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This article presents strategies to improve bioreactions by reducing contaminations by adventitious agents.

Simple Strategies to Improve Bioprocess Pure Culture Processing

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Bioreaction and fermentation processes of all scales – from 100,000 liter vessels to small development reactors – require pure culture for their successful, productive operation. In this article the term "pure culture" and "pure culture capability" will be used instead of "sterile" or "sterility assurance" to acknowledge that bioreactions are, by nature, the process of growing large populations of helpful microorganisms or cells as opposed to the more unwanted varieties. Contamination by adventitious agents costs time, money, and lost productivity; moreover, contaminants and their sources can be very difficult to locate and eliminate.

Many elements of pure culture bioprocess design and operation are straightforward, often even a matter of common sense. Most modern facilities have pure culture capability built into their design, including latest technology and control systems, and correct operating procedures to ensure sterility is achieved and pure culture maintained. However, these controls will become less effective over time, due to deterioration, obsolescence, loss of experience, process changes, and personnel turnover. Sometimes, many years of solid performance can lead to a false sense of stability, which leads to complacence (or a lack of attention to pure culture capability requirements) inevitably followed by one or more Foreign Growth (FG) episodes.

Ultimately, a process with robust pure culture capability is the goal of both technical support staff as well as management. It is clearly beneficial to *proactively* manage pure culture design, capability, and practices before problems occur rather than create unintentional sterility experts out of your support staff as they struggle with root cause investigations instead of more productive efforts.

Contained below are a number of strategies, illustrative case studies, and techniques to help maintain or improve pure culture capabilities of traditional bioprocess reactors and fermentation processes. They are targeted squarely for the practitioner in their simplicity, and based on many years of managing pure culture operations at many scales. The focus of this article is on preventing *bacterial* contaminations in traditional fermentation systems; much of the material applies to protection of *any* bioreactor systems from *any* adventitious agent. It is up to you to understand your system and process and to appropriately apply the principles outlined in order to meet the requirements of your process and business. Higher potential risk from longer growth times, longer inoculum trains, and lack of selective agents (e.g., antibiotics) can be offset through the use of disposables, newer equipment, and more stringent environmental and raw material controls.

The focus of this work is divided into four basic sections: 1. design aspects for sterile operations; 2. common contamination root causes; 3. troubleshooting FG events; and 4. applying rigorous microbiology to better understand and improve pure culture. Additionally, several examples and case studies are included to illustrate and emphasize concepts.

Facility Design and Sterilization Best Practices

The scope of this article is for scientists and engineers supporting existing bioreactor processes. However, a short survey of current sterile design best practices will be helpful to improve or troubleshoot your axenic process. It is fundamental to realize that *prevention* of FG is the most important factor to long-term successful pure culture performance.

Sterilize in Place (SIP) System Design Considerations for Sterile Operations

Design for optimal sterilization is covered in many texts and articles.[1,2] Main points are essentially as follows:

- Using steam, quick heat up of all points in the sterile boundary to 121.1°C (121.1°C is the United States Pharmacopeia (USP) standard sterilization temperature with a minimum moist heat sterilization requirement of 15 minutes.)[3]
- free drainage of condensate
- easy displacement of air
- replace collapsing steam with sterile air (collapsing steam creates vacuum, which must be avoided at all costs)

These, and other factors to consider are described below:

Sterile Boundary – process piping connected to sterilized equipment must be sterilized up to and through the closest valve which isolates the sterile from the non-sterile system. Another way to isolate the sterile system is through an appropriate 0.2 micron-rated sterilizing grade filter. Other sterile boundaries include vessel walls themselves, mechanical seals (subject to pressure gradient), feed nozzles, internal cooling coils, rupture discs, sterilizing filters, steam traps, exhaust lines, and o-rings (elastomers) on instrument ports. See a more detailed discussion of the sterile boundary, located in the next section on contamination root causes.

Disposables – disposable bioreactors and attachments are gaining in popularity because they can reduce risk of cross-contamination between cell culture batches, while providing flexibility, minimizing turnaround time, reducing cleaning costs, and easing validation restrictions. Additionally, disposables typically have fewer connections (sterile boundary points) than fixed reactors, which provide incrementally better FG protection. (Obviously, due to scale of disposables, this may not be feasible for large scale fermentation operations.) As bioreactor demands increase, the tradeoff between flexibility afforded by disposables will be outweighed by increasing costs and will justify more traditional fixed bioreactor systems. Increasing titers will continue to shift this tradeoff toward disposables.[4,5,6]

Steam – steam must not be superheated or diluted. First, a quick steam refresher: saturated steam is steam at its boiling point for a corresponding pressure. This differs from *superheated* steam, which is steam heated to a temperature *higher* than the boiling point at a given pressure. One reason superheated steam is undesirable for bioreactor sterilization is because it has further to cool in order for it to transfer its heat of vaporization, making it less efficient than saturated steam. Relatedly, *diluted* steam is steam that has air or other gases mixed in the vapor, which can be observed by steam temperatures that are lower than expected for a given pressure or higher observed pressure for a given temperature on the saturated steam curve.

Condensate – since condensate forms throughout steam sterilization cycles, systems must be designed for quick and complete drainage to a low point where a steam trap is installed.

Air Removal – air must be completely displaced by saturated steam for sterilization to be effective. Air must be either pulled by vacuum or displaced effectively by the steam itself. Typically, air is discharged through a sterilizing filter.

Cold Spots – temperature measurement must include the coldest spot in the system to ensure that all points are held above sterilization temperatures. Redundant temperature measurement is essential to verify sterilization temperatures are maintained.

Equipment Drains – all areas in process equipment must be totally drainable. Ideally, all equipment surfaces should drain toward one common bottom outlet (each drain point is a potential cold spot). A steam trap should be installed to remove condensate in this outlet.

Setup: During an investigation of a recurring Foreign Growth (FG) contamination series on a large microbial fermentor, experienced operators noted that the equipment SIP dynamics had shifted in the past few weeks. Specifically, the system was reaching correct sterilization temperatures, but was at a higher pressure in order to meet the required temperature. Additionally, FG contamination events were intermittent and also seemed to correlate with high level or "foam out" events in the system.

