we need to verify that the operators will work with our plans. Development of suitable SOPs and operator training are going to be vital in attaining satisfactory levels of containment and operator safety. These topics are covered later.

The Refurbishment Project: Accommodating a Potent API in an existing Non-Potent Facility

In order to get a feel for the key aspects, let's take a look at a theoretical solid dosage form facility that has been in use for 20 years handling "non potent compounds" and now must adapt to handling a new API with an Operator Exposure Limit (OEL) of around 1.0 microgram/M^3. Let's also be clear that in this scenario, the facility will be dedicated to handling the new compound on a continuous basis.

Key GMP/SHE parameters to address are:

- process specific containment
- improved isolation of areas handling the new API
- improvements to HVAC system
- additional protection to service crews carrying out maintenance

Figure 4. Machined acrylic airlock – easier operation than zipper doors.

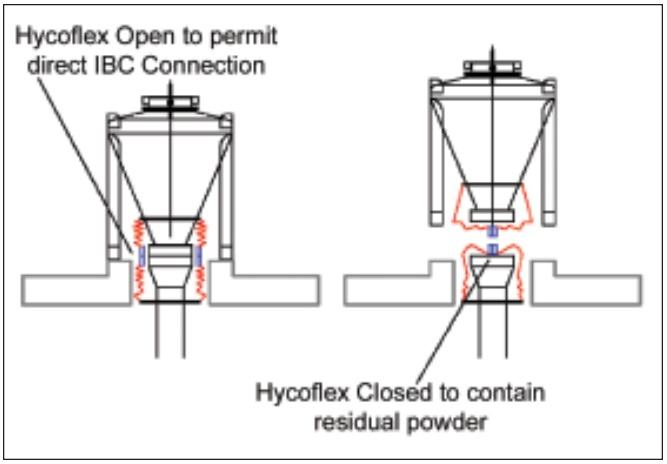

Figure 5. GEA Buck – Hycoflex disposable valve technology (Hycoflex ML shown).

Containing Powder Transfer Tasks

In our theoretical facility, we need to look at typical open powder transfer tasks forming essential processing stages, these could include the following:

- QA sampling of the incoming API
- powder weighing – sub division
- addition of the API to the batch

The facility has for many years operated a number of downflow dispensing booths that have provided satisfactory containment for non-potent products. Operator exposure monitoring within these booths suggests exposure levels of around 100+ µg/m^3 (dependant on operator practice). This renders the booths totally unsuitable for the new incoming API (1.0µ/m^3) that will arrive in a 10Kg fiber drum. The small quantity of the new API is a key factor in selecting our upgrade route.

The frequency of weighing the new API at just a few kilos every batch cycle suggests, at least at this stage, that a sophisticated rigid stainless steel isolator may be overkill. Containment needs:

- barrier isolation between operator and new API
- negative pressure enclosure to alleviate API migration
- ability to pass in API drums and pass out weighed without loss of containment
- mobile to permit storage when not in use

These features can be brought together in a relatively low cost glove bag type system as illustrated in Figure 3.

Of course the absolute lowest cost containment is the all PVC or Urethane envelope. The light plastic glove ports/sleeves allow for easy manipulation. However, to provide a workable and easy to use device, I have tended to differentiate between "hardware" and "software." The plastic envelope should be designed for the lowest cost of manufacture so its disposal on an occasional (campaign or batch basis) is not prohibitive.

To support the minimalist "software" with durable "hardware," this could be a rigid stainless work surface to carry weigh scales, a support frame and an entry airlock. On the subject of airlocks, the author has abandoned the use of zippered access chambers for frequent applications. Experience shows that zips may jam and or be subject to operator abuse, pointing to a disappointing short operational life cycle. Instead of the zipper door approach, look at the use of rigid Plexiglas/Lexan or even Trespa (phenolic resin) airlock chambers with proper hinged doors and gasket seals. These pass in chambers provide a reliable and easy to use airlock that permits easy entry of API containers into the handling chamber, without breech of containment. Built into this fabrication can be the inlet/outlet HEPA filter housings and fan unit. This permits validatable and replaceable HEPA filters to be used in glove bag applications. Figure 4 shows the type of airlock housing being considered.

For API drum and weighed material exit from the handling chamber, there are several well established methodologies:

- bag out with continuous liner
- Rapid Transfer Port (RTP)
- split butterfly valve

The most suitable method will depend on your process driver; however, focussing on lowest cost, we generally look to overbag empty drum containers exiting the powder handling chamber. The task is not frequent and therefore not a major inconvenience to the operators.

Figure 6. Lab scale fluid bed in ventilated glove bag.

This combination of lowest cost "software" and durable functional "hardware" is seen as providing the optimum relationship between ease of use, ease of decontamination, and low price. The design can be adapted to work for QA sampling, dispensing, or batch additions – all by varying the design of the base plate and envelope.

Will this type of design attain the 1.0 microgram target maximum operator exposure? Early user feedback suggests it will.

Operating at a negative pressure of 50pa the devices have been tested using placebo materials with the following procedural constraints:

- clean uncontaminated API drums entered via pass through door
- API bag out using continuous liner is carefully set up to avoid gross contamination of API powder in sacrificial liner bag

Difficult Containment Upgrade Applications

With small scale manual operations such as powder dispensing or sampling, we have the freedom to tailor the solution around the operator and process. Yet, other areas of the manufacturing process are often not as easy to contain via low cost methods.

Take for example the IBCs used for intermediate batch transfer of process powders and granulation lots.

Here, it is easy to foresee the escape of small quantities of dust at the IBC loading and docking stations. As our theoretical plant wishes to introduce APIs, these once acceptable emission levels (pre potent materials) could now easily breech the maximum Operator Exposure Target (OEL) when considering the newly introduced API.

How do we move forward? Should we consider the "engineered solution" and look at the wholesale conversion of 100s of existing IBCs to split butterfly valve operation? This is an established yet, costly solution.

Many plant managers would ask, can a containment upgrade be attained without this big investment step?

Some split butterfly valve manufacturers are looking toward a disposable docking solution in the form of a flexible docking flange system. The flexible docking flange takes the engineered split butterfly valve forward into a mass produced low cost disposable product. The smaller flexible docking flange is aimed at small scale powder handling (up to 20Kg), and may when fully developed, provide the ideal low cost docking system for glove bag type isolators. At the larger end of the product handling scale, is the flexible docking flange that is a collapsible flange that can either lie folded up and effectively flat (powder port closed) – or unfold – to form a 350mm Sq powder transfer opening (powder port open). Just as with precision engineered RTPs, the flexible docking flange (snap) dock together to form a contamination free make/break connection surface. When the large powder port of the flexible docking flange is open conventional IBC discharge spigots can be located inside the flexible docking flange. This means that our "marginally leaky" IBC discharge can now be contained by an outer flexible sleeve with flexible docking flanges. With this concept, docking onto the discharge station is possible – with containment provided by the clean make/break joint flange as illustrated in Figure 5. This developing technology should see the inclusion of low cost containment upgrades on an IBC/FIBC transfer system.

Figure 7. Microwave granulator in ventilated glove bag.

Large Scale Equipment Interfaces

With the introduction of APIs into the manufacturing process, some of the greatest containment problems are seen in the granulation suite where high shear mixers and fluid bed dryers are in use. Many of these devices may have been operated with open powder transfer procedures that cannot be tolerated when more potent APIs are introduced. Depending on the scale of the operation and the process validation that exists, we can provide a "containment upgrade" by enclosure methods or alternatively larger scale processes may elect to by-pass containment enclosures in favor of a closed vacuum transfer system. The latter may have the disadvantage of necessitating engineering changes to the granulation equipment, but if this can be accommodated, the process will benefit significantly from automated powder transfer. Several experienced vendors exist in the US and Europe, hence, in this article I will look at the smaller scale "enclosable" operations. High shear mixers and "one-pot" processors have been successfully isolated within glove bag type enclosures, as shown in Figures 6 and 7.

Larger scale equipment such as fluid bed dryers can be contained utilizing polythene liner "bag tricks" to contain removal of the dryer bowl from the main dryer body; however, the considerable bag manipulation needed by the operators may render this method risky for long term operation.

The key point to consider when looking to contain such

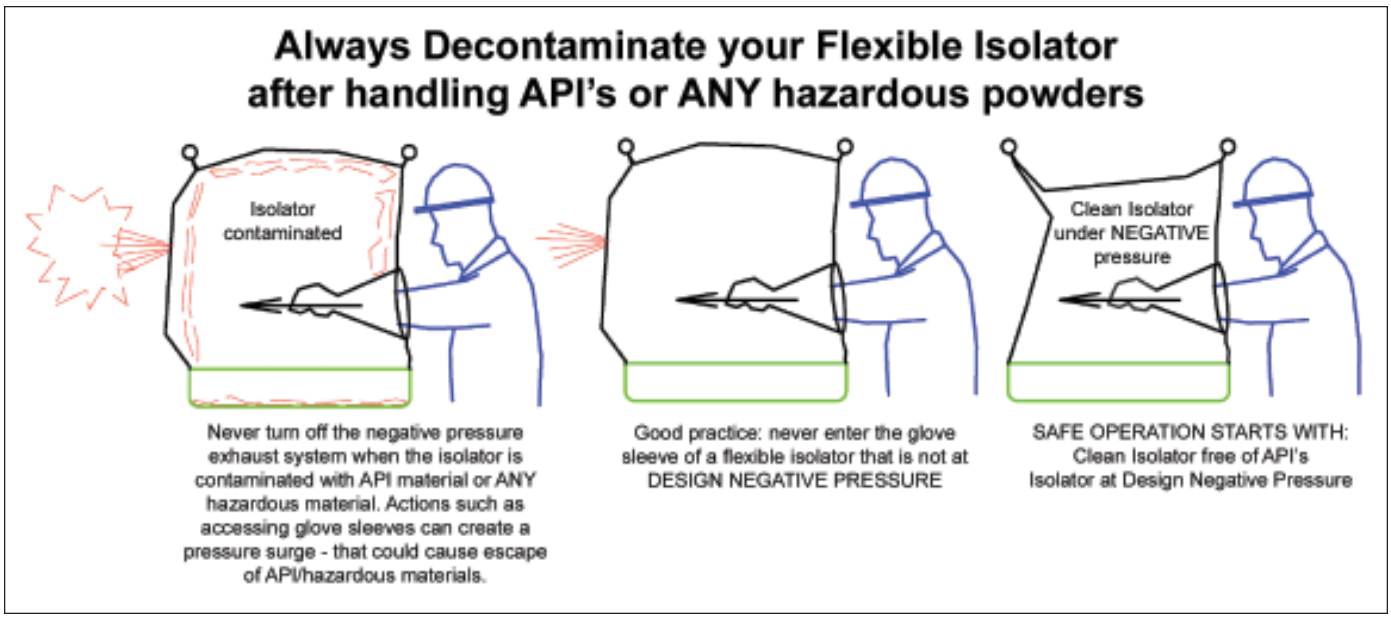

Figure 8. Typical operator training slide.

large items of process plant is operability and benchmarked containment levels. An engineering study with user group input to the development of any soft-wall containment solution is a sensible approach.

Operator Training For Flexible Isolation Systems

The cost saving and ease of installation benefits gained by using flexible containment solutions in a refurbishment project must be considered against the risks and hazards that could be created by incorrect operation of a 0.3mm thick PVC barrier. There is a strong case for extensive operator/user group involvement with the flexible containment equipment from the early design stage right through to installation. After this milestone, operator training needs to emphasize some of the golden rules of this technology as illustrated in Figure 8, and defined as the following:

- Always pre-load the flexible isolator with the cleaning and decontamination materials required to make it safe at the end of the campaign.
- Always clean the flexible isolator as soon as the operation ends.
- Never use the flexible isolator unless design negative pressure is attained.
- Develop safe material entry and particularly safe material/waste exit routes and procedures.

Other Refurbishment Project Considerations: Segregation of Production Areas (Environment Containment)

As we have seen, an increasing number of "low cost" and conventional containment devices now exist to create an effective process facility upgrade to ensure safe containment at critical powder handling stages during manufacture. Any containment device must be seen as a first line of defense, so when considering plant safety and environment separation, how do we create improved isolation between API handling areas and general work areas?

In our theoretical plant, we are considering the permanent introduction of an API compound for a dedicated manufacturing process. I think it's worth considering basic solutions for plants where APIs may be introduced on an occasional basis. Here, temporary segregation between work environments

Input / Elements	Chemical Supplier	Industrial Hygiene	Safety and Health Group	Operations	Maintenance Group	Quality Assurance Validation	Equipment System Designer
Hazard Group	✓	✓	✓				
Scale of Operation				✓			
Exposure Potential		✓	✓	✓	✓		
Frequency and Task Duration				✓	✓		✓
Operability of Device			✓	✓	✓	✓	✓
Cost of Device		✓		✓	✓		✓

Table B. Validating your containment equipment selection within your organization.

Figure 9. Temporary flexible enclosures: (a) Temporary containment enclosure for Comil (b) Walk in enclosure for active powder campaign.

may be required and the use of operator PPE may be an acceptable short term "fix" to get the required batch processed.

I say "fix" as in reality no respectable pharmaceutical manufacturer should be relying on PPE when so many containment solutions are available.

Nevertheless, at the most basic level, the use of welded PVC or Urethane material may be used to form a temporary work chamber with airlocks to segregate material entry/exit routes from personnel entry/exit routes. Fogging or misting showers can be accommodated where emergency decontamination is viewed as a possible requirement. As with their smaller glove bag siblings, these low cost processing enclosures cannot be considered as a permanent durable solution. However, for the facility considering the occasional processing of API materials, their use may be acceptable. Two examples of the use of such enclosures are illustrated in Figure 9.

Environmental Segregation

With the permanent handling of APIs within the mature facility, thought should be given to improvements to air lock pressure cascades, personnel, and materials flow to avoid cross contamination and to alleviate migration of the API into "safe" areas of the plant. In this area, facility door designs have seen major advances in the last 10 years. Doors are now available designed specifically for pharmaceutical facilities where cleanability and effective door seals are highly desirable. Key features to look for are flush and crevice free surfaces, flush glazed vision panels where needed, and some of the better designs feature door closer actuators concealed in the doorframe. While stainless steel doors have long been considered the norm, there is a growing acceptance of plate glass doors in pharmaceutical facilities. A typical example of a glass door in a pharmaceutical facility is shown in Figure 10. Glass doors are often significantly cheaper than stainless steel items, enhance the visual appearance of the upgraded facility, and add a touch of bold design flare. The downside of plate glass doors is obviously breakages, but it seems that the plant operators treat glass doors with much more respect.

Where migration of API between areas is totally unacceptable, the use of gas tight door sets with inflating seals, as shown in Figure 11, is becoming more popular.

Gas tight doors are now being applied to potent handling facilities – in the same way that leak proof vision panels are specified on isolator systems.

House Exhaust – Lev Systems

In this age of high containment solutions, the house exhaust system that extracts dust-laden air from compression machines, packing lines, and a myriad of other operations is still an object of contempt. It is very surprising to see all manner of "low tech" filtration systems placed in either the roof top plant space or in segregated exhaust filter rooms for service by technicians protected by PPE.

Not only are we creating a potential "time bomb" of API contaminated ductwork and dust filter housings, we are putting the service crew at risk.

Believe it or not, the unfashionable technology of local exhaust dust filtration has moved on. Not only has the filtration efficiency of the best devices moved up to nanogram level (guaranteed by some vendors), the entire service work routine has been re-designed to be totally contained. These new generation dust collectors permit designers to challenge convention regarding the traditional location for dust filtration technology. Tradition means "plant room" and all collected material "waste." The latest generation of pharmaceutical dust collectors may be set up to permit hygienic dust (process waste) recovery. These exhaust filter devices will utilise crevice free and highly polished powder contact parts. The collection hoppers are designed for vacuum transfer of collected powder recovery. Hence, what was traditionally considered waste may now be considered for either re-introduction to the process where regulatory authorities permit. Alternatively, the collected powder may be easily and cleanly

Figure 10. Plate glass doors a facility upgrade option.