Resolution: Detailed investigation found that a routine automation change on some unrelated control parameters inadvertently and subtly altered sterilization logic. The SIP logic change resulted in a minor delay in the cycling of certain valves that feed steam into the vessel's Vapor Liquid Separator (VLS), a small, separate vessel above the main fermentor. The delay in introducing steam caused air to remain trapped in the VLS, essentially "insulating" the VLS vessel from sterilization temperatures due to steam dilution. Foreign microbes, escaping proper sterilization conditions at these points, were allowed to gain a foothold on the VLS surfaces (presumably in cracks, crevices, corners, etc.). When foam or high level reached these contaminated surfaces, some refluxed back into the fermentor, carrying FG with it that eventually caused the tanks to become rife with foreign growth.

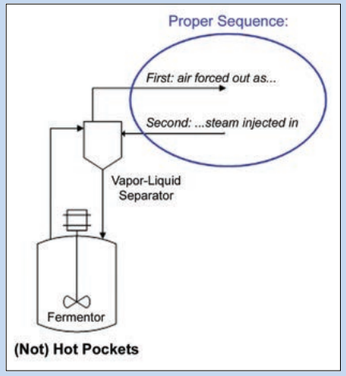

Figure 1. Displacing air with steam during fermentor SIP.

Lessons Learned:

- The shift in temperature vs. pressure observed by the operators was an indicator of trapped air in the system, because as the air dilutes that steam and a higher pressure is needed to reach the sterilization temperature.
- All process indicators showed that the equipment was reaching sterilization temperatures, but the increased air in the VLS tank created an insulated pocket and this localized area was not reaching correct temperature.
- Always need to be vigilant on unintended consequences of changes, as well as pay close attention to changes in the process. Nobody knows the process better than the operators, and this experience can be a valuable troubleshooting resource.

Table A. Case study – (not) hot pockets.

Setup: Microbial fermentor experienced sporadic foreign growths, especially common during periods of high tank volume or "foam outs." Extensive investigation into source of contamination did not reveal any sterile boundary flaws except a very minor one: the insulation around the top of the Vapor Liquid Separator (VLS) had been removed for repair work some time before, and was not replaced.

Resolution: Replacing the insulation decreased the frequency of foreign growth events, but did not eliminate them. Further investigation revealed that the VLS had a stationary Clean-In-Place (CIP) spray ring with spray holes drilled on the side of the ring, not the bottom, so that the cleaning solution was ejected horizontally outward from the spray ring instead of vertically downward.

Consequently, the spray ring was not free draining and always had a heel of water lying stagnant within, where environmental bacteria could gain a foothold between runs. Sterilization process in the upper portion of the VLS was adequate for surface sterilization, but was not as effective in sterilizing the heel of water when the insulation was removed and was occasionally ineffective even with the insulation in place. When the process broth or foam refluxed to the upper portion of the VLS, some of the foreign bacteria would be swept back to the main reactor, causing contamination.

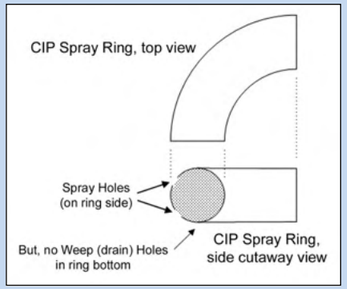

Figure 2. Schematic sketch of an internal CIP spray ring with no drain hole.

Lesson Learned: An effective CIP design, the spray ring was not a good aseptic design for fermentation. Besides assuring that criteria for vapor liquid separation, cleanability, and surface sterilization be considered throughout the VLS qualification, good concepts for pure culture design should have been considered as well.

Table B. Case study – hidden spray ring design flaws.

Piping and Pipe Slopes – process piping to be sterilized should be configured to completely drain back into the equipment if possible, minimizing the number of separate drain points. Sterilized piping should be sloped to eliminate holdup points. Slopes need to be much greater if against the direction of steam flow. Never branch a line from the bottom because it could promote condensate buildup. A key quality of pipe insulation is the ability to wick moisture and freely drain so that it won't retain leaks (wet insulation is less effective and provides potential cold spots in steam seals).

Elastomers – o-rings, gaskets, and such are often a critical element of the sterile boundary simply because they have no backup in case of failure. Thus, they need to be designed with the optimum material of construction for conditions of the bioreactions (which usually means the temperature exposure from SIP) and replaced on a set frequency rather than be allowed to run to failure.

Valves – clearly, not all valves are equal in sterile services. For valves sterilized through, diaphragm valves with high temperature-rated diaphragms are better than ball valves because of the difficulty cleaning behind the ball. However, ball valves typically hold up better in steam services. For diaphragm valves, care must be taken to control steam temperature, flow, and differential pressure across the diaphragms in order to prolong service. Use of condensate seals as opposed to steam seals also can prolong valve elastomer life.

Trade-Off between In-Line and Off-Line Monitoring Devices – in some cases, the number of required in-line monitoring devices can be reduced by using external lab sampling or indirect relationships between key operating parameters. The appropriate number and location of analytical instruments and in-process checks must be reconciled against: 1. capital and operating cost constraints; and 2. pure culture concerns, due to the fact that an increasing number of instrument ports raises FG risk to the bioreactor.

Dead Legs – the piping configuration of the sterile system is one of the most critical attributes that contributes to maintaining a system free of FG. Avoiding so called "dead legs" is crucial. Basically, a dead leg is defined as a one-way system, typically on the end or a branch of a piping distribution system, which results in a process hold-up area that is difficult to clean and sterilize. The ASME BPE standard suggests that bioprocessing systems, such as fermentation, along with other bioprocesses, should be designed with a target L/D ratio of 2:1. L is defined as the length of the dead leg extension measured from the ID wall normal to the flow pattern. D is diameter of the dead leg extension. This tight ratio ensures that process piping can effectively complete SIP and CIP cycles without concern of building up cleaning solution or condensate which could contribute to sterilization failures and FG events.

Agitator Shaft Seals – double-mechanical seals are standard. The key idea is to ensure that seals in pure culture operations are lubricated with a sterile fluid, such as steam or clean condensate.

Setup: A new state-of-the-art bioprocess facility shortly after start-up was experiencing foreign growth events in a particular bioreactor. Swabbing of locations was used to determine hiding spots of the contaminating organism. Removal and swabbing of the pH probe ports on the bioreactor found the organism of interest lingering behind the pH probe o-rings (i.e., outside the sterile boundary).

Resolution: The o-rings on the pH probes had a small nick or deformation that allowed media from the vessel to migrate into the nonsterile region behind the probe o-ring. This area outside the o-ring would not reach sterilization temperatures, providing a place for foreign agents to reside and proliferate on the media. Contamination of the fermentor occurred when the invading microbes migrated backward through the defect into the axenic contents of the fermentor.

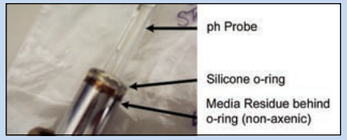

Figure 3. Internal pH probe with media leaking past o-ring.

Lesson Learned: The practice of routine o-ring replacement was instituted and the material of construction was optimized to minimize swelling and deterioration through SIP cycling. Additionally, the o-ring groove design was optimized to further reduce leak-by.

Table C. Case study – elastomer headache.

State of the art sterile design equipment and components are often costly, and typically, only able to be justified by facilities that produce high-value specialty chemicals and pharmaceuticals. These include large-pipe diameter diaphragm and sanitary valves, sanitary tubing, specialized aseptic fittings, removable components and instruments, automated SIP/CIP systems, and ultra pure water for process use. Still, reliable pure culture capability can be achieved with lower cost designs; for example, standard industrial valves with welded pipe connections, more rigorous SIP/CIP procedures, and valve/piping preventative maintenance are all cost effective ways to improve pure culture capability. (It is worth noting that validation of processes using lower cost designs can be more difficult and maintenance costs higher.)

Contamination Root Causes

A Foreign Growth (FG) is essentially a failure: 1. of the process to either kill all adventitious organisms at the start through the sterilization processes; or 2. to successfully keep the process isolated from outside invaders. Or, more simply put, you didn't kill them or keep them out. Furthermore, the system fault can be grouped into one (or several) of the following:

- Design and Sterile Boundary
- Equipment
- Human Error [Procedures, Execution]

Design and Sterile Boundary Faults

As previously discussed, the sterile boundary is defined as the point in your system where you plan to maintain an environment free of foreign microorganisms. Any breach of (or migration across) sterile boundary has potential to bring FG into the system. Therefore, the first goal in protecting your system from FG is to know your boundary.

You need to understand not only every element of the sterile boundary, but also how the boundary's sterility might change over time. An imperfect sterile boundary condition – for example, a small crack in a weld – might maintain sterility if the pressure differential is always favorable, but if the pressure equalizes or if vacuum were to develop in the process at some point, even for an instant, then sterility will no longer be maintained. So thorough process understanding is essential, including microbial challenges in and around the boundary and how and when process interacts with boundary points (steam, feeds, process, gases, etc.).

The most common sterile boundary failure is, of course, a leak. Leaks in a sterile system provide a route for bacterial contaminants to enter your process, a nutrient-rich, climate controlled environment reserved for your chosen cell line. Foreign bacteria can either "ride in" or "grow in." "Ride in" is where the contaminant is present in a feed or gas and carried into the process. "Grow in" is where the contaminant finds a fault in the system, proliferates at a leak point, and eventually migrates into and through the leak point, sometimes even against a flow gradient.

Leaks and defects are a natural consequence of inevitable system decay, so identifying and eliminating leaks in your process is a continuous challenge. A proactive leak detection program where systems are periodically inspected and leaks repaired prior to operation is essential for successful pure culture capability. System pressure checks and light gas (hydrogen, helium) checks are standard tools to check for leaks in the sterile boundary, but have limitations. For example, if a line leaks upstream of a valve at the reactor (referred to as a "near-to" valve), a pressure check won't find the leak since the sterile boundary is the "near-to" valve. Also, some defects do not become detectable until after the extreme heating and cooling cycles of SIP, at which point a pressure check may already have been completed. So these tools must be combined with other proactive efforts to detect leaks, from thorough preventative maintenance to as simple as a detailed visual and hands-on inspection.

Sometimes leaks are simple to find by inspection. Figure 5 is a picture of a leaky valve (the valve handle cannot be seen due to the angle of the photograph) in a sterile fermentation dextrose feed line. A messy leak such as this may not result in an immediate FG, but nonetheless should be repaired as soon as detected. An organizational tradition that encourages frequent visual and hands-on inspections, as well as vigilance and wariness of all leaks, is consistent with long-term, foreign-growth free operation.

Setup: In a microbial fermentation facility, a system started to have repeat contamination events associated with one seed vessel.

The seed vessel employed two rupture disks in series on vent line from Vapor-Liquid Separator (VLS). Rupture discs had burst disc indicators to alarm in case of vessel over pressurization. There were no burst alarms and by visual inspection, rupture discs appeared to be intact.

Resolution: Over many years, both rupture discs on the VLS had developed pin-hole leaks which allowed non-sterile moisture and environmental microbes from the top side of the discs to reflux into the vessel and cause foreign growth events. This was confirmed by sampling and bioburden assays.

The rupture disc design was non-optimum, and consisted of a membrane sandwiched between a stainless steel upper and lower piece, where the membrane provided a sealing surface for the disc. As the system underwent many heat cycles from SIP, the stainless sections had worn small holes in the membrane, creating a breach in the boundary.

Moreover, the placement of the rupture discs was poor. A breached disc would allow non-sterile material to directly fall back into the process.

Finally, the additional failure mode of the system which made it difficult to troubleshoot was the burst disc alarming mechanism. The burst disc indicator was not showing that the disc had a failure (as it was not a rupture of the disc); therefore, the operations staff initially did not realize that there had been a rupture disc issue.

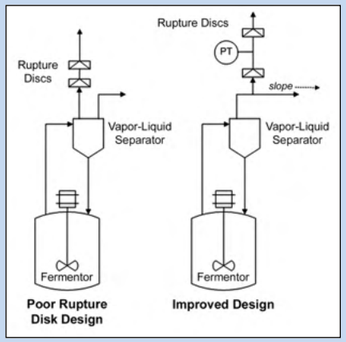

Figure 4. Poor rupture disc design and the improvement.

Lessons Learned:

- A new design was installed (solid piece of stainless steel) that was less likely to develop leaks from SIP cycling.
- If possible, it is better to have the rupture disc located in the exhaust system and orientated in a manner that if the disc were to leak, contaminants could not enter the vessel.
- The recommendation out of the investigation was to install a pressure transmitter between the two rupture discs to determine, based on pressure, if the main near-to disc had lost integrity.

Table D. Case study – poor rupture disc design.

Figure 5. A leaking dextrose hand valve.

Equipment Faults

Equipment faults as a source of foreign organisms may simply be the mechanism by which a sterile boundary leak develops, such as a sterilizing filter flaw, a weld defect, or an imperfect o-ring. In addition, as equipment ages, faults and defects begin to arise that could compromise sterility. Also, even though sterilization and cleaning was qualified/validated for the equipment at one point, over time the system might decay in subtle ways, creating equipment defects that could alter the dynamics of the system to create sterilization issues. Simple illustrations: debris in a spray ball that could alter cleaning patterns in a vessel and allow for media hold-up or a weld defect could harbor pockets of unsterilized FG.