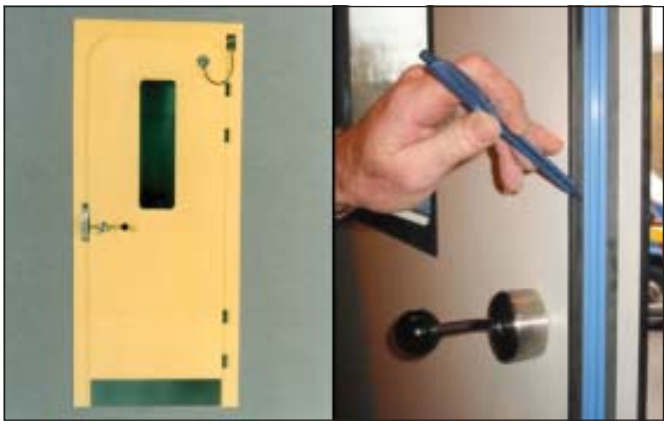

Figure 11. Gas tight door with inflatable seal technology.

weighed for accurate calculation of in processing losses.

Some pharmaceutical companies are taking advantage of these new generation high efficiency dust filtration systems and are locating the filtration devices directly into the production area. The benefit of placing the filtration plant in the production zone is much shorter (often demountable for cleaning) exhaust duct lines. Powder recovery or waste measurement is performed directly by the production staff. Many engineers will be appalled at the thought of a "dust collector" handling potentially explosive dusts being located in a production zone. Surely, these devices create a lethal explosion hazard. Not so, just as we see large scale fluid bed driers now fabricated to 10 or 12Bar pressure rating – so too are these new dust filtration devices built to these standards.

Some of the advantages are:

- guaranteed dust filtration efficiency – safe clean exhaust air
- dust free filter service and dust recovery – no risk to work room environment or service crew
- wash in place clean down technology available
- can be located in a production zone – filter housings fully pressure rated and smooth cGMP fascia for architectural integration

The Way Forward

Before any decisions are made about the containment add on equipment, the issues must be clarified and the operators must support the decision. Down stream of this in what we may call the detail design or engineering phase you will see great benefit in having prototype or mock-up devices delivered for the user group to critique. A well designed prototype will often permit preliminary performance testing, whereby the ability to attain the required levels of operator protection can be benchmarked.

While nobody can feel comfortable developing serial number 001 for any device in a production facility, what we are hoping to achieve in a facility containment upgrade is not rocket science and often relies on a variation of proven technology. As a safeguard to ensure the selected equipment/designs are up to the job, the selection criteria must be validated. The data in Table B suggests interface with the various groups responsible over the life cycle of the project.

Conclusion

In this article, some of the new approaches to upgrade a "standard" facility to a level capable of handling potent compounds and new APIs safely were presented.

- Product (the SHE and GMP implications of the new molecule)
- Process (identify critical activities needing containment)
- Procedures (define new SOPs and emergency procedures to ensure staff safety is not compromised by the new molecule)
- People (seek "buy in" of the operating teams to develop effective ways of handling the new molecule and its associated containment devices.

In conclusion, my optimistic view is that the growing need for facility upgrades to standards capable of handling APIs need not be prohibitively expensive.

However, the key issue when introducing alternative containment technologies is to get the buy in from the operators and user group. They then understand the risks posed by the new compounds, they appreciate the efforts being made to assure their safety, and they work with us rather than against us in attaining reliable and safe working conditions.

References

1. Turner, K.: AstraZeneca UK – Refurbishment as a catalyst for improvement. ISPE Zurich seminar October 2003.
2. Dayre, S.W.: AstraZeneca France – Renovation of pharmaceutical facilities – maintaining compliant operations. ISPE Zurich seminar October 2003.
3. Hirst, Brocklebank, and Ryder. Institution of Chemical Engineers UK – Containment Technology a Design Guide. 2001.
4. Andrasfalvy, K.: Fette-Absolut gmbh. Fine 04 Symposium Stockholm January 2004.

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Martyn Ryder was educated at Leeds University in HVAC and Building Services. Ryder was a founder of Extract Technology in 1981, now part of the CPS Pharma Group of companies with operations in the US, Europe, and Asia. CPS Extract has grown to be one of the world's leading suppliers of pharmaceutical powder handling related containment systems, currently exporting more than 70% of its production capacity to major manufacturing sites around the world. Ryder now provides support to the CPS Pharma Group on an exclusive consultancy basis and shares his time between his CPS duties and farming.

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This case study presents early contamination detection in an established WFI and PW system through the use of on-line particle counters.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
January/February 2006, Vol. 26 No. 1

On-line Particle Counters Provide Detection and Control in Water for Injection (WFI) and Purified Water (PW) Systems

by Dr. Hans-Walter Motzkus and Joe Gecsey

Creating an effective water system to provide Purified Water (PW) or Water for Injection (WFI) in a life science application is a careful adjustment of design, materials, monitoring, and maintenance. By convention, certain parameters must be monitored in a WFI system: endotoxin levels, conductivity, TOC, and microbial (CFU) values.[1,2] In the EU, other parameters that must be monitored are nitrates and heavy metals.[3] It has been common in the past to obtain grab samples of the water at a predefined frequency and to later perform a laboratory analysis for the key parameters. In recent times, some of the instrumentation for these parameters, for example, TOC, has allowed continuous on-line measurement to be accomplished. Determination and monitoring of particulate levels in WFI systems are not required by regulation, but can provide an enhanced degree of control, as described in this article, resulting in early detection of potential breaches in the integrity of the water system.

The water system in Building S166 at the Schering facility in Berlin provides PW to an oral dosage forms manufacturing area and PW and WFI to a parenteral area for manufacturing clinical trial supplies. In 2000, an on-line particle counter was installed on the WFI system - *Figure 1*. The instrument was connected to monitoring software that provides water system information from three different buildings - *Figure 2*. The software includes operational details of various parameters such as the system temperature and pressure in the various piping systems on the campus. Based on the performance of the initial analytical monitoring system on the WFI system, a second particle counting system was installed in 2005 on the PW system in Building S166.

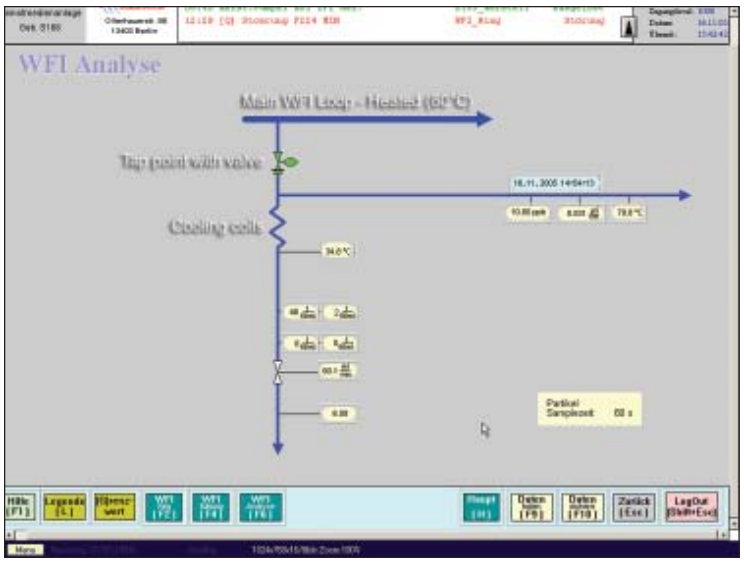

Figure 1. WFI system with instrumentation and valves.

As with most WFI systems, the water is circulated in a continuous flow loop at an elevated temperature of at least 80°C (176°F) to exclude bacterial growth. Neither the pH sensor nor the particle counter are designed to operate in this temperature range so a heat exchange system is positioned up-

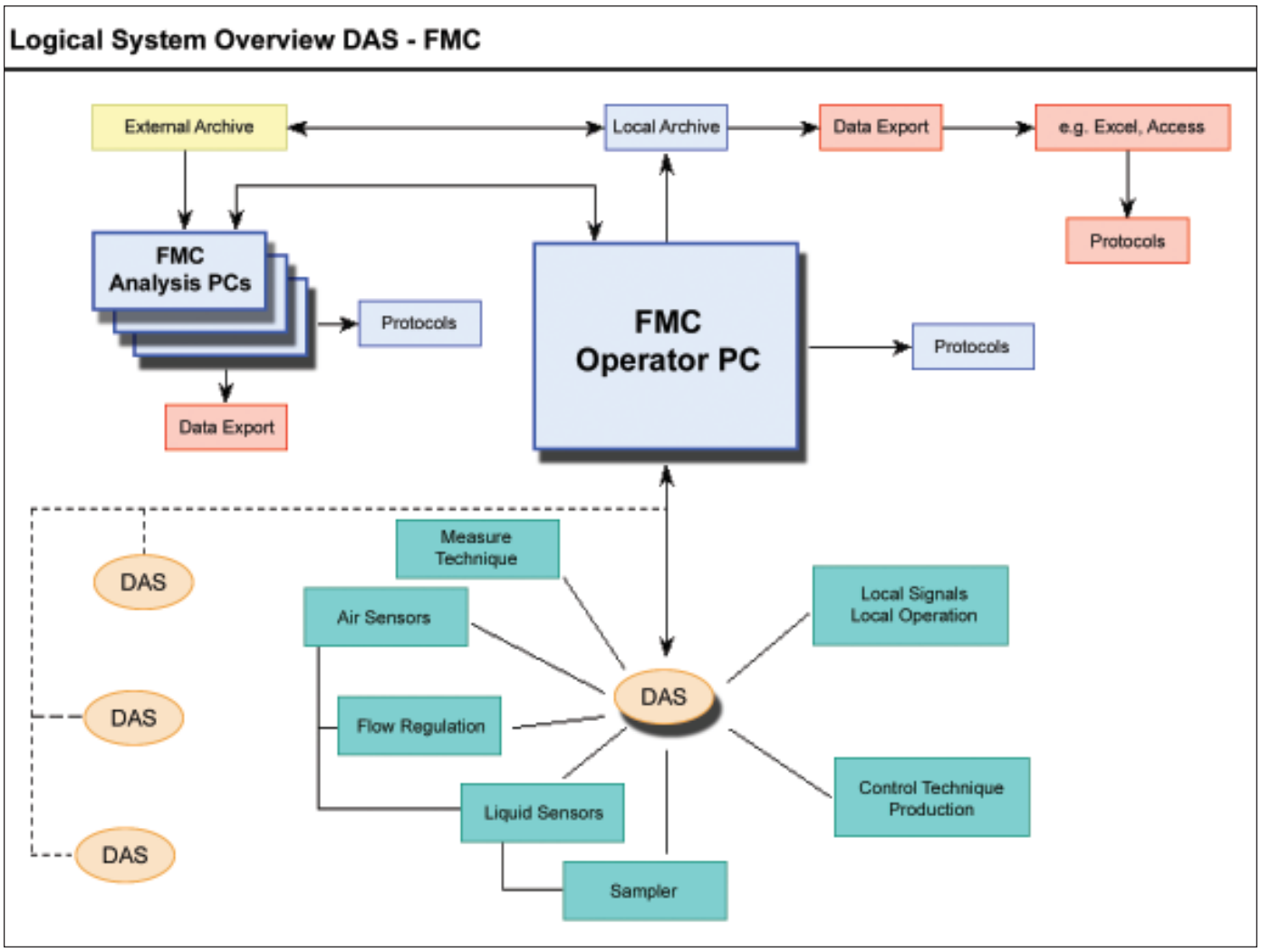

Figure 2. Overview of DigiPlan FMC-DAS software architecture.

stream from the counter to reduce the temperature of the sampled water to approximately 35°C (96°F) - *Figure 3*. The cooled water flows through the particle counter with the flow controlled to 60 milliliters per minute (0.95 gallon/hour) and then through the pH meter. It is then sent to drain. Sending the sampled water to drain avoids potential introduction into the WFI system of chemical contaminants such as the reagents used in the pH sensor.

At this time, alarm indications in the monitoring software are provided only for conductivity and TOC pending establishment of appropriate limits for the pH and particles through further monitoring.

Conductivity, TOC, and temperature are measured directly on the heated loop. Separate temperature transducers are used to monitor the temperature in the main loop and in the sample line following the heat exchange unit. Downstream from the particle sensor is a flow controller, followed by the pH sensor. The output of the pH sensor goes to drain.

Particle Detection

The sensor provides detection of particles starting at approximately 2 µm through 400 µm. The counter updates the particle count data each minute in each of four size channels: ≥5, ≥10, ≥25, and ≥50 µm. The data is shown on the monitoring system screen in terms of "counts per 60 ml" in each of the four size ranges (channels). During steady-state operation, some counts are observed in the first two size channels (≥5 and ≥10 µm), usually less than 100 counts per 60 milliliters at 5 microns. Counts are rarely seen in the upper two size ranges (≥25 and ≥50 µm) during steady-state operation - *Figure 4*.

Observed count values of particles with this system are well below 1% of the USP limits [25 counts per mL at ≥10 microns and 3 counts per ml at ≥25 microns] for Large Volume Injectables (LVI). Care has been taken to monitor not only peaks in particle count values, but also changes in the baseline readings. Peak readings convey information on system performance that previously were never recorded with grab sample methods at Schering due to their once-per-week schedule. Today, the consistent and minute-by-minute data readings of the on-line system permit relevant data to be gathered for trend analysis and even SPC methods in the future.

Because the system is still regarded as being in the investigative stage regarding particle counts, alert and action levels have not been set. Particle count changes are

Figure 3. Instrumentation panel with HIAC HRLD sensor.

monitored by the Quality Group, evaluated, and then reported and discussed with both the Production Group from Clinical Supplies and Engineering. Elevated readings are now used to initiate maintenance and repair of the systems in cooperation with the Engineering Department.

Detected Particulate Matter in the WFI System

One of the major reasons for investing in an on-line particulate monitoring system was the significant variance in the data obtained from the hand-drawn grab samples Schering had previously employed. Often, these variances were false positives due to sample handling. In one incident, Raman microscopy was successfully used to determine that the probable source of high readings of particles larger than 5 microns in the grab samples was particles generated from a polyethylene component of the screw-on caps of the jars used for the grab samples.

The on-line system avoids false positives caused by manual sample gathering technique and materials. Note that sample point valves are another notorious generator of particles and potential false positives; grab samples should be drawn only after waiting long enough for the particles generated by the opening of the valve to be flushed out of the sample port.

A further impetus for the on-line system installation was the reduction of manpower needed to obtain samples from the water system. Previously grab sampling was carried out on a weekly basis and the results of the sampling were delayed by the time needed for the laboratory analysis. The on-line monitoring system now provides current data minute-by-minute at an estimated annual savings of at least one man-month of labor.

Within Schering's water system, high-purity membrane valves are used to control flows. The membranes of these valves are exposed to the circulating WFI. Particle shedding from compromised membranes will therefore also show up as baseline rise in the detected particle levels. A significant improvement in the valve system was triggered by the detection of black particles in the WFI; it was discovered that the initial EDPM membrane material was deteriorating more quickly than expected in the hot WFI and clean steam systems. Changing the contact surface to a Teflon-coated EDPM material and establishing scheduled annual or bi-annual replacement [depending on use and application] of these membranes eliminated this particle source.

In another incident, particles recovered from the system following detection of increased counts were determined through Atomic Absorption Spectroscopy (AAS) to be metallic particles from the piping system itself. Recent construction and repairs to the piping system were identified as the probable cause. After the data was brought to the attention of the maintenance group and contractors, procedures were initiated both to reduce the amount of particulate matter generated during maintenance and to more effectively clean repaired sections before they were re-connected to the system.

High Flow Demand Triggers Particulate Release

An on-line system can show events that grab sampling would be unable to detect; on-line systems also permit the possibility of correlation to other parameters of the system in order to help establish the root cause of the abnormal readings.

Figure 4 shows the normal, steady-state values. Compare this to the screen capture Figure 5 that recorded episodes of elevated counts following both a sudden reduction of the level of water in the WFI holding tank by high rapid demand and also two successive events of rapid refilling action by the still.

The red line in the graphic display represents the output of the level detector for the WFI tank. The supply system (WFI still) works to keep the tank from dropping below approximately 70% of 3000 liters (793 gallons). Upon reaching the trigger value, the supply system adds water from the still and brings the tank level back to a nominal "full" value of approximately 74%.

The green trace shows the particle counts obtained in the first channel (≥5 µm) of the particle counter. Although some counts are present during normal circulation, the rapid drop in level (marked as **1**) caused the detected counts to jump significantly.

Figure 4. Chart with typical steady-state or "normal" values.

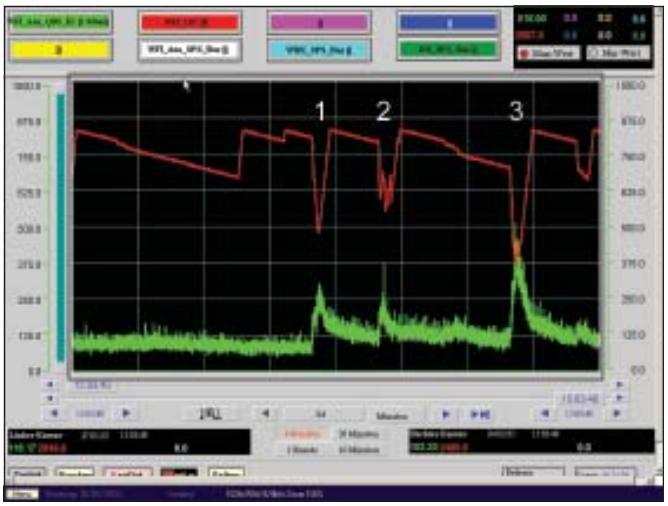

Figure 5. Particle surge as result of rapid drop in level of WFI holding tank.

The large drop in the tank level could have been caused by a cleaning operation in the main facility or, for instance, the initial high demand of a vial washing machine.

Note that there also are significant increases in particle counts when there are rapid, but lower volume demands on the WFI system, causing a rapid activation of the refilling system. In these cases (marked as **2** and **3**), the refilling system had the capacity to return the holding tank to its "full" state, but the demand for WFI was maintained at a slow, but steady rate so that that the refilling cycle occurred at a high frequency. This activity also was accompanied by high counts. It has been determined that these spikes of counts are the result of the turbulence in the holding tank caused by the refilling action. Trapped particles or sediment on the bottom of the tank could be released into the WFI circulation - *Figure 6*.

This tank and the general piping system go through a scheduled maintenance including annual cleaning. If this annual cleaning event is delayed, the spikes of particles triggered by the high demand/refilling cycle increase in amplitude and continue until the cleaning is undertaken. Cleaning of the system causes a definite reduction of the baseline counts and of the spikes triggered by the refilling action. By analyzing the debris material removed from the tank during cleaning, it is expected that further improvements to the materials and the operation of the water systems will be made.

By comparison, the responses of the other instruments on the system during a refilling spike are not at all as strong as the response of the particle counter. In Figure 6, the green trace again represents the first size channel of the particle counter. The red trace is the tank level, the yellow one is the output of the conductivity sensor, the magenta one is the TOC data, and the blue is the pH value. The reaction of the other sensors is very muted compared to the very observable response of the particle counter clearly detecting the increased particle concentration.

The reaction of the particle counter correlates precisely with the rapid depletion of the holding tank contents.

The particle counter has become an excellent indicator of the resident particulate content of the tank and has been used to determine the frequency of the cleaning cycle necessary for this part of the WFI system, as well as a superior indicator of unexpected increases in baseline particle count levels.

Because of the positive experiences with the automated WFI analysis system, Schering AG has now equipped a PW loop with a similar system of sensors including particle measurement.

Evolution of the WFI Monitoring System

At this time, daily review of the on-line monitored parameters is conducted as a joint session attended by Quality personnel, the Production personnel for Clinical Supplies, and Engineering personnel during which any observations are reported and discussed. This investigative phase will continue through 2006, after which it is likely that automatic alarms will be initiated; SPC limits also may be implemented. Alert and action levels will be decided based on the ongoing observations of the baseline values and unique events that occur. Analysis of any sediment collected during annual tank maintenance cycles will lead to further improvements in the system and its operation.

On-Line Monitoring and the FDA's PAT Initiative

The increasing movement toward on-line sensing technology and automation in the pharmaceutical industry has the support of the main regulatory agencies worldwide. The growing interest in Process Analytical Technology (PAT) is due to the potential for improved control of the process, improved product quality, and shortened analysis times for In-Process Controls (IPCs). Minute-to-minute monitoring of the key utilities in support of production – such as WFI – can aid in the assurance of product quality and rapid release of product because there is more complete data to back up a decision for product release. Particle counters can assist plant operators in maintaining and assuring an appropriate quality of water for use as a rinsing agent and as an ingredient in a product.

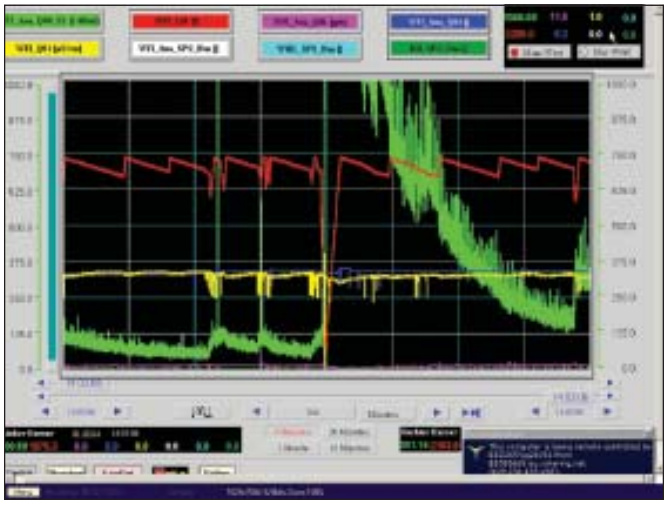

Figure 6. Comparison of outputs from particle counter, TOC, pH, and conductivity during a particle spike event.

The FDA has provided encouragement and support for the conversion of existing processes into PAT processes. Data collected can at first be regarded as "research data" until the user has decided that the additional method is sufficiently robust.[4] This allows a PAT process to be developed by the addition of suitable analytical and control processes of which this might be one.

Conclusion

Real-time sampling helps avoid errors common in manual sampling, such as compromised cleanliness of glassware, contamination generated when sample point valves are opened, and contamination contributed by the screw caps of the sample jars.

If a product contamination event were to occur, the monitoring details from the WFI system would allow investigators to quickly determine if the WFI was a contributing element to the contamination. Generally, the root cause for a contamination event will be found to be something other than the quality of the WFI system, but with the continuous monitoring data available, investigators can be on solid scientific ground when they eliminate the WFI system as a suspect. And there is an economic benefit due to the reduction of labor required to obtain and analyze grab samples, in this case, estimated to be more than one man-month annually.

Particle counters can be placed in key positions of critical systems such as PW and WFI systems to assist in developing maintenance cycles and as "watchdog" instrumentation to monitor the continuing stability of the system. This technology, based on stable, field-proven light-extinction sensors, can be an affordable adjunct to existing monitoring systems by providing a highly sensitive and real-time reaction to perturbations in water systems.

References

1. United States Pharmacopoeia Twenty-eighth Revision (2005), U.S. Pharmacopoeia Convention, Inc. Rockville, MD.
2. European Pharmacopoeia Fifth Edition 2005. Council of Europe, Strasbourg.
3. Santoro, M. and Maini C. Which water for pharmaceutical use? *Eur J Parenteral Sciences* 2003; 8 (1):15-20.
4. Heinze, C.L., and Hansen, J.R., "Implementing PAT Step by Step as a Process Optimization Tool," *Pharmaceutical Engineering,* May/June 2005, Vol. 25, No. 3, pp. 8-16.

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Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
January/February 2006, Vol. 26 No. 1

PHARMACEUTICAL ENGINEERING Interviews

Emer Cooke, Head of Sector, Inspections, Veterinary Medicines and Inspections, EMEA

Personal Background

Q How long have you been in your current position? What experiences prepared you for this and what is your educational background?

A I have been in my current position since 1 July 2002. Prior to this, I spent nearly four years working in the pharmaceutical unit in the European Commission covering international issues (ICH, enlargement, mutual recognition agreements on GMP), pharmacovigilance, orphan medicines, and GMP and quality matters. From 1992 until 1998, I worked for the European pharmaceutical industry association (EFPIA) as manager of scientific and regulatory affairs, and before this, I spent some time working in Ireland as an R&D manager for a pharmaceutical development company and as a pharmaceutical assessor in the Irish drug regulatory authority. I qualified as a pharmacist, did a post-graduate degree in pharmaceutical chemistry, and subsequently a masters degree in business administration. I believe that the combination of my formal education and my varied work experiences have been excellent preparation for my current position, as they have provided me with a combination of technical, legal, and regulatory skills within a multicultural European environment.

Q What has been your most fulfilling role so far in your career?

A I have been very fulfilled in all of my European positions to date, but for different reasons. I love the challenge of "helping to make Europe work," and achieving solutions through working together with people from different nationalities.

Q What kind of activities do you enjoy in your free time?

A In my spare time, I try to spend as much time as possible with my 11-year-old twins, and also enjoy swimming, reading and walking.

Agency Background

Q How, why, and when was EMEA founded?

A European Medicines Agency (EMEA) is a decentralized body of the European Union with headquarters in London.

Its main responsibility is the protection and promotion of public and animal health through the evaluation and supervision of medicines for human and veterinary use. The EMEA coordinates the evaluation and supervision of medicinal products throughout the European Union. The Agency brings together the scientific resources of the 25 EU Member States in a network of 42 national competent authorities. It cooperates closely with international partners, reinforcing the EU contribution to global harmonization.

The EMEA is headed by the Executive Director and has a secretariat of about 400 staff members in 2005. The Management Board is the supervisory body of the EMEA, responsible, in particular, for budgetary matters.

The EMEA began its activities in 1995 when the European system for authorizing medicinal products was introduced, providing for a centralized and a mutual recognition procedure. The EMEA has a role in both, but is primarily involved in the centralized procedure. Where

the centralized procedure is used, companies submit one single marketing authorization application to the EMEA. A single evaluation is carried out through the Committee for Medicinal Products for Human Use (CHMP) or the Committee for Medicinal Products for Veterinary Use (CVMP). If the relevant Committee concludes that quality, safety, and efficacy of the medicinal product is sufficiently proven, it adopts a positive opinion. This is sent to the Commission to be transformed into a single market authorization valid for the whole of the European Union.

In 2001, the Committee on Orphan Medicinal Products (COMP) was established, charged with reviewing designation applications from persons or companies who intend to develop medicines for rare diseases (orphan drugs). The Committee on Herbal Medicinal Products (HMPC) was established in 2004 and provides scientific opinions on traditional herbal medicines.

A network of some 3,500 European experts underpins the scientific work of the EMEA and its committees.

Q Could you please give us an over view of the responsibilities and activities in your organization? How large is your staff and what are their qualifications?

A As head of the inspections sector, I am responsible for a team of about 18. Although some colleagues were "inspectors" in previous positions, EMEA staff does not actually perform inspections; this is the responsibility of the European inspectorates in each of the 25 member states. Of the 18 staff in the sector, eight are support staff, one with a financial degree. The remainder of the staff have degrees in the life sciences or pharmacy (four) with a range of post-graduate experience from 6 to 19 years.

My primary responsibility is to manage my staff to ensure that the objectives and performance measures outlined in EMEA's work program are achieved effectively, and that work on implementing provisions outlined in EMEA's roadmap to 2010 is begun.

The tasks of EMEA's inspection sector include the following:

- coordinating GXP and pharmacovigilance inspections for centrally authorized medicinal products
- coordinating any product defects and associated follow-up and/or recalls
- chairing and providing technical, scientific, and administrative support to quarterly meetings of inspectors (GMP, GCP) from all EU member states
- providing technical, scientific, and administrative support to the joint CHMP/CVMP quality working party
- establishing and providing secretariat to the EMEA Process Analytical Technology Team
- development/improvement of the GMP Guide and the Compilation of Community Procedures on Inspections and Exchange of Information in partnership with the European Commission
- implementation of Mutual Recognition Agreements (MRAs) on GMP
- coordinating the sampling and testing of centrally authorized products
- producing certificates of medicinal products in line with WHO recommendations
- The sector is also, in close collaboration with other EMEA sectors, responsible for the EudraCT database on clinical trials and the establishment of a European database on manufacturing authorizations and GMP certificates (EudraGMP).

Q What are your current key priorities?

A Our current key priorities reflect our core business and are outlined in the inspections' chapter of the EMEA work program for 2005.

The major priority for 2005 was to prepare for the implementation of the pharmaceutical legislative review, in particular the new requirements for GMP for starting materials and the setting-up of a database on manufacturing authorizations and GMP certificates.

Other 2005 objectives included:

- Support the implementation activities relating to GCP inspections under the Clinical Trials Directive 2001/20/EC for human medicines and the directive on GCP, in particular the implementation of the second phase of the EudraCT database.
- Support the European contribution to international discussions on GMP/quality systems in cooperation with the FDA and within the ICH and VICH framework.
- Coordinate activities in the context of the joint audit program for GMP inspectorates to ensure maintenance of consistent quality standards and harmonized approaches.
- Work on implementation of mutual recognition agreements is expected to move toward consolidation as all agreements with the exception of that with the US, become fully operational.
- Completion of the internal evaluation work with new Member States in the context of the Canadian mutual recognition agreement.
- Coordinate and manage effectively the requests for GMP, GCP, pharmacovigilance, and GLP inspections relating to applications for products through the centralized procedure within the timeframe laid down in Community law and to the standards required by the Agency's quality management system.
- Implement an action plan for revision of the sampling and testing program for centrally authorized products in cooperation with EDQM to streamline activities and focus resources taking a risk-based approach. Improve general transparency and communication between all stakeholders.
- Provide support to all 25 Member States to optimize compliance with Community requirements in relation to GMP and GCP and Pharmacovigilance, and cooperate on planning initiatives to secure the allocation of sufficient resources for the conduct of inspections throughout the EU and in third countries.

Priorities for 2006 are due to be published shortly.

Q How is your organization funded? How are the funds allocated?

A EMEA is funded by a combination of fees for scientific services (marketing authorization applications, variations, inspections, annual fees, etc.), and a contribution from the Community budget. The fee income is used to cover payments to Member States for scientific services and the coordination work done by the EMEA on product related matters. The contribution from the community budget covers much of the coordination work of the EMEA on matters such as pharmacovigilance, harmonization activities, telematics projects etc. A special fund is provided to support work on orphan medicinal products, i.e., intended for the treatment of rare diseases.

Q What is the mission for EMEA? What do you see as the challenges or barriers to achieving EMEA's goals?

A Perhaps the best way to answer this question is to quote EMEA's mission statement:

"The EMEA's Mission Statement is, in the context of a continuing globalization, to protect and promote public and animal health by developing efficient and transparent procedures to allow rapid access by users to safe and effective innovative medicines and to generic and non-prescription medicines through a single European marketing authorization, controlling the safety of medicines for humans and animals, in particular through a pharmacovigilance network and the establishment of safe limits for residues in food-producing animals, facilitating innovation and stimulating research, hence contributing to the competitiveness of EU-based pharmaceutical industry, and mobilizing and coordinating scientific resources from throughout the EU to provide high-quality evaluation of medicinal products, to advise on research and development programs, to perform inspections for ensuring fundamental GXP provisions are consistently achieved, and to provide useful and clear information to users and healthcare professionals."*

* GXP means Good Clinical Practice (GCP), Good Manufacturing practice (GMP), and Good Laboratory Practice (GLP) collectively.