Small patches of media that accumulates and builds up in the vessel, either from poor cleaning, incomplete draining, or exposed seams, seals, defects, etc., will over time, become insulating and prevent heat penetration during SIP. Eventually, this will become a spot to harbor foreign microorganisms.

Consider the case of bolted and screwed connections in a bioreactor as a source of media buildup. Bolted connections are less prevalent in newer vessels, but still exist in many bioreactors, especially legacy fermentors. Bolts, screws, and washers will occasionally and unpredictably loosen from repeated heating and cooling cycles, creating pockets and crevices for environmental bacterial contaminant to fester. Over time, media or biofilm buildup will create insulated pockets and allow colonies of foreign bacteria to survive sterilization, which eventually contaminate the vessel.

The solution is to remove as many bolted connections as possible – replace with welded connections – and for those that remain, institute a periodic inspection cycle to remove, clean, and replace worn out connectors with new ones.

However, with the transition to more welded connections, weld integrity becomes the new point of emphasis in the discussion of FG prevention.

Weld defects can have the same material hold-up implications as bolted connections by allowing bacterial contaminants a place to fester and perpetuate in a system. This is especially true when a weld defect is in a location where it can become hard to sterilize. When welding stainless steel, it is critical to maintain temperature of the weld material with heating and pace of the weld both impacting weld integrity. Welding too fast, for example, can place waves in the weld material, which create pockets where material can migrate or corrosion can take hold, or worse, be inaccessible to SIP steam. Temperature of the weld is critical at overlap points between two welds, especially at the end of a welding pass. If the weld at an overlap becomes cool, an open pocket at the seam of the weld can result. An example where this defect can be found is when there is a circular or square pad welded onto a vessel wall with the end of the weld overlapping the starting point. Figure 7 is a photo of a welded pad in an older fermentation vessel which contained weld defects that may have contributed to FG problems.

When locations and welds like the one shown in Figure 7 exist, the best approach is to grind away all suspect areas,

Setup: A large legacy fermentor had been experiencing intermittent foreign growth events. Investigation included a detailed internal inspection to locate potential defects where contaminants could be held up in the system. Inspectors noted that the fermentor had a threaded nozzle on the inside of the vessel that was plugged and no longer in use.

Resolution: This particular threaded plug was located on the internal head space of the fermentor. The cavity space on the top side of the plug, just past the sterile boundary, was filled with standing moisture, grime, and oil that had seeped from the top of the fermentor agitator gear box over a long time. After years of SIP temperature cycling, the threaded plug was found to be leaking a minute amount, intermittently introducing contaminates – both microbial and traditional – into the fermentor's axenic contents. Incidentally, the leak was not detected by routine pressure checks because it was so small.

Figure 6. Leaking internal threaded connection in legacy fermentor.

In order to remedy this issue, the threaded plug was welded closed and vented caps were placed on the atmospheric side of the nozzle. The vented cap would prevent the accumulation of oil and dirt from building up again inside the unused head space nozzle.

Table E. Case study – threaded connection space invaders.

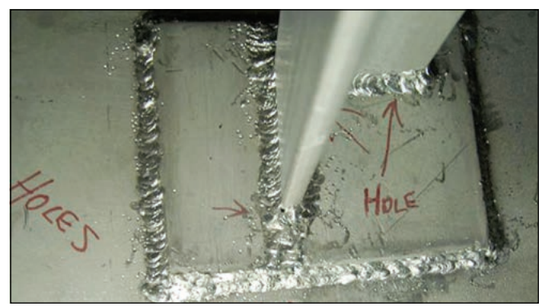

Figure 7. Bioreactor internal welds displaying defects.

re-weld, and finish the weld to a smooth finish. This finishing of the weld to a smooth surface will significantly reduce the opportunity to hold up material around the weld and also be easier to inspect.

Human Error [Procedures, Execution]

No matter how much a process is automated, human intervention is still essential for all pharmaceutical manufacturing. In one sense, every FG root cause can be traced back to human error: from error in design, to errors in maintenance, operation, procedures, handling non-routine events, negligence, or even sabotage. The following section illustrates a few key issues associated with human decision-making, judgment, and operator technique that could affect pure culture operations.

Preventative Maintenance

Preventative Maintenance (PM) is clearly essential to maintaining reliability, safety, and pure culture capability of biotech manufacturing facilities (regardless of the age of the equipment). However, PM work itself is only half of the strength, the other half is designing an effective PM *schedule*: understanding the systems enough to determine both **what** needs to be done, and also the correct **frequency** of when it needs to be completed. Unfortunately, to make the optimal decisions, different technical expertise is often needed for different types of equipment. And if that weren't complicated enough, the pressure to minimize *non-urgent* maintenance costs (by definition, *preventative* maintenance is always non-urgent) is usually prevalent. It is beyond the scope of this work to cover the correct PM work and frequency for all sterile barriers, but here are a few examples to illustrate the importance of the concept:

- Steam Traps: a steam trap will no longer be an effective sterile barrier if it is either malfunctioning or set-up incorrectly (i.e., bypassed). Therefore, all critical steam traps need to be on some kind of PM plan. And, considering the cost of a "run to failure" maintenance strategy for your sterile boundary, the steam trap "PM" may actually need to specify *replacing* the trap at regular intervals. Traps have been known to malfunction if they go unused for an extended period of time, so if your equipment is idled, pay special attention to the traps upon restart (you may even want to run a sterile hold test after long periods of facility idle time).

  Most importantly, it should be the responsibility of the operators to inspect critical sterile boundary traps to ensure they are set-up properly, and then temperature check (via adjacent temperature sensors or even a temperature stick) the trap at the proper location to ensure that it is currently functioning. This obviously can't be done on a PM since it needs to be done for every run so it needs to be spelled out in the batch record or on a separate checklist.

- Valves: the diaphragm in diaphragm valves will wear out over time so it is essential to inspect and replace them on a periodic basis. The exact timing should be based on the frequency of use and exposure to high temperatures, etc.

  Likewise, the ball surface or socket in ball valves also can develop defects that could harbor FG. A ball valve will typically stand up to harsher services longer than a diaphragm valve so that will need to be factored into the PM schedule.

- Vessel: fermentors and bio-reactor internals should be inspected regularly by experienced sterility experts (in addition to vessel experts) to ensure that they remain free of corrosion and defects that could cause media hold-up and eventually lead to a FG.