Agency Partnerships and International Harmonization

Q What is your role and involvement in international harmonization? Why do you think that this is important?

A Europe has, of course, a long tradition of international harmonization between the EU member states, formally dating from the first pharmaceutical directives in 1965. In addition, the EMEA contributes to a number of international harmonization activities, particularly within the ICH and VICH frameworks. In the area of GMP, GCP, and quality related matters, international harmonization is essential as the pharmaceutical industry is a global industry, and should apply the same scientific standards irrespective of where the product is developed, tested, marketed, or produced. Due to historical reasons and different regulatory frameworks, this goal may not always be immediately achievable. International harmonization activities are important because they help to identify what the current barriers are and to develop mechanisms to resolve differences that may exist. Technical and scientific differences are generally easier to solve than regulatory differences. When it comes to international harmonization, I currently have both a personal involvement in and a role derived from my responsibilities within the EMEA. I have personally been involved with the work of the International Conference on Harmonization (ICH) since 1992. When I worked for EFPIA, I started off as Steering Committee member and ICH coordinator, and then retained the role of ICH coordinator for the best part of six years. When I moved to the European Commission, pharmaceuticals unit, I became ICH coordinator for the European Commission. I started working again within the ICH framework just after the FDA launched its GMP for the 21st Century Initiative and am currently one of the EU topic leaders for the Q9 topic on risk management.

At an organizational level, work on international harmonization within the quality and GMP area comes within the scope of the ad hoc GMP inspectors meetings, and the work of the Quality Working Party respectively and in those respects, I am responsible for coordinating the input into the various discussions from the side of the EU. Veterinary harmonization activities in the quality areas within the VICH Framework are also addressed in the Quality Working Party.

Currently, the Quality Working Party has produced a draft guideline on inhalation products jointly with Health Canada, and a number of annexes to the EU GMP guide were prepared jointly by the ad hoc GMP inspectors meetings and the Pharmaceutical Inspection Cooperation Scheme (PIC/S), which, apart from the EU member states, involves Switzerland, Canada, Australia, New Zealand, Singapore, and Malaysia.

Q There have been several Mutual Recognition Agreements (MRAs) signed over the past few years – what benefits have these achieved? Do you envisage that there will ever be such an agreement between Europe and the US?

A EU has signed MRAs in the GMP area with Canada, Australia, New Zealand, US, Switzerland, and Japan. Apart from the MRA with the US, which is not operational, all of these MRAs have been extremely beneficial for the EU. The MRAs are dependent on the recognition of equivalent GMP standards in the regions concerned, and mean that the results of GMP inspections by an MRA partner can be accepted within the EU framework and vice verse and that no retesting of each batch that enters the EU is required. The benefits for EU regulators include the saving of resources as additional inspections need not be performed and the focus of foreign inspection programs can be on areas of higher risk. From the industry side, less regulatory inspections need to be hosted and the expense of re-

testing can be avoided. e.g., Switzerland figures.

In addition to the immediate resource benefits for both industry and regulators, the MRAs include provisions for exchange of information on quality defects, alerts, and recalls which help to ensure that coordinated approaches to responses are taken and that patients can be protected at a global level. They also provide for annual maintenance programs so that all partners are aware of regulatory or organizational changes that may have an impact on the agreements.

While there is a common basic framework, all the MRAs differ slightly with respect to the implementation details. Contrary to popular belief, a Mutual Recognition Agreement between the US and the EU was actually signed in May 1998. However, in the GMP area, this provided for a three year transitional or confidence building phase, which was never actually completed, therefore rendering the agreement non-operational from the point of view of recognition of inspection outcomes. However, exchange of information on defects and alerts continues to take place.

Business Strategies/Vision

Q What do you think the major barriers are for you and other regulators?

A Availability of resources, effective implementation of risk management principles in the interests of patients, and developing communication networks so that issues such as fraud and counterfeiting can be tackled in a global framework.

Q What is the long term vision for EMEA?

A The long term vision of the EMEA is outlined in EMEA's Roadmap to 2010 and key aspects of this are reproduced below:

The main challenge for the EMEA over the next few years will be its ability to meet the increasing expectations of its stakeholders. The Agency will particularly focus on the needs and expectations of patients and users of medicines. The EMEA will have to find the right balance in terms of expectations such as applying high scientific knowledge for the timely delivery of science based opinions, increased involvement in the protection and promotion of public and animal health, regulatory and scientific consistency, predictability, greater transparency, better information, and enhanced communication.

In addition, the EMEA will have to address issues stemming from the Lisbon strategy for economic, social, and environmental renewal since the Agency's role in enabling the pharmaceutical industry to achieve the objective of industrial competitiveness is crucial. The EMEA has an essential role in bringing safe and effective innovative medicines as quickly as possible to patients and users of medicines. Apart from economic competitiveness, the EMEA also contributes to the EU citizens' quality of life. In responding to the above challenges, the Agency will have to adequately address:

1. additional tasks allocated to the EMEA in accordance with new Community legislation
2. new developments such as the perception of the safety of medicines and the environmental impact of the use of medicines
3. the assessment of new types of products (such as gene therapy, pharmacogenomics, proteomics, xenotransplants)
4. bi/multilateral scientific cooperations

In addition, specific segments of the pharmaceutical market deserve special attention, such as Small and Medium-sized Enterprises (SMEs).

The EU Regulatory System concept requires the EMEA to find adequate answers to the above challenges in close cooperation with its Member State partners. Therefore, the continuation and adaptation of the Agency's networking model also will require that MSs are able to adequately respond to the changing environment, which will result from the political, institutional, legislative, and scientific developments. In order for the EU Regulatory System to position itself successfully in the international environment as one of the world's foremost regulatory systems, NCAs should carefully examine how they can best contribute to the future system since this will be key for the overall success. It should be emphasized that the network between the EMEA and NCAs can only be optimized if there is a stronger cohesion between all parties concerned, looking at complementing the achievements already obtained by introducing further actions aiming at reinforcing the networking model. In order to achieve such aims, a common understanding on the architecture of the future EU Regulatory System is paramount. Once such common understanding has been obtained, in a next step, important issues such as roles and responsibilities (in different fields such as regulatory, scientific, organizational, and technical), of all involved parties need to be addressed in order to reach complete transparency on the accountability for the different activities to be undertaken in the context of the EU Regulatory System.

Leadership Style

Q What type of strategy works best for the management of a regulatory agency?

A First let's be clear, I don't manage a regulatory agency, I manage a small sector within a regulatory agency and I can only comment from my own experience. I think it is very important to realize that, in general, the tasks of a regulatory agency are laid down by legislation and the funding of activities is very tightly controlled. In the case of the EMEA, this means through oversight of its management board, the European Commission, and the European parliament. This means that the planning and budgeting process tends to become part of a negotiation process rather than as much of a management tool as would be the case in an operations management company.

I also think working in a European multicultural environment is a unique challenge that requires specific adap-

tation of management skills. Out of my 18 co-workers, I have representatives from nine different European countries with three countries being dominant in terms of numbers. I am very lucky to have a great team working for me, all highly motivated and with excellent experience. I try to be as non-interventionist as possible, as long as results are achieved and performance standards are met, I would leave it up to the individuals to decide how to meet the goals of the organization. I have regular bilateral meetings with all of my professional staff and if there are issues or difficulties, I may suggest that focused brainstorming meetings on specific topics be organized. Personal feedback on performance matters also is very important.

I am passionate about efficiency, avoidance of as much bureaucracy and duplication as possible, "not reinventing the wheel," and transparency so I try to encourage integrated thinking and learning from others' experiences.

I think I have learned a lot about management styles in every aspect of my career and I try to use my training and experience in my current position. The first priority is to listen to what other people have to say; there are always new ideas that may be useful. People with different backgrounds and different cultures have different perspectives so that there can be no assumption that there is "one right way" of doing things. It is impossible to impose solutions without "buy in." This applies equally to my own staff, other staff of the Agency, as well as in the context of inspection coordination, and harmonization activities involving EU member states. It also is extremely important to be transparent – I have seen too much resentment and distrust develop from lack of communication.

Finally, I think one of the keys to effective management and getting things done is never ceasing to believe that mountains can be moved if this is what is necessary to make things better. And no matter how slow or hard it is, never to give up!

Manufacturing/ Operations Inspections

Q The US FDA believes that developers and manufacturers need to increase efficiencies and recently issued a guideline on Process Analytical Technology (PAT) which aligns with their Initiative for the 21st Century. Is EMEA working on something similar?

Part of the PAT initiative involves using new technologies (i.e., on-line sensors, advanced controls, etc.) with the ultimate goal of improving process efficiencies and product quality. How do you see new technologies impacting the future? If so, what types and how?

A Let me tell you a bit about the work of the EMEA PAT team. Over the last two years, the EMEA has done a lot of work to support and develop the PAT concept within the EU regulatory framework. This has included the organization of focused combined meeting of assessors and inspectors from all 25 member states, inviting a number of companies to present to this group on the status of their activities, and the subsequent establishment of an EMEA PAT team made up of assessors and inspectors and the chairs of the QWP and Ad Hoc GMP inspectors groups respectively. We organized a specific and dedicated PAT training session for inspector and assessors in October 2004 and a second training session is planned shortly.

In order to support the PAT activities in EU, an EMEA PAT team was created in November 2003. It is a forum for dialogue and understanding between the Quality Working Party and the Ad Hoc Group of GMP Inspection Services with the aim to review the implications of PAT and to ensure that the European regulatory framework and the authorities are prepared for and adequately equipped to conduct thorough and effective evaluations of PAT-based submissions. The team's mandate provides further information on the make-up and aims of the team. The meeting is chaired by Dr. Keith Pugh of the UK regulatory authority and nine meetings have taken place since the end of 2003.

Part of the work of the PAT team has involved an open invitation to companies to provide us with mock PAT submissions. In association with these, we have organized two specific site visits.

The team has examined the FDA guidance document, and indicated that the EU is in general agreement with the principles outlined. For this reason, the value of a specific EU guidance document, which would have outlined much of the same philosophy, was questionable. However, the PAT team has developed some simple questions and answers that may be more specifically applicable in a EU context and continues to work on expanding these. All these are published on the Process Analytical Technology section of the EMEA's Web site.

The key message we would like to stress is that the current regulatory framework in Europe is open to the implementation of PAT in marketing authorization applications, and that all efforts to facilitate these applications will be made.

Regulatory, Quality, and Political Concerns

Q What involvement does EMEA have in anti-counterfeiting?

A The national competent authorities of the EU member states are engaged in the prevention and detection of counterfeit medicines into the legitimate supply chain. EMEA has no legislative role in this area, but we fully support the work of the member states. The European Heads of Medicines Agencies have established a bi-annual meeting of European Medicines Enforcement Officers (EMEO). EMEA attends this meeting and provides a liaison between the EMEO and the GMP inspectors meetings.

The establishment of this group provides a formal method of developing further the close liaison and cooperation between the EU agencies, as well as a mechanism for dissemination of information, the establishment of common objectives, and the development of training programs in the area of enforcement. The EMEO are currently

surveying the extent of the problem of counterfeit medicines in the EU legitimate supply chain and have been asked by the Heads of Medicines Agencies to develop an EU wide anti-counterfeiting strategy.

Industry, Government, and ISPE

Q What is your involvment with ISPE? When did you first encounter ISPE?

A The inspections sector of the EMEA has been involved in interactions with ISPE since shortly after its establishement in 1995. Since I joined as head of sector, I have continued this collaboration and committed to provide EMEA speakers to key ISPE events, as well as ensuring the voice of ISPE is heard in consultation on guidelines and relevant interested parties meetings. I think my first personal encounter with ISPE was in Brussels when I worked for EFPIA.

"Good traceability yields benefits" – guidance from the GAMP® Forum on achieving the correct level of traceability between requirements, design, and testing documents for regulated GxP applications.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
January/February 2006, Vol. 26 No. 1

GAMP® Traceability for GxP Regulated Applications

The purpose of this document is to provide guidance on how to achieve an appropriate level of traceability between requirements, design, and testing documents for regulated GxP applications. Although the expectation for traceability by regulatory authorities has been clearly stated,[1,2] there is little definitive guidance on the practicalities of achieving and sustaining traceability.[3]

This guidance addresses this gap and should be treated as a supplement to GAMP® 4, GAMP® Guide for Validation of Automation Systems.[4]

Principles

Processes and supporting documentation should be established and maintained to link requirements, design, and testing. In addition, it should be possible to trace back from testing to both design and requirements - *Figure 1*. This traceability provides a means to ensure that all elements of design, as well as all requirements, have been tested. It also enables the identification and flow of documentation in the event of requests during an audit.

The linkage between requirements, design, and testing is not necessarily limited to a 1:1:1 relationship:

- Multiple requirements may be covered by a single design specification and tested by a single test.
- Multiple design specifications may be linked to a single requirement.
- Multiple tests may be required to address one requirement or one design specification.

Whatever process is used to achieve traceability, it should be:

- appropriate to the system size, complexity, impact, and risk
- documented and approved in the validation planning stage
- an integrated part of the overall life cycle of the project and beyond into the support and maintenance of the system

Benefits of Traceability

Good traceability yields a number of tangible and intangible benefits. Examples include:

- Traceability will assist risk management. Focus should be placed on any critical requirements as part of the risk assessment. Traceability will help to identify critical design elements and necessary testing. There should be increased testing rigor applied to the critical aspects of a system, compared to the non-critical aspects of the system.
- Traceability will improve test coverage. Traceability should make it possible to demonstrate which requirements and design elements are tested. Therefore, duplicate or redundant testing may be avoided.
- Traceability can help demonstrate that validation is complete. All requirements should be functionally tested, covered by an audit, handled through a user operating procedure, or accepted as not requiring testing, and monitored in the live environment.

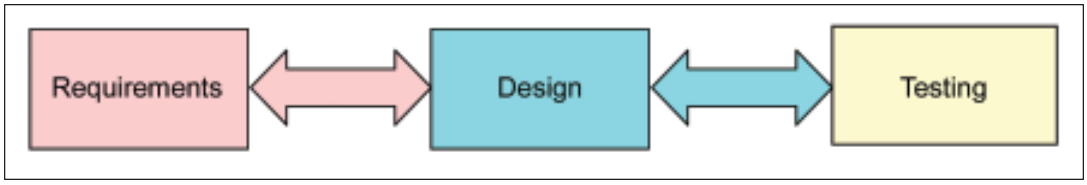

Figure 1. Principles of Traceability.

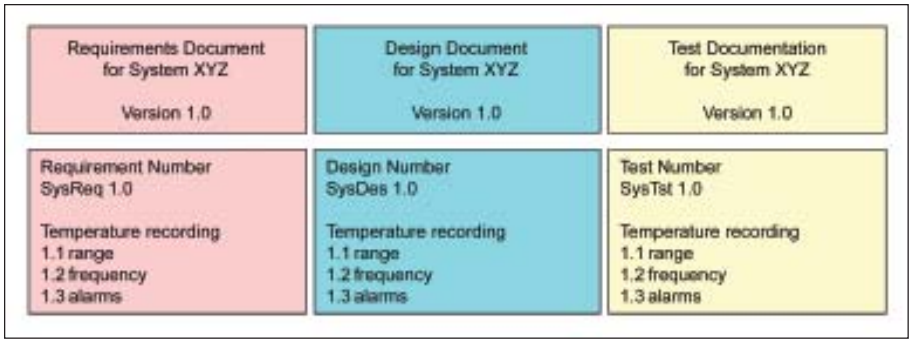

Figure 2. Example of embedded traceability for simple systems.

- Traceability will improve change management. When a change control is raised, traceability enables an accurate assessment of its impact by identifying related requirements, design elements, and test scripts. Regression testing can thereby be clearly scoped.

- Traceability will help root cause analysis of software malfunctions. It should be possible to more easily track and trace design element interdependencies when conducting root cause analysis of incidents attributable to software malfunction.

- Traceability will help audits and inspections. It should be relatively easy to identify any and all supporting documentation for any given operation. It should be much easier to provide timely responses to requests for information.

Methods of Achieving Traceability

Traceability may be achieved in a number of ways, including:

- a Requirements Traceability Matrix (RTM)

- automated software tools

- excel spreadsheets

- embedding references directly within documents

If an RTM is chosen, it may be generated as a separate deliverable or as part of an existing deliverable, such as the requirement document: the choice will be dependant upon maintainability of the deliverable.

Traceability for simpler systems may be achieved through common or consistent numbering of requirements, design statements, and testing - *Figure 2*. The numbering for "temperature recording" in this example is the same in the requirements, design, and test documentation; thereby enabling traceability without creating a separate traceability matrix. This approach works well with smaller systems in low risk situations.

For purely Commercial Off-the-Shelf (COTS) software products, the traceability may be reduced to that of requirements to testing (or qualification) only. However, this will depend upon the user's knowledge of the supplier and their processes, the system usage within the company, and the level of acceptable risk. In most cases, the design column in Figure 2 could be replaced with a link to configuration items, providing traceability between requirements, configuration, and testing (or qualification).

The user of the COTS software products will need to be able to demonstrate an intimate knowledge of the supplier's quality process, as a mitigation of risk to the user processes when using the COTS system. This may necessitate multiple visits to the supplier during the project phase, as risks are identified at points throughout the project, and during the ongoing contact of the support and maintenance phases of the system life cycle.

The depth or granularity of the requirements will be influenced by the size and complexity of the system, along with its potential to impact drug product:

- Safety

- Identity

- Strength

- Purity

- Quality

This granularity will influence the need for the traceability matrix and its contents; the greater the granularity the larger the matrix, and therefore, the greater the need for a tool to maintain the matrix.

An example Requirements Traceability Matrix (RTM) is shown in - *Figure 3*. Each reference within the traceability matrix, e.g., U1.1.2, F3.1, D1.2, T8.2, could be a reference to a section or subsection within the relevant document, or to a totally separate document. The method used and the process should have been declared and approved within the validation plan.

Level of Detail Practicalities

It can be difficult to determine the level of detail required for traceability. The following information is intended to help pitch the detail at a level which satisfies regulatory expectations for traceability, while remaining practical to maintain.

A strategy for traceability should be established during validation planning. User requirements should be developed with traceability in mind.

The level of traceability could stop with a reference to vendor documentation; if documentation needs are met by the vendor documentation when supported by in-depth supplier assessment and a vendor management plan.

The supplier should have their own traceability for the documentation and testing under their control. This should be verified during Supplier Assessments, where appropriate.

Requirements need not trace to technical controls in all circumstances. Requirements may trace to procedural controls, in which case cross-references to identified SOPs is appropriate.

- For simple systems, an RTM is not recommended, as sufficient trace-

ability may be incorporated within document cross-references.

For global systems, planning for traceability in the validation plan is imperative since the control of local and global requirements needs to be resolved at this point for tracking the combination of local and global requirements.

Extending RTMs

There are other features that may be added to a basic traceability matrix that can assist with the overall effectiveness and efficiency of validation activities. Examples include:

- A column to include a brief written description of each requirement, which may assist in the verification that matrix contents are referenced correctly.
- A column to include change control numbers to enable tracking the system history and change impact. Reference also may be made to other documentation and processes which impact the system, such as deviations or SOP changes.
- A column to indicate the criticality of the requirements to assist levels of testing applied to any given requirement. High criticality requirements may have greater testing applied; therefore, may reference multiple tests, whereas low critical requirements may have a reference to a single test. There may be a need to reference the executed tests and the supporting test result documentation along with any failed tests.
- A column to indicate where a requirement has been met by procedural controls, along with the reference to the procedure and its version number. In this case, the requirement and design columns should be blank, but the testing column may not, as the use of the procedure may be tested at the system test level.
- The test column may be expanded to indicate at what level the testing occurs: unit, integration, acceptance (hardware or system) or where and when the testing occurs, development, qualification, production, or global, local. In this case, the level of effort in testing should relate to the criticality of the requirement and the level of acceptable risk. For example, a high-risk requirement may be tested many times and at many levels, whereas a medium risk requirement may be tested just once, and a low risk may not be tested at all, only verified through system use.
- A column linking a test to a maintenance or calibration record for the instrument required for a test and requirement. For process automation documents such as installation records, loop checks and tuning, cable integrity checks may be linked, enabling traceability from the calibration certification on an instrument all the way through to the use of that measurement in the business process and system testing.

The above additions increase the difficulty of navigating and maintaining the traceability matrix. Therefore there needs to be a balance between what is expected of the traceability matrix and the maintainability of the method chosen. Where large projects are being installed, such as ERP/MRP II, LIMS/CDS, or large process control systems, it may be prudent to seek out a document management system which has the capability to both maintain the links between documents within the document management system and references to documents generated and stored outside.

Documentation and Maintenance of Traceability

The chosen process and method which any given system will use for traceability should be documented and understood. It is recommended that this be achieved within the validation plan for smaller systems, or perhaps proceduralized for larger and more complex systems. All members of a system development team should be acquainted with the process and method to ensure that it is adopted and maintained throughout the system development life cycle.

Once a system has been accepted into use, the maintenance of traceability is required to preserve its usefulness. The method of maintenance will always be linked to whatever process is used to maintain the requirements, design, and test documentation, all of which must be updated to reflect the current system. In addition, the version control may be linked to enable system configuration controls, e.g., version 1.0 of the requirements, design, test, and traceability are in use at go-live of any system, then all versions may be increased at the same time to maintain this configuration control periodically throughout the system life cycle.

Whatever changes are made to the documentation they will be controlled through the control of a change process. Within this process, the method by which the documents will be updated should be documented, for example:

- at every change
- with a number of changes batched together
- on a chronological basis

Requirements	Design		Testing
	Functional Specification	Design Specification	
U1.1.1	F2.4.1	D2.5	T1.1
U1.1.2	F2.4.5	D2.4	T1.1
U1.2.1	F3.1	D1.1	T2.3.1
U1.2.2	F3.2	D1.2	T8.1
U1.2.3	F3.3	D3.3	T8.2

Figure 3. Example Requirements Traceability Matrix (RTM).

The method should be justified within the process and based upon documented and reasoned risk.

Conclusion

Although traceability is a valuable tool for any system, its scope, depth, granularity, and level of detail should be commensurate with the criticality and risk associated with the business process being controlled by the system. If traceability is sized correctly it may be the one tool which can influence the success of the project, support and maintenance, and 'auditability.' However, like any other tool it can achieve this success only if it is maintained throughout the system life cycle.

References

1. PIC/S Guidance on Good Practices for Computerised Systems in Regulated "GxP" Environments (PI011-2) (available at www.picscheme.org).

2. FDA, 'General Principles of Software Validation: Final Guidance to Industry and FDA Staff,' published in 2002 by the Food and Drug Administration's Center for Devices and Radiological Health (CDRH), (www.fda.gov)

3. Wingate, G.A.S. (Editor), 'Computer Systems Validation: Quality Assurance, Risk Management, and Regulatory Compliance for Pharmaceutical and Healthcare Companies,' published in 2003 by Taylor and Francis (www.crcpress.com), ISBN 0-8493-1817-8.

4. *GAMP® 4, Good Automated Manufacturing Practice (GAMP®) Guide for Validation of Automated Systems*, International Society for Pharmaceutical Engineering (ISPE), Fourth Edition, December 2001, www.ispe.org.

Acknowledgements

The GAMP Forum would like to thank Scott Lewis (Eli Lilly), Guy Wingate (GlaxoSmithKline), and Mark Cherry (AstraZeneca) for leading the development of this guidance.

Country Profile

A look at the Pharmaceutical Industry in

THAILAND

Produced in collaboration with ISPE Thailand

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
January/February 2006, Vol. 26 No. 1

ENGINEERING PHARMACEUTICAL INNOVATION ISPE

Dear ISPE Members,

It is my pleasure to present the Thailand Country Profile on behalf of the ISPE Thailand Affiliate for this issue of Pharmaceutical Engineering. Thailand is an active participant within the rapidly changing and developing ASEAN region and is ideally placed to take advantage of the exciting and ever increasing opportunities of the region, its neighbors, and the world.

Thailand has both a rich cultural heritage full of proud achievements and an ambitious outlook to further development that will be accomplished using the resourceful and entrepreneurial nature of her people. Thailand has successfully rebounded after the financial crisis of the late '90s and external investment is steadily increasing. Consistent financial growth, social stability, her close relations with surrounding countries, and an experienced and well educated labor pool are all hallmarks of Thailand's potency.

I hope you will be interested enough by this Country Profile to consider Thailand as your base for investment in manufacturing, research, and development.

Yours truly,

Chernporn Tengamnuay

Chairman
ISPE Thailand Affiliate

For more information, please visit the ISPE Thailand Affliate's Web site at www.ispeth.org or contact:

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This feature in *Pharmaceutical Engineering* is designed so that you can tear it out, three hole drill (if desired), and keep it with other Country Profiles as they are published.

Look for the Country Profile on Argentina in the March/April issue of *Pharmaceutical Engineering*.

A Look at Thailand: History and Financial Profile

Introduction

"The land of smiles" as Thailand is often referred, is famous for her variety of beautiful nature and rich culture. It's also known for its ancient ruins, fine arts and handicrafts, delicious food, and the contagious warmth of the Thai people.

A unified Thai kingdom was established in the mid-14th century. Known as Siam until 1939, Thailand is the only Southeast Asian country never to have been taken over by a European power. A bloodless revolution in 1932 led to a constitutional monarchy and since 1946 King Bhumibol Adulyadej, also known as Rama IX, is the Chief of State.

Thailand has an area of 513,254 sq km. It is situated in the heart of Southeast Asia, and shares borders with Myanmar in the West, Laos in the Northeast, Cambodia in the Southeast, and Malaysia in the South. Bangkok is the capital city and center of political, commercial, industrial, and culture activities. It is the largest city with approximately one sixth of the Thai population of roughly 64.5 million. Thailand is home to various ethnic groups with the largest being Thai and Chinese with 75% and 14% respectively.

Thailand is a participant in international organizations like the Association of Southeast Asian Nations (ASEAN), the United Nations (UN), the United Nations Educational, Scientific, and Cultural Organization (UNESCO), the World Health Organization (WHO), and the World Trade Organization (WTO).

In the past three decades, the overall physical health indicators for Thai people have been improving. For instance, life expectancy at birth has increased from 59 years in 1964 to 71 years in 2004 (Source: National Statistical Office). Significant improvements in the quality and standard of the Thai healthcare system have contributed immensely to this success. The country's healthcare system has evolved from a system dependent and built on local wisdom to one that relies heavily on technology and collaborative efforts of healthcare professionals from multiple disciplines.

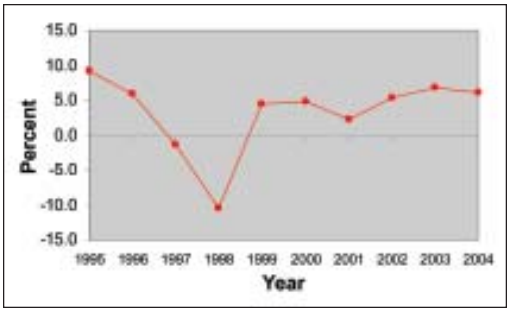


Figure 1. Real GDP Growth %. (Source: National Statistical Office, 2004)

Thailand ranks as the world's fourth most attractive nation for foreign investment in a survey by the UN Commission for Trade and Development in 2004. Thailand enjoys a strategic location right at the heart of Asia – home to what is regarded today as the largest growing economic market. It serves as a gateway to Southeast Asia and the Greater Mekong sub-region, where newly emerging markets offer great business potential.

Financial

Thailand has a well developed infrastructure and a free-enterprise economy. She has fully recovered from the 1997-98 Asian Financial Crisis and was one of East Asia's best performers in 2002-04. Increased consumption, investment spending, and strong export growth pushed the Gross Domestic Product (GDP) growth up to 6.9% in 2003 and 6.1% in 2004. The growth outlook for 2005 is set to remain impressive, despite a sluggish global economy and the tragic 2004 tsunami that took 8,500 lives in Thailand and caused massive destruction in the southern provinces.

The highly popular government lead by Taksin Chinnawat has pursued preferential trade agree-

Member	Land Area (sq. Km)	Population (thousand)	GDP (million US$)	GDP/Head in US$	Population per sq.km	monthly US$
Thailand	513,254	64,469	163,525	2,536	126	211
Cambodia	181,035	13,589	4,517	332	75	28
Indonesia	1,890,754	216,410	258,266	1,193	114	99
Laos	236,800	5,760	2,439	423	24	35
Malaysia	330,257	25,580	117,776	4,604	77	384
Myanmar	676,577	54,745	10,463	191	81	16
Philippines	300,000	82,664	86,407	1,045	276	87
Singapore	697.0	4,240	106,884	25,208	6,083	2,101
Vietnam	330,363	82,022	45,277	552	248	46
ASEAN	4,465,502	549,852	800,735	1,456	123	

Rank Order - GDP (purchasing power parity):
20th in the world Thailand $ 524,800,000,000 2004 est.

Rank Order - GDP - real growth rate:
46th in the world Thailand 6.10% 2004 est.

Rank Order - GDP - per capita:
93rd in the world Thailand $ 8,100 2004 est.

Rank Order - Industrial production growth rate
37th in the world Thailand 8.50% 2004 est.

Figure 2. Thailand fact sheet. (Source: CIA factbook, 2005)

Continued on page 10.

Thailand Pharmaceutical Industry Overview

Market Size and Growth

The Thai pharmaceutical market has a current value of $1.32 billion. IMS Health has projected that Thailand will soon join China as one of the fastest growing areas for pharmaceuticals. Figures for 2004 show that the market has grown by 6% from 2003.

Key Data	Value	Year	World Ranking
Pharmaceutical Market (US$ millions)	1,320	2004	33
Pharmaceutical Market per capita (US$)	21	2004	54
Market Growth (%)	6	2004	-----

Table A. Market overview. (Source: Espicom Business Intelligence, 2004)

The pharmaceutical spend per capita in Asia is forecast to continue its strong growth, and Thailand has one of the highest growth rates which was 19 million US$ in 2004 and projected to be 36 million US$ by 2009 (Source: IMS Health, 2005). The largest share of the Thai market for pharmaceuticals is occupied by locally made products according to IMS Health, 2005.

Of the total market share, locally produced products amount to 65% with imported goods back up toward pre-financial crisis levels at 35%. This local growth also has been reflected in the local manufactures with strong increases at 14% in 2002 compared against 11% for foreign based companies (Source: Diethelm, 2003).

Healthcare

Thailand has a universal healthcare scheme that is in place since 2001 allowing Thai citizen's greater access to medical services. The popular scheme setup by the government is expected to be further funded with taxes on cigarettes and alcohol sales. Currently, more than 95% of the population has health security in Thailand with an increase of 2.85% in 2004 (Source: IMS Health, 2005). However, there have been some negative impacts attributed to the scheme on the finances and number of medical staff leaving state hospitals.