- Elastomers: elastomers used in and around fermentors to seal connections should be replaced regularly to ensure they don't wear or crack in service. Again, a "run-to-failure" strategy is generally not advised since they are a key element in the sterile boundary, as described above.

- Miscellaneous connections: some preventative activities will be unique to each process. For example, on the piping manifold external to a large-scale fermentor, there was a threaded nipple connection for the occasional addition via a portable inoculum vessel (similar to a threaded hose connection port you have at home). The nipple was normally sealed with a screwed plug and kept under steam block. However, the connection went for many years without being used, and eventually the screwed connection loosened to the point where it would no longer hold pressure. During a standard sterilization process on the vessel, steam collapsed near the connection, and outside, non-sterile air was drawn into the tank post sterilization and caused a contamination. To prevent recurrence, a start-up checklist was developed to include ensuring the nipple was tightened, among other sterility checks.

Operator Technique

In an ideal world, procedures and batch records would be completely objective and able to be followed in a standard, repeatable way, every time. However, in the real world, some operational steps require a certain manual technique gained through experience or coaching to be performed optimally.

An example where good operational technique is required would be the process of transitioning from deadheaded steam to sterile feed in a pipe, such as manually filling a sterilized feed header. After closing all steam traps, while the header is still pressurized, the steam must be closed *while* (or *immediately* before) the feed header is being opened to fill the line. Technique (or a precise automation sequence) is critical because the steam must *not* be given a chance to collapse (creating trapped vacuum) and the header must remain pressurized with steam or feed at all times.

Changes

GMP operations require a formal change control process to ensure that product Safety, Identity, Strength, Purity, and Quality (SISPQ) and process safety are not negatively impacted by process or equipment alterations. For bioprocess operations, it is equally important to carefully scrutinize pure culture impact, both intended and unintended, with just as much emphasis as process safety and SISPQ.

Pure Culture Bioprocessing

Contamination Investigation and Recovery

If you have supported bioprocesses for very long, you have experienced a FG contamination in your tenure. And if you have been unlucky enough to deal with multiple contaminations, you know that each event is wholly unique. Unfortunately, the investigation into the root cause can be similarly unique with no way to predict what factors and conditions might be significant. Indeed, sometimes events outside of your control or changes external to your process facility could be key causal factors in an eventual contamination (see Table F for a case study illustrating this fact).

Nonetheless, even though a comprehensive investigation and recovery guide cannot be developed to cover every FG incident, there is enough in common with any FG investigation that a general strategy can be formed.

The first step in troubleshooting a FG event is to determine if there are any abnormalities observed in process operation. Adverse trends can often suggest where the FG event originated. Conversely, FG or sterile boundary flaws also can be non-detectable by continuous process monitoring measurements. The worst luck of all is to have a system that fails intermittently or in some non-repeatable pattern. The next section will spell out investigation points that have yielded success in troubleshooting FG events.

The challenge of the investigation is to find and fix the design/sterile boundary, equipment, or human factor faults. Table G provides a sample checklist for attacking a FG investigation systematically. A discussion of the key actions contained in the checklist follows. Remember, just because something has worked or been maintained correctly in the past is *no guarantee* that it is *not* an issue now.

Setup: Process air is fed to a large fermentation facility from a plant utility at a separate location. As a part of the compression process, the air is heated to potentially sterilizing temperatures. It is then cooled at the utility facility by large shell and tube heat exchangers with chlorinated tower water.

The fermentation facility began to experience significantly higher rates of foreign growth. The entire process and sterility controls were checked and rechecked for vulnerabilities, but nothing was found that suggests root cause for increase in foreign growth incidents.

Resolution: Finally, the utility department discovered that the air cooling shell and tube heat exchanger has developed a large leak in the tubes, leading to a significant amount of non-sterile tower water sparging into process air. Compounding this problem was the fact that the air filter design for the fermentors was such that free water can promote channeling through the filters as well as alter key electrostatic capabilities of the filter that aid in bioburden removal.

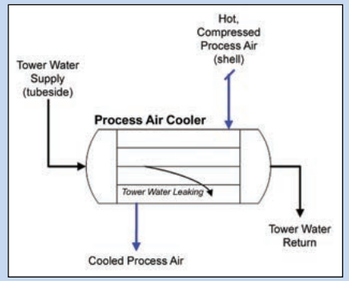

Figure 8. Compressed air cooler with a tower water leak.

The only clue that the fermentation support staff could have used was the dew point meters on their process air. But these were not checked during the intense phase of the investigation. (Admittedly, if the supply air had been sampled, increased bioburden might have been detected, but this action is normally not employed because of the lack of a bioburden baseline or control data for the non-sterile supply).

The real issue in this case was a lack of a preventative maintenance plan on the heat exchanger tubes. They were inadvertently set up to "run to failure;" however, production consequences of this failure were either not fully understood or likely never considered at all.

Lesson Learned: Besides the obvious lesson of looking outside facility boundaries for root causes of poor performance, it is the realization that you need to keep bioburden challenges down around process sterile boundaries. After all, for example, no filter – even a well-designed HEPA – is 100% effective.

Table F. Case study – process air challenge – literally.

Time is of the Essence

If you are able to detect a FG while your process is in operation (as opposed to a post-production analytical contamination test), it is critical to inspect the "on-run" condition of the process, including feed tanks, seed vessels, bioreactor/fermentor, headers, valves, and so on. You are looking for any set-up faults, unusual observations, leaks or other upsets, process alarms, cold spots, or visual faults.

Go for Data

The next step is generally to capture as much data as possible about the process and FG, such as:

- age of FG
- pattern of FG
- any recent changes or unusual observations
- identity of FG
- history of vessels
- recent audits/inspections/Environmental Monitoring (EM) data
- utility upsets
- foaming issues

Widen the Search

To continue to widen the data search, investigate automation and process profiles from your data visualization system, including batch plots, sterilization temperatures, control valve positions, back pressures, feed flows and timing, any process interventions, or unusual previous metabolic trends.

Performing post pressure checks or more sensitive checks with light gases (hydrogen or helium) will help to locate leaks that may have appeared at SIP or on-run. An important note: pure hydrogen should never be used as trace gas. A standard industrial grade mix of five percent hydrogen in nitrogen is used for modern leak detecting. This mix is inexpensive, non-flammable (per ISO standard #10156), easily available, and still holds the important features needed for using hydrogen as trace gas.