Pharmaceutical Manufacturing in Thailand

In Thailand, there are three categories of drug manufacturers:

1. Multinational corporations: manufacture active ingredients and pharmaceutical formulations in their own manufacturing facilities
2. 171 privately-owned Thai companies: primary focus is on producing pharmaceutical formulations and to a smaller extent, manufacturing active ingredients
3. One Government-owned Thai company: the Government Pharmaceutical Organization (GPO), which primarily prepares pharmaceutical formulations for public medical establishments

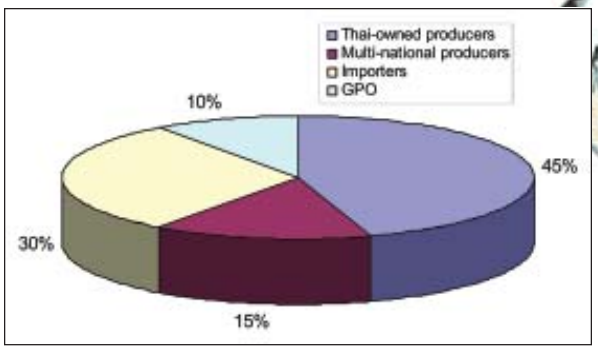
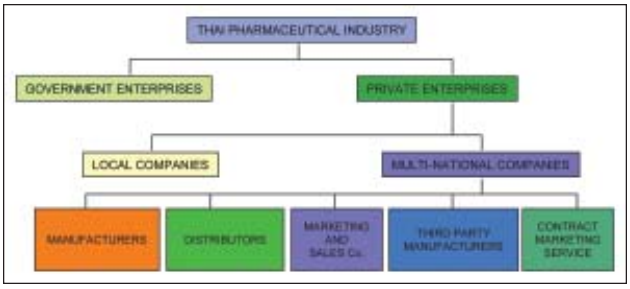


Figure 1. Share of market by manufacturers. (Source: International Trade Centre UNCTAD/WTO, 1999)

Market leaders include: Pfizer Inter. Corp., Siam Bhaesaj Co., GSK, GPO, Biolab, Aventis Pharma, AstraZeneca, Novartis, Berlin Pharma, and Roche (Source: Diethelm 2003).



Industry structure.

Distribution

Access to pharmaceutical products for the consumer is mainly through the general and specialist hospitals in Thailand. The distribution of manufactured drugs is through independent distributors or self distributed by the manufacturers themselves.

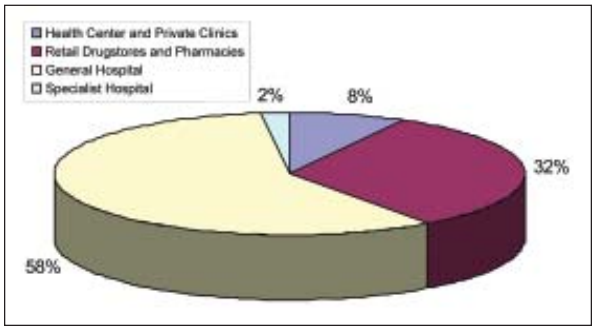


Figure 2. Pharmaceutical distribution at the point of consumption. (Source: Diethelm, 2002)

Thailand: Moving Forward in Biotechnology

by Dr.Thanit (on behalf of Prof. Dr Morakot Tunticharoen, Director, National Center for Genetic Engineering and Biotechnology)

Like other countries in Southeast Asia, Thailand's biotechnology has been rapidly developed in the last two decades as a result of government backing. Biotechnology is a priority sector for the country; therefore, it is receiving soaring financial support. Biotechnological activities can be found in many research institutes and universities throughout the country. One of the institutes supporting biotechnology development in Thailand is the National Center for Genetic Engineering and Biotechnology (BIOTEC). BIOTEC provides resources for the country to support Thailand's development of biotechnology. This can be achieved through conducting R&D projects, facilitating the transfer of advanced technologies from overseas, developing human resources at all levels, providing information services, developing collaboration with world class institutes, and promoting public understanding of the benefits of biotechnology.

Strong Political Support for the Promising Future of Biotechnology

Reinforcing biotechnological development, Thailand has formulated the National Biotechnology Policy Framework in line with the government's policy to promote sufficiency of living and enhancement of competitiveness for the country, toward a proper balance and direction. One of the six goals for biotechnological development in Thailand is that Thailand represents a Healthy Community and Healthcare Center of Asia. With this political back-up, the country is anticipated to drive biotechnology forward with a speedy pace. And this also will guarantee any necessary support for investment in biotechnology.

Figure 1. National Center for Genetic Engineering and Biotechnology.

Key Factors for Pharmaceutical Success: Infrastructure and Skilled Research Personnel

Recognizing that research and development is a driving force for pharmaceutical success, Thailand has developed a variety of scientific infrastructures. The 323,748.5 Sq Metres Thailand Science Park (TSP) is a landmark government initiative. It was built with an initial investment of $175 million. TSP provides main laboratories, incubator units, pilot plants, greenhouses, and accommodations, as well as financial, management, and legal support for TSP customers. The TSP also offers long term leases of land for construction and ready made wet-lab space for rent.

Skilled research personnel is another key workforce of biotechnological development. Most universities in Thailand have educational programs in biotechnology at all levels, ranging from bachelor to doctoral degrees. The development of the qualified human resource system is one goal under the National Biotechnology Policy Framework. This aims that in the year 2011 Thailand will produce no less than 5,000 professional biotechnology researchers, no less than 500 biotechnology managers, and no less than 10,000 students. On average, Thailand can produce 400 Bachelor's degrees, 150 Master's degrees, and 10 Doctoral degrees with the growth of 10% per year. Also, the Thai government has sent Thai students to study biotechnology overseas. The first two phases (1990 -1995) aim to produce approximately 330 biotechnologists, whereas the third phase anticipates to see 370 graduates.

World Class Research and Development Initiatives

Thailand has initiated many world class R&D projects in biotechnology:

1. Thailand SNP Discovery Program

BIOTEC and Centre Nationale de

Figure 2. Thailand Science Park.

Continued on page 6.

Thailand: Moving Forward in Biotechnology

Continued from page 5.

Genotypage (CNG), in cooperation with the national collaborators, namely Ramatibodi hospital, Rajanukul Institute, and Chulalongkorn University have initiated a collaborative project with an aim to analyze candidate DNA samples from 32 healthy Thai volunteers. The resulting information is curate in Thailand SNP database (ThaiSNP) that could serve as a reference for various SNP spin-off projects. For example, there are several research attempts to study multi-factorial genetic influenced diseases endemic greatly in Thailand, including the investigation of genetic susceptibility to clinical malaria or the search for biomarkers in the development of genetic tests for the prevention of osteoporosis.

To assist these spin-offs, the SNP discovery process covers mainly SNPs inside a certain group of genes believed to be associated with important diseases such as cancer, cardiovascular, SLE, and others. Exonic regions are the main coverage inside these genes. The Thai SNP database also hosts SNP data from public domains such as dbSNP (NCBI) and JSNP (Japan SNP). This allows us to compare SNP properties across different populations. This database also will serve as a basis for Thailand's future research programs in systematic genome screening, pharmaco-genomics, and anthropology. The Thai SNP database also will be used for the Asian SNP consortium as a contribution from Thailand. The preliminary analysis of this data is being conducted by providing bioinformatic Web-based applications for interested researchers. Examples include tools for designing SNP-free primers and tools for inferring a consensus haplotype of SNP from various haplotype inference algorithms. With these current features, ThaiSNP database project can host more SNP information from submitters, which will then better ThaiSNP allelotype mapping. In parallel to this database project, an automatic SNP discovery program is being developed. Based on a direct SNP discovery method, this tool can reduce the time researchers spend on correctly identifying SNPs or mutations from input Chromatogram traces. Furthermore, if successful, this SNP discovery tool has good potential in being commercialized.

2. From Biodiversity to Drug Discovery Program

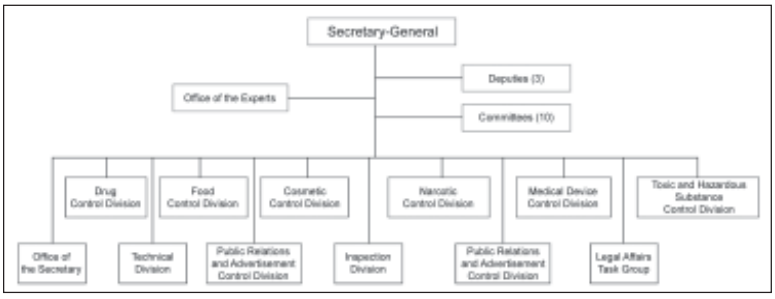
Thais have a long tradition of using nature as a healing tool. Medicinal plants and other remedies from nature have played a vital role and are still important even today. With the advance of scientific methods, Thai scientists started searching for biological active ingredients that confer beneficial activities more than 40 years ago. At that time, the main objective and most activities were confined to identifying new chemical compounds from medicinal plants and reporting the results in scientific publications. Many new compounds were reported, but none have been further developed into modern drugs even though there were many scientists working in this field. The major obstacle was that these 'newly discovered' chemicals did not show beneficial biological activities like those found in medicinal plants or natural remedies. In general, biological assays that should guide every step of the fractionation process have not been used as part of the isolation and identification. Although some scientists have conducted biological assays which offer a better chance of finding potentially useful compounds, most of the assays are low throughput, and thus greatly reduces the probability of success. In 1997, the National Center for Genetic Engineering and Biotechnology (BIOTEC) established the Bioassay laboratory to systematically screen natural products for different biological activities in a rapid and cost effective manner. The service was first offered to BIOTEC's in-house research group, which focuses on identifying compounds from microorganisms as well as plants using bioassay guided isolation techniques. The number of assays has been subsequently expanded and the service has been offered to scientists within the country and even to foreign researchers. Currently, the discovery of lead compounds from natural resources in Thailand has been conducted more systematically and a number of compounds with relevant biological activities have been discovered which has allowed the private sector or international agencies such as WHO with drug development experience to have access and evaluate them for commercial potential or for the good of humanity. In addition, in the last seven to eight years, the focus of biological resources has shifted from plants to other organisms, such as fungi, bacteria, and marine organisms. This trend has greatly increased opportunities for finding new active compounds beyond those from plants alone. Currently, Thailand is utilizing recent advances in biotechnology that have accelerated the discovery of new drug targets that can be incorporated into biological assays, as well as new techniques to make the existing assays more sensitive, less time consuming, and more cost efficient. With these improvements in the lead discovery process, we aim to be more internationally competitive employing our existing wealth of biological resources.

Pharmaceutical Regulations in Thailand

by Dr. Nithima (on behalf of Wilai Bundittanukul, Director of Drug Div., Thai FDA)

Overview

Thailand's Food and Drug Administration (FDA) is one of the departments under the Ministry of Public Health (MOPH). It is a national agency responsible for six health products, i.e., foods, drugs, cosmetics, narcotic/psychotropic substances, toxic and hazardous/volatile substances, and medical devices.



Organizational structure of the Thai FDA.

In relation to pharmaceutical products, the Thai FDA has consulted or cooperated with experts in science, medicine, pharmacy and public health, consumers, manufacturers, importers, distributors and retailers of drugs. It works closely with several other organizations (e.g., universities, industries, hospitals, healthcare professional groups, consumer groups, other relevant agencies, and foreign governments) in the drug development and review processes.

Its mission continues to be protecting the public health by assuring the safety, efficacy, and quality of pharmaceutical and biological products. It also is responsible for advancing the public health by helping technological development and researches to make medicines more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines to improve their health.

Drug Laws and Committees

To achieve the mission in consumer health protection, the FDA functions under the Drug Act BE 2510 (1967). The 1967 Drug Act has been employed for almost two decades and it has quite substantially improved all aspects of drug control. However, four more revisions subsequently emerged in order to cope with the growth of the pharmaceutical industry and the global situation. In the future, a new Drug Act will be promulgated to supersede the 1967 Drug Act. When the new Act becomes effective, many features will be changed accordingly, for example: reclassification of medicines, renewal of product licenses, establishment of product liability, revision process of Good Manufacturing Practice (GMP), and practices of pharmacists and prescribers.

The FDA is not a stand-alone Agency, but works closely with the Drug Committee, which is appointed by the Minister of Public Health every two years to advise him/her on both regulatory and technical aspects concerning the administration of pharmaceutical control. The committee also is authorized to approve or withdraw pharmaceutical registration, standard specifications, criteria and guidelines, including suspending or withdrawal of licenses to manufacture, import, distribute, or sell. There are 14 regular members on the Drug Committee: five of them being ex-officio members who are appointed based on their positions in pharmaceutical-related organizations and the others being appointed from among pharmaceutical and medical experts. The Committee can then appoint subcommittees to assist them with certain tasks. Presently, 19 subcommittees have been appointed.

Pharmaceutical Control System

The pharmaceutical control system is divided into two phases: **pre-marketing** and **post-marketing.** The pre-marketing phase involves licensing regulations (regarding manufacturing, importing, or selling pharmaceutical products), drug registration, and drug advertising regulation. The post-marketing phase focuses on surveillance activities (e.g., inspection of GMP compliance at manufacturing sites, adverse drug reactions, monitoring the use of marketed drugs for unexpected health risks), responding to consumer complaints, and reevaluation of pharmaceutical products.

Pre-Marketing Phase

Licensing

The Drug Act requires that any person who wishes to sell, manufacture or import drugs into the Kingdom must obtain a licence from the licensing authorities. The Drug Control Division is the licensing and registration authority for manufacturing, import, and sale of drugs within Bangkok metropolis and its territories. Provincial Public Health Offices are the licensing authorities for manufacture and import of traditional drugs and sale of drugs in other provinces.

Applications for licenses must be submitted to the licensing authority. Their buildings and facilities will then be inspected. A license will be issued after the inspection has confirmed that the applicant has adequate capabilities of doing such business, and he/she can secure appropriate facilities and personnel for that purpose. Licences are issued, according to the business

Continued on page 8.

Pharmaceutical Regulations in Thailand

Continued from page 7.

of the applicant, in the following nine categories:

- license to manufacture modern medicines
- license to import modern medicines
- license to sell modern medicines
- license as a wholesaler of modern medicines
- license to sell modern medicines in sealed packages which are classified as neither dangerous nor specially-controlled medicines
- license to sell modern veterinary medicines in sealed packages
- license to manufacture traditional medicines
- license to sell traditional medicines
- license to import traditional medicines

Good Manufacturing Practice

The Thai FDA has begun campaigning on GMP compliance since 1984. Projects on development of the local pharmaceutical industry up to internationally acceptable standards were part of the Sixth National Economic and Social Development Plan (1987–1991) and also of the Seventh Plan (1992–1996). The projects aimed to promote and support local drug manufacturers in implementing good manufacturing practices. The first guidelines of Thai Good Manufacturing Practices were published in 1987. Since then, numerous workshops, seminars, and conferences, as well as consultative visits have been held or carried out to promote the guidelines adoption. Currently, the GMP is a mandatory requirement for all manufacturers of modern medicines.

A current GMP standard used in Thailand is the World Health Organization's Good Manufacturing Practices. However, the Pharmaceutical Inspection Cooperation Scheme (PIC/S) is planned to replace this current one to ensure that medicinal products manufactured in Thailand will be in line with international drug market requirements. Additionally, Thailand is speeding up its standard upgrading as ASEAN plans to allow free trading in healthcare products in 2010 and is likely to require all its 10 member countries to adopt the PIC/S standard. Therefore, Thailand is going to apply for PIC/S membership in 2006, expecting to be endorsed in 2008.