Reviewing the batch record and procedures for comments/remarks, as well as interviewing operations personnel associated with the run, can help uncover any unusual execution

- ☐ If possible, as soon as foreign growth is detected, examine on-run condition of process (vessels, feed tanks, headers, etc.)
  - ✓ Valves set-up properly
  - ✓ Steam traps set-up properly and sufficiently hot
  - ✓ Leaks
- ☐ Isolate and identify foreign organisms
- ☐ Gather relevant process data, including tank/process history
- ☐ Check automation/computer profiles of feed tanks, inoculum, and fermentor…
  - ✓ Batch plots
  - ✓ SIP temperatures, including temperature control valve positions
  - ✓ Backpressures
  - ✓ Feeds and timing, including feed control valve position if continuously feeding
  - ✓ Other process interventions
- ☐ Review manufacturing batch record and procedures for observations/remarks
- ☐ Track recent history of facility (environmental monitoring, cleaning, etc.)
- ☐ Note any equipment or process changes
- ☐ Identify recent maintenance that has been performed on the system; check work notes for observations
- ☐ Check for recent process upsets or deviations
- ☐ Interview operations personnel who set-up and monitored process
- ☐ Integrity check and inspect any process air filters
- ☐ Leak check tanks, valves, flanges, and piping
- ☐ Check calibration on temperature probes
- ☐ Inspect pH, DO, etc., probes (install new probes if applicable)
- ☐ Inspect rupture discs
- ☐ Internal vessel inspection
  - ✓ Obvious visual defects – initial inspection
  - ✓ Other tank defects – conduct a very thorough examination of the tank walls and interior hardware
  - ✓ Agitator shaft and seal areas
  - ✓ In a tank with older welds: visual inspection, dye penetrant check, flame check, X-ray examination
  - ✓ If the tank has internal coils, pressure, or leak test
  - ✓ If the tank has internal bolted connections, inspect them for hold-up
  - ✓ Swab suspect areas and test for organism of interest
- ☐ Perform SIP cycle, check all areas within the sterile boundaries to ensure areas are heating up to target temperatures, utilizing probes, temperature sticks, IR technology, etc.
- ☐ Carefully consider changes or shifts to processes and facilities outside of your immediate control (air, water, utilities, media, etc.)
- ☐ Brainstorm other less likely scenarios with investigation team; follow-up and check off items
- ☐ Formulate "return to service" strategy

Table G. Foreign growth investigation checklist.

issues. Tracking recent facility data (such as EM and cleaning records), compiling recent equipment and process changes, and reviewing recent maintenance work (check work notes if available) all help to identify where the facility or its design might be migrating from the original design capability.

Get Hands-on

Walk the system; look for anything out of the ordinary; including: leaks, cold spots, steam traps set up incorrectly, incorrect connections, etc. Inspect and integrity check air filters. Remove (and check calibration on) temperature probes, pH, DO, etc., probes to inspect the probe and o-ring/gasket and groove.

Time to Open Up

If efforts to locate the root cause from the above actions are not successful, a more thorough internal inspection process may be warranted. Internal inspections should include any of the following relevant checks: obvious visual defects, subtle defects detected by a very thorough examination of all wall and internals surfaces, agitator/shaft vulnerabilities, weld defects or hold-ups (typically older tanks), coil leaks (if any tank has internal coils, they always need to be inspected, and should be on a regular inspection program), and bolted connection defects (again, typically older vessels).

Experimental

This is hypothesis and scenario testing. For instance, if the sterilization process is suspected, conduct sterilization runs in which as much of the area within the sterile boundary can be checked to ensure it is meeting the minimum temperature. This can be as sophisticated as temperature mapping or Infra Red (IR) sensing technology to the low-tech temperature stick check of lines. Investigative media holds are another example.

As the investigation proceeds, microbiological data on the adventitious agent could be essential to understanding the FG and its root cause. The discussion below will provide details on how understanding the microbiology of the FG agent will aid the investigation.

Microbiology Investigation

To begin, you must understand the sensitivity and limitations of your FG control strategy and test methods. This understanding is crucial to evaluating the impact to process quality and understanding how and at what point the FG may have been introduced into the process. Some critical factors associated with a control system include sample frequency, test volume, testing media, test method, risk of false positives, confirmation testing, retest/resample options, and so on.

By definition, FG testing is screening for the presence of a small population of unknown organisms within a high background of known organisms; thus, it is essential to have a method for isolating the foreign organism so it can be identified and evaluated. Selective broths and agars are indispensable in this activity. Streaking for isolation onto non-selective agar from a test plate or tube may be sufficient to gain isolated colonies for identification. However, odds are greatly increased if selective agars are employed to inhibit the growth of the production culture and/or stimulate the growth of the potential contaminant. This is illustrated in Figures 9 and 10.

Once the foreign organism is isolated, appropriate identification testing should be completed. Biochemical and/or genetic ID methods are useful in comparing one isolated organism to another (i.e., from a different location or an earlier FG event) to confirm a potential common source. Confirmation of the contaminating organism as genetically identical within the limits of the method may be helpful in focusing the investigation on a common system or alternatively, focusing the investigation on independent root causes.

Studies to determine phenotypic characteristics for carbon/nitrogen utilization and growth rate in the production medium, as well as media for a "media hold study," should be initiated concurrent with ID of the isolated organism.

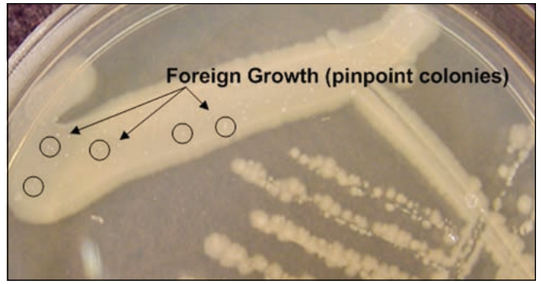

Figure 9. Non-selective agar plate. Note visible foreign growth (pinpoint colonies) mixed within the lawn of production microbial cells.

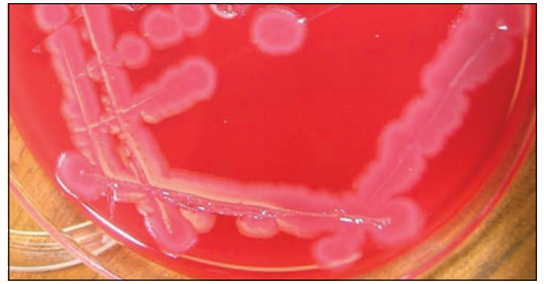

Figure 10. Selective Columbia CNA agar plate with Bacillus foreign growth (pinpoint colonies from Figure 9) isolated from Gram negative production cells.

(**Media hold** refers to a "sterile" test run of the fermentor and associated systems utilizing a suitable nutrient medium capable of supporting growth of likely foreign organisms.) Phenotypic characteristic studies will facilitate hypotheses about the potential source of the organism and potential time of ingress. They also provide a foundation for determining an appropriate media hold strategy.

If antibiotics are included in the production medium for plasmid selective pressure or are being produced by the culture determining the Minimum Inhibitory Concentration (MIC) for the FG organism is again beneficial in theorizing potential root cause and time of ingress.

Caution should be taken when considering non-routine testing of systems that have no baseline data for comparison. In this situation, to avoid erroneous data or interpretations, additional work may be required to demonstrate recovery of various organisms and to 'qualify/validate' the test method.

Fit for Purpose Strategy

The ideal scenario, but unfortunately not realistic, is to have a bioreaction system that could be sterilized and remain free of FG for an infinite period of time. Further, a decision to initiate media holds to confirm process capability following a FG event is not trivial since it may have a huge impact on your ability to return the equipment to service. Therefore, it makes sense to define a "Fit for Purpose" timeframe based on the process being run, and then design your media hold test strategy to demonstrate system capability within this timeframe. Again, it is worth noting that the discussion below is derived from a traditional microbial fermentation process. However, the principles can be applied to any bioreactor system by adjusting for specific process and business requirements.

Proper Fit For Purpose definition of your equipment scope, medium, end time, sampling/testing strategy, and number of repetitions is crucial to maintaining operational flexibility. For instance, it is recommended to define end time based on your process cycle time (or alternatively, the longest process time performed in that equipment set), plus an appropriate safety factor.

Safety factor can be represented by both additional hold time and testing sensitivity. The longer you hold your medium, the more likely to detect FG if it is present. Also, the larger volume tested, the more likely you are to detect FG. An appropriate combination of these factors should allow you to obtain a suitable safety factor that can be agreed upon by both technical and quality partners.

For more rigorous sterility challenges, such as mammalian cell cultures, a fit for purpose study might be focused specifically on maintaining sterility for the required process time plus an additional hold time as a safety factor (granted, for very long perfusion-type bioreactions, even maintaining a sterility test for the length of the process might not be a practical restart condition). For shorter microbial fermentations overcoming a specific bacterial contamination, a different approach can be employed. For example, a process takes 24 hours from SIP to harvest and typically tests 50 µL (5×10^{-5} L) of pre-harvest broth. A FG is detected and analyzed to have a one-hour doubling time. A media hold is designed to test 5mL (5×10^{-3} L) of broth and extend hold time by six hours to a total of 30 hours. This provides a 100X ($5 \times 10^{-3}/5 \times 10^{-5}$) sensitivity increase from volume and a 64X (six additional hours equals six doubling times = 2^6) increase from hold time for a total safety factor of $100 \times 64 = 6{,}400$X.

Growth testing of each batch of sterile hold medium with suitable FG organism(s) is required to confirm the validity of your hold medium. At the very least, this should include the current organism of interest and may include previous FG organisms and/or USP organisms.

If the investigation has not yielded a root cause, a more extensive, *investigative* media hold can be a beneficial tool to uncover the source of the contamination. However, this should be initiated only after establishing your Fit for Purpose acceptance criteria in order to avoid getting operationally limited by unreasonable expectations. A typical Fit for Purpose hold strategy may include all feeds added at the start of the hold period to demonstrate that the system, as a whole, can remain free of detectable FG for the required Fit for Purpose time frame. In contrast, an investigational media hold may separate these feed additions by an appropriate hold time to allow for identification of a contaminant source. The amount of each feed added should be based on an adequate volume representative of the process. The hold time between additions needs to be long enough to reasonably detect a contaminant if

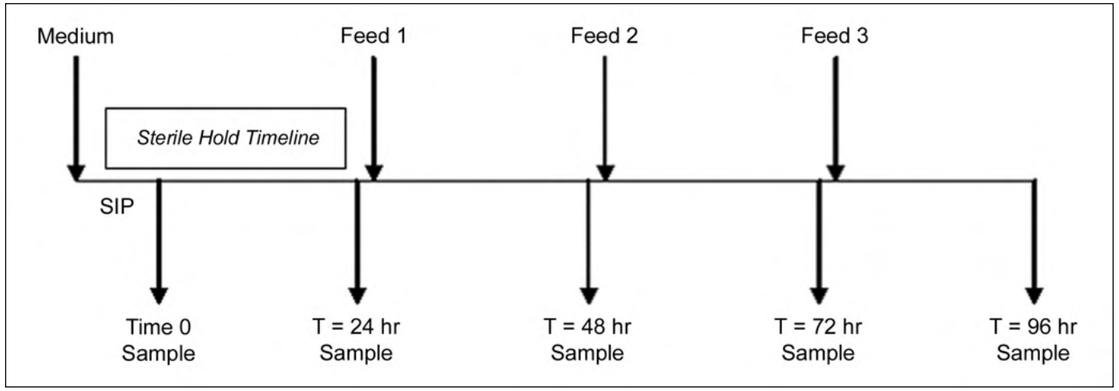

Figure 11. Timeline for investigative media hold detailing feed and sample times.

introduced. Again, you can increase your test volume in order to increase test sensitivity and reduce the time interval. See Figure 11 as an example of an investigative media hold based on a 24-hour addition interval.

Conclusion

FG events in fermentation processes are a significant cause of factory loss and reduced productivity, to what degree depending on the process being run and the tolerance for FG. Natural product processes may suffer a loss of productivity or a shift in factor ratio as a result of FG but the broth may still be harvestable. Most microbial and cell culture processes have a zero tolerance for FG so any detectable FG represents a complete loss.

As the biotech industry matures improvements will be made in the following arenas: reactions will become more concentrated as titers and specific activities increase, disposable systems will become more prevalent as smaller amounts of the therapeutic compound are required, operational excellence will continue to improve as companies become more skilled at running bioreactions (or outsource them to specialized third party contractors), and equipment will perform more efficiently – and more reliably – through engineered improvements. As a company evolves on these fronts so does their competitive advantage in the biotech industry.

Correspondingly, as bioreactions become more concentrated and reactors more specialized, the need to improve pure culture capability becomes more critical to achieve this competitive advantage. Basic fundamentals that are well-understood and practiced for decades are implemented to achieve successful operations with low contamination rates. Why then do contaminations continue to plague bioreactions even as technology improves and the industry becomes more mature? A recent study found that the contamination rate in production-scale bioreactors is still over 2%.[17] The answer is it takes more than good sterile design to eliminate contaminations; human factors and system decay, combined with adventitious agents that continuously and relentlessly probe every possible and improbable vulnerability, are all invariably working against your pure culture operation.