Drug Registration

The registration process is necessary to ensure quality, safety, and efficacy of the drugs being marketed in Thailand. Only authorized licensees are qualified to apply for product registration. Manufacturing plants, in which drug products are manufactured, are subject to inspection for GMP compliance. For the purpose of registration, drugs are categorized into three groups:

- **generics** or pharmaceutical products with the same active ingredients and the same dosage forms as those of the original products, but manufactured by different manufacturers
- **new drugs** include pharmaceutical and biological products of new chemicals, new indications, new combinations, new delivery systems, and new dosage forms
- **new generics** are pharmaceutical and biological products with the same active ingredients as new drugs, which need to prove for their therapeutic equivalent by conducting bioequivalent studies on the same doses, and dosage forms as those of the new compounds registered after 1992

The amended registration procedure for new drug products, adopted in August 1989, involves a two-year period of safety monitoring program. This means that new drug products will be firstly approved for use only in hospitals or clinics for at least two years. Then safety reports must be submitted for consideration as to whether general marketing should be allowed. Meanwhile, new generic products have to pass bioequivalence studies to assure comparatively therapeutic outcomes. The bioequivalence data must be submitted to the authorities as proof of the product bioavailability along with product information and quality dossiers.

Quality assurance of drug safety and efficacy before marketing can undoubtedly be achieved through GMP. Inspection of drug manufacturers and sampling of drug samples from manufacturers, importers, or retail pharmacies for analyses by the regulatory authorities cannot effectively solve the problems encountered. Drug manufacturers, importers, and distributors must establish their quality assurance systems according to the GMP guidelines to ensure that the drug products have and continue to have the quality as claimed.

Drug Advertising

Drug information available to healthcare professionals and consumers is as important as drug quality for the safe use of drugs. Drug advertisements and other promotional materials need to ensure truthfulness, non-misleading, and non-exaggeration.

Advertisements through any means must be approved by the authorities before actually being disseminated. Advertisements of prescription or pharmacy-dispensed medicines are permitted only to professionals, but prohibited to the general public. Drugs in the household remedy category may be advertised directly to the general public.

Post-Marketing Phase

To further ensure quality, safety, and efficacy of the approved drug products, the marketed products are regularly sampled for testing at the drug analysis laboratory of the Medical Sciences Department, Ministry of Public Health. In addition, contracts have been signed with some qualified laboratories of local universities to assist in solving the problems of drug quality.

The surveillance tasks involve the following activities:

- inspection of GMP compliance at manufacturing sites
- monitoring of manufacturing process changes to ensure no adverse effects on the safety or efficacy of the medicines
- monitoring of the use of marketed drugs for unexpected health risks, taking action if risks are detected by informing the public, investigating the cause, and removing the drugs from the market
- lot release system is carried out for biological products to ensure the consistency of the products
- receiving and handling of complaints
- safety monitoring program for new drugs
- re-evaluation of pharmaceutical products

Re-Evaluation of Pharmaceutical Products

Even though drugs have been strictly examined for their quality, efficacy, and safety before being approved for marketing, chronological consumption data in a large population, new findings, and pharmaceutical progress may later reveal very serious side effects that were not previously seen. A balance between efficacy/benefit and potential risks or serious adverse reactions is frequently questioned, especially those in combination. The Drug Committee in 1991 appointed a subcommittee to evaluate the registered products. Some criteria have been set and the evaluation process has been ongoing.

Strategic Directions and Challenges

While continuing with efforts to ensure the availability of safe and effective medicines, the Thai FDA also takes active roles relentlessly in many activities. Among these are, for example, efforts in pharmaceutical harmonization and initiatives to enhance capacity of the domestic pharmaceutical industry.

Toward ASEAN Pharmaceutical Harmonization

Thailand along with other ASEAN member countries moves toward harmonization of pharmaceutical regulations in order to facilitate trade by minimizing technical barriers posted by regulators without compromising drug quality, efficacy, and safety.

To achieve the goal, ASEAN Consultative Committee for Standards and Quality-Pharmaceutical Product Working Group (ACCSQ-PPWG) had agreed to first develop ASEAN Common Technical Requirement (ACTR), ASEAN Common Technical Dossier (ACTD), and Technical Guidelines, followed by training and relevant capacity strengthening. For implementing, the ASEAN had agreed to start from a trial period, then full implementation at the agreed specific timeframe. Along with these implementations, the training, as well as question and answer forum also will be provided to ensure appropriateness, applicability, feasibility, and sustainability of the ASEAN agreement's implementation. In addition, the ASEAN also will develop some Mutual Recognition Agreements (MRAs) in particular issues, e.g., GMP's Inspection Report, laboratory testing report, and will finally be endorsed.

Prior to and along with the trial period for implementing the ASEAN pharmaceutical harmonized guidelines and requirements, the Thai FDA has arranged seminars and meetings to enhance understanding and know-how to implement the ASEAN pharmaceutical harmonized requirement including methods and procedures to all relevant stakeholders, both in public and private sectors. Brainstorming and workshops about the implementation of harmonization are planned. All comments and suggestions from all stakeholders are welcome to ensure that the implementation of harmonization requirements will pose the minimum obstacle and impact to all.

Enhanced Capacity of Domestic Pharmaceutical Industry

In the face of rising drug expenditures in Thailand, the Ministry of Public Health has realized the necessity to develop initiatives to promote accessibility, availability, and affordability of medicines for Thai people. Currently, the Thai FDA has conducted one important program titled, *Promotion of Domestic Pharmaceutical Industry*. Primarily, the program is designed to assure the public of high quality, safe, and effective generic drug products manufactured by the local drug industry. The ultimate goal of the program is to improve the potential, capacity, and competitiveness of the local industry. To achieve the goal, the Thai FDA has developed strategic plans for the program as follows:

- Provide and improve infrastructures and facilities that are necessary for the manufacturing of generic drug products.
- Create collaborative partnership with related organizations (both public and private sectors) to facilitate generic drug product production.
- Develop mechanisms to assure quality, safety, and efficacy of generic drug products.
- Promote widespread use of locally manufactured generic drug products among prescribers, dispensers, and consumers to substitute imported drug products.
- Promote investments on domestic generic drug industry and increase its competitiveness for the international market.

Currently, one important activity undertaken by the Thai FDA is to upgrade existing bio-equivalence centers to meet the international standards so that we can assure that locally produced generic products are of same quality as that of the innovative drug products. Such an activity is an integral part of our endeavor to increase the competitiveness of our local pharmaceutical industry.

Concludes on page 10.

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A Look at Thailand...

Continued from page 2.

ments with a variety of partners in an effort to boost exports and maintain high growth, and in 2004 began negotiations on a Free Trade Agreement with the US. Thailand's industrial production is orientated toward exports with Japan as the leading country for Thai imports, totalling 23.6% of Thailand's total export (Source: CIA fact book, 2005).

Pharmaceutical Regulations in Thailand

Continued from page 9.

Bibliography

1. Background information of organization. Available at: http://wwwapp1.fda.moph.go.th/drug/eng/files/backgrou.pdf
2. Current status and practice in pharmaceutical regulations and technical requirements in Thailand. Available at: http://wwwapp1.fda.moph.go.th/drug/eng/files/status.pdf

Questions relating to the article may be directed to:
Drug Control Division, Food and Drug Administration, Ministry of Public Health, Web site: http://www.fda.moph.go.th.

This article describes a new configuration for the layout of an OSD facility that closely integrates all of the facility contents plus optional R&D and administration areas. It presents a number of operating and GMP advantages, as well as potential capital and operational cost savings.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
January/February 2006, Vol. 26 No. 1

A Hub Layout Concept for Oral Solid Dosage (OSD) Facilities

by M.P. Brocklebank, J. Lam, and P. Mehta

Introduction

Oral Solid Dosage (OSD) facilities producing tablets and capsules use well-defined unit operations, regardless of differences in production volumes or usage of such facilities for single or multi-product manufacture. The contents of such a facility typically include warehousing with receipt and dispatch areas, clean process rooms (which are conveniently called 'white' areas) containing process equipment, clean support process areas for items such as washing, movements, and staging, QA/QC laboratory, and black normal factory finish technical space for process ancillary equipment and ventilation, and basic utility supply equipment if it is a stand alone facility. To gain competitive advantage, companies aim to minimize capital and operating costs for such facilities, which primarily means reducing the size of such a facility, as well as improving the operational and internal logistics of the facility without compromising current good manufacturing and engineering practices.

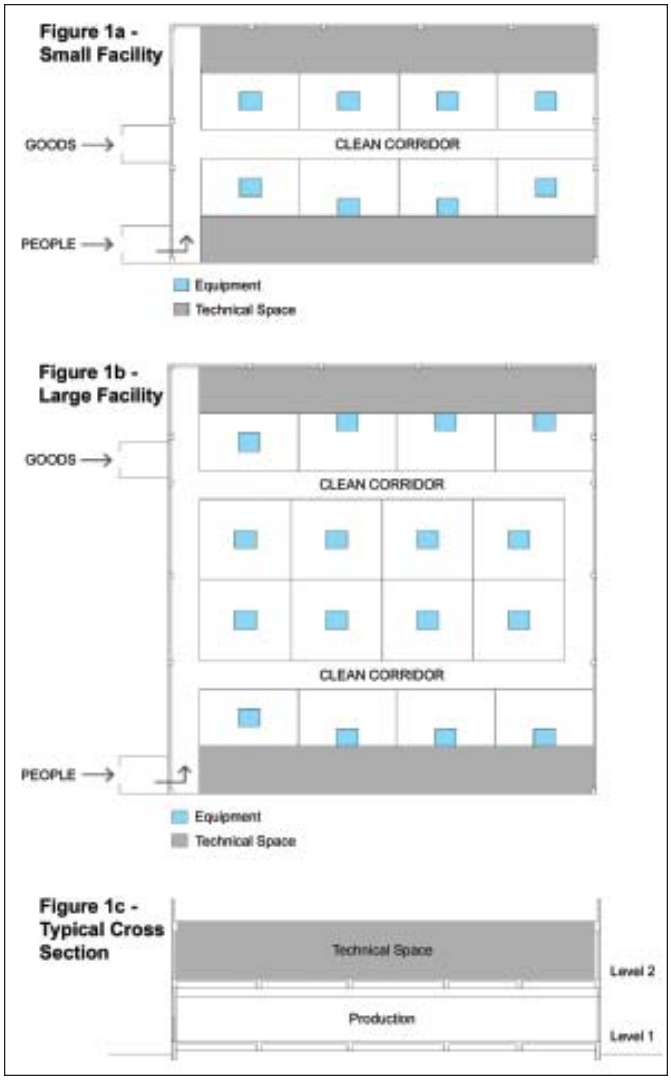

Figure 1 (a, b, and c). Typical production suite arrangements.

Process and Facility Outputs and Size

Dispensing with sieving, blending, granulation, compression to form tablets, capsuling, tablet coating, blister packing or bottle filling, cartoning, and packaging are some of the discrete batch unit operations in an OSD facility plant. The numbers, capacity, cycle times of the equipment, and daily operating time will determine the output of the facility. Different companies may require different facilities whose outputs can range from 100 million to two to three billion tablets a year. Increasing equipment capacity by factors of 5-10 does not greatly affect facility size (area), though its capacity may increase by a factor of 5-10. Increasing plant utilization from a one day shift for five days per week operation to a 24 hour, seven days

operation will increase outputs by a further three to four times without any significant increase in production area sizing. However, increasing equipment numbers and types to achieve more capability and flexibility will greatly affect facility size, and efficiencies in space utilization. Nevertheless, since the facilities are expensive, any unnecessary increase in OSD plant size will have a significant cost impact.

Materials Handling

A key requirement of an OSD plant is solids materials movement between each batch unit operation. Movements of solids between unit operations can be achieved by gravity flow from 'directly' coupled equipment (advantageous in large output single product stream plants) or more frequently by collecting the batch in an Intermediate Bulk Container (IBC) and moving this to the next stage by emptying the contents of the IBC by gravity to the equipment.

One or two level plants are common for smaller plants with smaller batch sizes (e.g., typically up 500L), while the three level plant is often used for larger batch sizes (e.g., above 1000L).

Process Arrangement - The Cleanroom Suite

For OSD plants, ISO Class 6 (equivalent to Class 100,000) particulate environments are typically used for process equipment rooms and adjoining areas where 'open' product or items which could be in contact with the product (including people) are present. Consequently, the process area is typically composed of a 'clean' room suite with 'clean' corridors and 'clean' process rooms for production equipment. Technical areas are needed for ancillary supporting equipment to the production equipment, e.g., blowers, heaters, vacuum systems, being located either 'behind' the wall of the production equipment at the same level and/or in a technical space above the production suite. Technical areas adjacent to production rooms allow 'through the wall' installation of some process equipment, e.g., coaters. Such desirable facility features also can facilitate the process equipment installation.

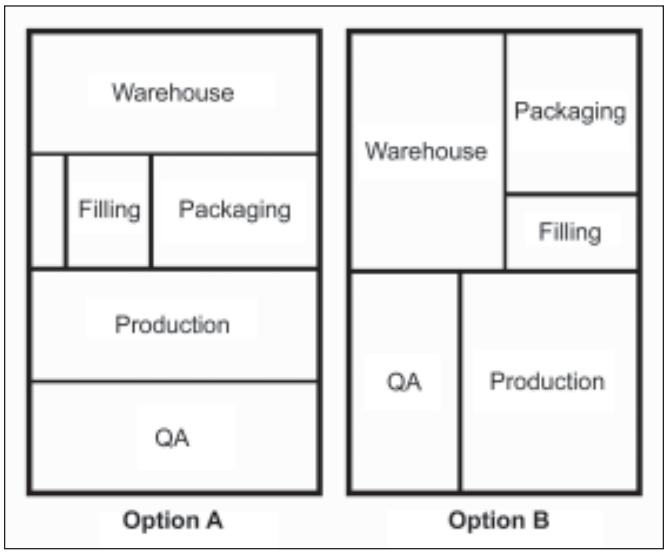

Figure 2. Typical conventional facility layout arrangements.

In addition to the production rooms, the cleanroom suite also will require space for materials staging, wash rooms, store rooms, and sometimes a small operator batch log room and an in-process control laboratory.

Figure 1a shows a typical arrangement of a plant with a single corridor and adjacent process rooms, allowing a technical space on either side of them. In Figure 1b, a larger multi-corridor cleanroom suite facility is schematically indicated, and in Figure 1c, a cross section is provided of a single, level plant with a technical level above it.

Operator access to the cleanroom suite will be via a change room and materials enter or leave via one or more airlocks.

Filling and Packaging

While a number of OSD plants may just make the capsules or tablets in bulk to be shipped to other filling and packaging facilities around the world, most OSD plants incorporate these operations within them. For multi product plants, it is usual for the filling equipment to be in a cleanroom with the 'line' then extending into the lower GMP category packaging and cartoning room. Thus, the filling rooms are typically accessed off the process cleanroom suite with the associated packaging area next to them accessed directly or indirectly from the warehouse.

Mechanical Ventilation

OSD plants require large ventilation systems where 15 or so air changes per hour are required for the cleanrooms, and low humidity may be needed for specific product requirements. The ventilation systems typically consist of Air Handling Units (AHUs) and their associated control dampers and ducting systems, plus chemical dehumidifiers if required. There may be six plus such systems in a facility supplying clean areas, support areas, warehouse, laboratory, and support offices depending on the product(s) and plant type.

AHUs and their ducts are primarily located and distributed in technical areas, which are located near the clean areas. The conventional approach is to provide a top floor of the facility dedicated to AHU system as indicated in Figure 1c. This area also may include water chillers and other services if the plant is remote from central facility services. Quite often the process and support functions (i.e., the overall facility) floor area requirement is greater than the space required by the AHU systems, and this can result in under-utilization of the floor created at this level.

Good Manufacturing Practice (GMP)

GMP guidelines cover all aspects of manufacturing including validating process methods and analytical control, equipment usage, facility layout, environments, storage, documentation, labelling, and the required training of personnel employed. Regardless of the arrangement of the facility, a number of key principles should be applied, including:

- avoiding mix ups
- provide suitable environments
- take measures to avoid contamination
- provide suitable materials flow around the facility
- provide adequate space for operations taking place
- design to allow for cleaning
- adequate labeling (at point of operation)

Some layouts are better than others, to meet these GMP guidelines, but in practice the following are preferred:

- segregate raw materials and final products
- segregate different production suites involving different classes of products
- closed operations where possible
- segregate physical barriers or other proven means 'open' operations with different products
- ensure an orderly flow direction
- provide distinct staging areas if required between process steps
- provide cleanable production suites and equipment
- provide suitable environments for controlled areas where products and their active material are stored and processed

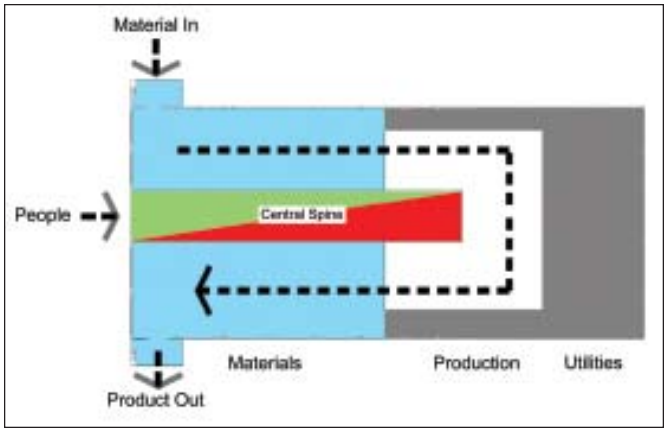

Figure 3. U SPAH concept.

Typical Overall Layout for a 'Conventional' Design Facility

As stated previously, there is no one single arrangement adopted by facility designers to meet the following issues affecting the layout:

- relative location of warehouse to the production and packaging suites
- cleanroom suite arrangement
- usage of different levels and IBC movements

Figure 4. Ground Floor (Level 1) U SPAH facility layout.

Parameter	Approximate Facilities Comparison(1)					
	U SPAH 1	U SPAH 2	Project A	Project B	Project C	Project D
'White' production	20	21	28	17	15	14
Production staging (w + g)	7	7	12	5	5	4
Production support (w + g)	19	14	14	15	15	11
Technical black areas	29	31	39	45	51	47
Warehousing/Dispatch	25	27	7	18	14	24
Total facility area – approx m2	3200	7000	18000	10000	7400	8000
Approx Output (billions tabs/yr)	0.2 – 0.6	2	3.5+	2.5+	0.1 – 0.3	1

Notes: (1) Numbers are percentage of total facility area required by this part of facility
w 'white' area, i.e., clean area in facility used for production support, e.g., washing areas, staging
g 'grey' area, i.e., areas of facility used for production operations/support, but lower level of cleanliness

Table A. U SPAH vs. conventional facility features.

- adjacency of technical areas to production rooms
- QC laboratory location
- separate raw materials and finished product routes
- minimization of expensive 'clean' areas
- avoidance of 'white' areas adjacent to external walls
- dispensary location

Other layout considerations, which could be taken into account in facility design, but are often lacking, include visitor viewing access, central supervisor area, and external visibility of process room operation.

Two generic schematic arrangements for OSD plants are shown in Figure 2 indicating potential locations of the key components. In these schemes, the technical area is generally on the upper floor of the facility.

The Proposed Hub Facility Arrangement

Overall Concept

A proposed hub arrangement for an OSD plant has been developed,[1] which is believed to offer advantages over conventional layouts. It can be applied for plants with outputs of 0.2 to two billion tablets a year or more, in principle, where a one or two process level approach is adopted. Its first application is considered for a 'standalone,' greenfield two process levels plant manufacturing a number of similar class products on a campaign basis. The scope and requirement for the facility includes warehousing, manufacturing, support areas, technical space, and utilities generation, and company administration offices. In addition, its scope includes a GMP pilot plant for process R&D plus small-scale manufacture for trial material.

In developing this layout arrangement, a number of key attributes and features were sought, namely:

- adopt an overall unidirectional materials flow through the plant starting with raw materials in and final product out with two (relatively) small warehouses
- maximize adjacency of materials storage with production suites
- adopt a central 'spine' in the building in both the support areas and process area around which materials flowed and the process functional rooms are located
- maximize technical space adjacency to production rooms
- provide an IBC handling and discharge level above the process and filling rooms
- integrate the R&D suite into the facility in an optimal way
- close adjacency of the QC/QA laboratory to all operations
- avoidance of a separate upper floor technical area above all of the facility footprint
- minimize under-utilized technical plant space and clean corridors
- provide a visitor viewing gallery through the plant which maximizes visibility of the process areas without entering them
- analysis of final product only with no inter-stage QA hold points, thus minimizing staging area requirements
- optimize facility space need for minimal cost

In order to achieve these aims, the facility concept was developed by adopting an overall U flow of materials and process operations around a central spine at the two building levels, and designated as the U Satellite Process Assurance Hub (U SPAH) layout - *Figure 3*. There are three geographical zones along the building within the overall 'U' flow pattern where materials handling and production operations are 'wrapped' around the central spine which provides access for people, the QC laboratory at Level 1 (ground), and people circulation at Level 2. The spine forms the hub in the production suite.

The proposed hub layout is shown in more detail in Figures 4 and 5 for each of its two levels for the production

scope of the facility which includes dispensing and IBC filling, two granulation rooms, three tablet rooms, two coater rooms, one capsule room and three filling lines plus support areas.

Material Handling and Support Services

This consists of warehousing and QC at Level 1 with offices, support areas, and technical space at Level 2. Two separate warehouses are provided for raw materials and final products respectively, with raw materials entering at one side and going into the production area and final packaged product coming out the other side of the 'U' into the final product warehouse and dispatch area. The larger raw materials warehouse extends to roof height, while the smaller final product warehouse is limited to Level 1.

The QC/QA laboratory is located in the central spine at Level 1 between these two areas to give it adjacency to sampling, production, and packaging.

Level 2 provides the main space for office staff and people circulation to the production suite by incorporating in the 'spine' corridor a clean change (gowning) area for production and R&D staff.

R&D Pilot Plant

Although the GMP 'mini' production suite pilot plant is embedded in the facility, it is located in a discrete separate zone within the building. Given that this part of the facility is separate, but adjacent with the production facility, it is believed that such arrangement has decreased cost and increased efficiency and control in technology transfer, and such implications may lead to corporate competitive advantages.

Adjacent to the cleanroom R&D suite is the stability chamber room and R&D staff offices with visibility into the suites and a technical space on the outside wall to facilitate installation of supporting items to the processing equipment in the suite.

Production Area

The key concept developed is to 'wrap' the process rooms around the central hub in the 'spine,' and 'wrap' the technical space at Level 1 around the clean process rooms. Hence, raw materials directly enter the production area via the adjacent pre-dispensary/dispensary on one side of the building with filling and packaging on the other side of the building such that final product then directly enters the final product warehouse.

This concept provides at Level 1, the minimum clean corridor and a compact production room arrangement. Process support rooms have been allocated to the 'central hub' including a wash area, small process control lab room, supervisor office, and storeroom.

The operational concept is that IBCs are filled in the dispensary and then taken via the lift in the production area

Figure 5. Upper floor (Level 2) U SPAH facility layout.

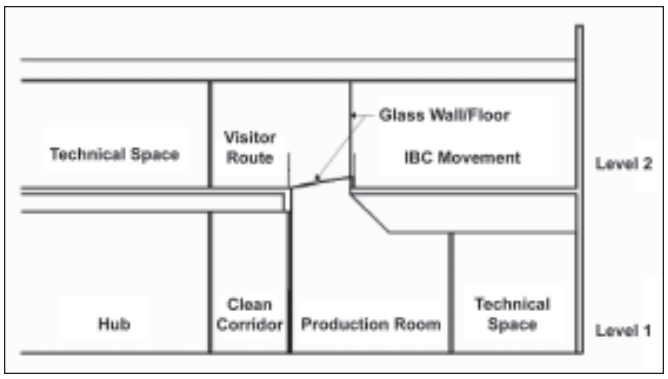

Figure 6. Visitor viewing gallery concept.

for blending at Level 2 and charging to the various equipment items below. Different IBCs are then filled with process material after each unit operation in the various process rooms at Level 1. Finally, tablet IBCs are filled with tablets and then fed from Level 2 to the filling machines below. The usage of the second floor IBC discharge minimizes the plant footprint, which was a key requirement.

Within this 'U' concept, the number and size of all rooms can be adjusted to suit the amount and size of the equipment. The surrounding technical space has in it support equipment for the production equipment such as coater air handling units, together with pipework, cabling, and ducts. The filling rooms are accessed off the clean corridor extension from the hub area.

Level 2 consists of the IBC handling/discharge station area around the 'black' central hub. The IBC handling area consists of lift access, closed IBC discharge stations to the floor below, IBC blender room and IBC washroom.

Since all operations are nominally closed, and since the products are nominated to be of the same activity class, then it is not considered necessary to segregate each IBC discharge station in its own room, but a partial height barrier and different time discharge procedures could be used.

Central Hub

We believe the central hub area offers a number of advantages. At Level 1, it provides a central location for common functions. At Level 2, it provides a central area adjacent to and above the cleanrooms in which to locate their AHU plant in a space efficient way, and it allows circulation around the clean area for personnel in factory 'black' clothing. In this central hub arrangement, a viewing gallery as indicated in the partial building cross section can be provided in the facility - *Figure 6*. In this arrangement, visitors and company staff can have un-precedented direct visual access into most of the production rooms below and across into the IBC handling area via transparent material ceiling/walls. A control and information room also can be located at Level 2.

This is an advantageous arrangement to companies who deem accessible visitor viewing into production operations a good feature to support company image and sales.

Utility Plant

The green field site facility necessitates the need for basic utility generation equipment and this equipment has been located at Levels 1 and 2 at the end of the building strategically adjacent to the technical space for cost minimization. These include chillers, air compressors, hot water system, process water, purified water, and electrical MCC room.

Believed Advantages of U SPAH Layout

Efficient Space Utilization and Cost Savings

A key aim of the project was to develop a compliant lowest cost 'lean' plant design incorporating all of the components many manufacturers could need in their facility and operation. Cost reductions can be considered both in lower overall facility floor area for the same production output, and the lower area of the high cost clean areas for production.

A preliminary comparison of this facility against other designs has been carried out using a number of criteria. In order to attempt to provide a numerical comparison with other production facilities, we have normalized the new

SPAH vs. Conventional Facility Features		
SPAH Feature	**Benefit**	**Conventional**
Control hub overlooking production suites	For monitoring production processes for safety, compliance, quality	Usually not available
Tech corridor wrap around production suites along perimeter of plant	Non-intrusive maintenance of thru-the-wall process equipment	Usually not wrapped around
Viewing gallery	Non-intrusive visitor viewing	Usually not available
Uni-directional U-shaped layout of production suites according to process flow	More efficient and ergonomic operations	Usually not in a compact U-shaped flow
QC labs in close proximity to production suites	Speeds up QA time	Usually not in close proximity
Separate raw materials and finished goods loading areas	Eliminate mix-ups	Usually shared areas
One cost effective security Hub (concentration) at the entrance monitoring both material and people flow	Better and cost effective monitoring of people and material flow	Material and people flow entrances and exit are not in close proximity to facilitate one security hub
R&D pilot lab well embedded and integrated with the production facility in single building	Facilitate cost, compliance and performance of technology transfer from process lab to production	R&D pilot lab unavailable or not well embedded and integrated with the production building

Table B. Comparative area requirements - U SPAH vs. conventional facilities.

facility by taking out area allocated to administration and R&D area since these are specific to this facility. Comparative values are given in Table A, where we have included two SPAH sizes, one for 150-600MM tablets a year for the production scope given and another estimated for two billion tablets a year containing two dispensaries, two blenders, two granulators, four compression stages, two coaters, one capsuler, and four filling lines.

It can be seen that the area ratio profile generally follows the same shape for all plants. However, it can be seen that the SPAH layout differs to the benchmark and the other plants in that it appears to have a distinctly lower black technical space percentage.

As stated earlier, due to the variations in equipment numbers and plant weekly operation times, normalizing facility area to output is difficult to judge, but from the Table A data, at least a 20% reduction in area appears achievable overall, which could provide significant savings when fully serviced facilities typically cost $3000-5000/m^2 to construct.

We believe the lower white circulation area can be attributed to the 'loop' white corridor in the process area and the lower black technical area percentage can be attributed to the absence of a space inefficient upper floor technical area for the ACMV plant since this has been located centrally in the 'hub.' These two items result in reductions in facility floor area and consequently provide capital and operating costs savings compared to conventional designs.

GMP and Technology Transfer Considerations

While all qualified OSD plants in production meet GMP requirements, the degree of attainment of GMP objectives above "basic" levels can vary from plant to plant. It is proposed that the new layout concept has the following intrinsic GMP advantages over conventional plant designs:

- segregated raw material and final product warehouses
- clear and separate raw materials and final product flow paths through the plant
- good access control of process personnel to production areas
- availability of the technical space behind every production room, allowing easy use of 'through the wall' technology to minimize congestion in the rooms
- convenient location for a centralized information room to facilitate the implementation of the FDA initiative
- through the wall technology is available for each production room, allowing less congested process rooms easier to clean for multi product facilities

Another wider GMP consideration is the benefit of the integration of the R&D pilot/development plant with the production plant. Even though segregation of such activities is common, integrating these two operations on one site for many companies will allow much easier technology transfer from a regulatory and speed/cost of transfer perspective.

Operational Considerations

We propose there are operational considerations and potential benefits with the SPAH concepts as indicated in Table B. The production suite 'U'shape around the hub has a number of advantages. The transparent wall and ceiling at Level 2 allows production management outside the cleanroom areas to observe operations and provides visitor access to see the cleanroom operations with no disturbances to operations in them and the costs incurred by this. This ease and scope of direct visual access to the unit operations can facilitate supervisors or managers to identify and monitor the stage and situation of the unit operations. Such visual accessibility benefits can easily be taken advantage of for the entire life cycle of the plant operation, including equipment hook-up, qualification, validation, assurance of good practice of cleaning and manufacturing operations etc.

Also the corridor around the process rooms allows easy materials movement between each room, and with the relative near location of the IBC lift to all the suites, it allows easy logistical access to the charge points and operations at Level 2.

The central hub area at Level 1 provides a convenient strategic location for cleaning operations as well as supervisor office and in process IPC lab.

Each production room has a rear wall to the technical space, and can be easily isolated from ongoing production operations for equipment change or new equipment installation and hook up via the technical space.

Project Implementation - Standard Design

Many different dosage form facility designs have been developed to date in terms of content and layout configuration, both horizontally and vertically. Each 'new' design costs money and time to develop which can significantly affect project implementation. We believe that this compact arrangement could offer a lower cost standard design solution for many companies either as a small and strategic new product launch facility or as a production facility with the consequent capital and project cost and time savings when utilized.

Conclusion

Many different designs and sizes of OSD facilities are utilized by most pharmaceutical companies to manufacture dosage forms. In this article, we have proposed a compact layout design concept. We have made a preliminary comparison of the area and facility space usage with a number of other layout facilities. Through this comparison, it is believed that the hub design offers a smaller and lower cost facility in addition to some key GMP and operational advantages that the SPAH presents. Such advantages and feature benefits – with or without R&D operational support – could initiate the SPAH concept to become an adopted design standard for companies embarking on future production facilities or for a new drug launch facility.

References

1. USPTO Patents Publication Figure 20030230031.

About the Authors

Dr. Michael P. Brocklebank has been involved in the pharmaceutical industry for more than 30 years both working initially with a major manufacturer and then for most of this time with engineering design and construction companies. Over this period, he has developed a wide knowledge of the developing trends and design principle of a number of plant types for API, biological science, and dosage process. Brocklebank is currently the Manager of the Pharmaceutical Division of Foster Wheeler's Singapore Office. He is responsible for developing pharmaceutical business in Singapore and Southeast Asia, and is currently serving as the Vice President of the ISPE Singapore Affiliate.

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