In this work we have illustrated the basics of sterile design and sterilization. We have detailed through examples and case studies the importance of building an organizational tradition where bioreactor staff are always vigilant regarding system decay, changes in equipment or procedures, and who are dedicated to preventative measures to keep systems performing at peak. Moreover, when contaminations occur, we describe how effective and comprehensive investigations are managed, including the microbiological elements required to minimize future recontamination by the same adventitious agent.

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A Methodology for Knowledge Management in Biopharmaceutical Production

by Jennifer Coakley, Nicola Hogan, Linda McGuire, Brendan Griffin, Colman Casey, Cliff Campbell, and Abina Crean

This article presents a novel ontological, stepwise approach undertaken to itemize and standardize a biopharmaceutical manufacturing process into a multidisciplinary plant and process knowledge model.

Introduction

Within the biopharmaceutical manufacturing sector, a staggering amount of documented information is required to meet corporate and regulatory requirements. In July 2003, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[1,2,3] introduced an integrated approach to quality risk management. This 2003 workshop agreed on a vision for moving forward with harmonizing finished product GMP to achieve "a harmonized pharmaceutical quality system applicable across the lifecycle of the product emphasising an integrated approach to quality risk management and science."

This agreement led to the establishment of three key topics, or "incremental steps," namely Q8, Pharmaceutical Development,[1] Q9, Quality Risk Management,[2] and Q10, Pharmaceutical Quality Systems.[3] Other key drivers for changes in interpretation of GMP were the FDA's PAT initiative (2002)[4] and the 'cGMPs for the 21st century' initiative,[5] both of which promote a science-based approach to quality systems management and utilizing modern knowledge management techniques. Both ICH Q10 and

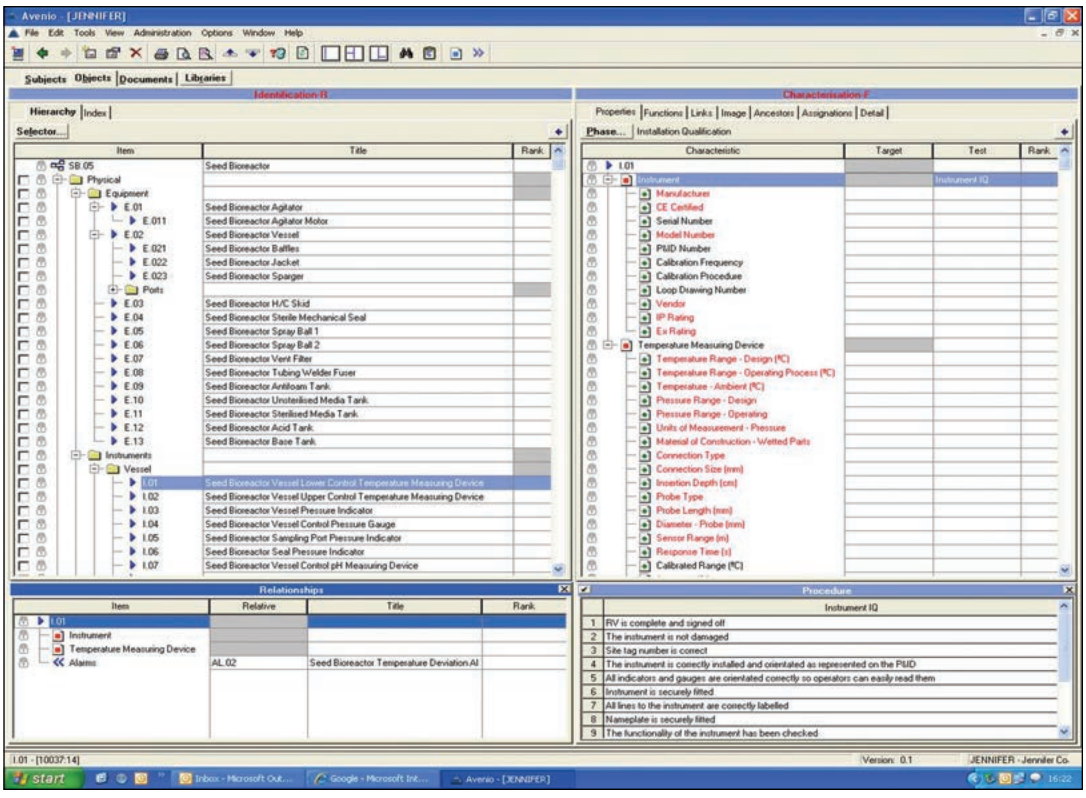

Figure 1. Screenshot of a system, a bioreactor, within the model.

the FDA's PAT initiative specifically highlight the need for centralized databases to capture technical standards, multidisciplinary knowledge, and multi-factorial relationships within a manufacturing environment. One major advantage of such systems would be the potential to standardize plant and process information throughout the biopharmaceutical sector.

The National Institute for Pharmaceutical Technology and Education (NIPTE) in its 2007 strategic roadmap[6] identified "Informatics-Based Model Development and Integration Infrastructure" as a key research requirement to support the pharmaceutical manufacturing sector. *"The lack of formal standards and protocols for representing, sharing, and integrating different types and sources of data and models to facilitate automated decision making,"* was cited as a barrier to the development of these technologies. A research need particularly highlighted was the development of standards and related formal structures, such as ontologies for representing and sharing data and models. In this document, NIPTE also underlined process understanding as one of 10 key areas for research emphasis, indicating the importance of and the need for an increase in fundamental understanding of critical operations and critical process parameters.

While there are many definitions of what is meant by ontology in the fields of philosophy and artificial-intelligence,[7] with respect to the development of a model, which in our case is the biopharmaceutical manufacturing environment, an ontology refers to a formal explicit description of classes. A class can be essentially viewed as a 'type of object' or a 'kind of thing.' The classes within the ontology are described by their properties, i.e., the various features and attributes belonging to the individual class. In creating many instances of these classes, we created the biopharmaceutical knowledge base or model.

The objective of this article is to outline a novel ontological, stepwise approach undertaken to itemize and standardize a biopharmaceutical manufacturing process, into a multidisciplinary plant and process knowledge model. The model developed was structured and inter-connected, yet flexible. The model was primarily used to generate commissioning and qualification documentation across the required lifecycle phases, but also it acts as an easily accessible, centralized repository for knowledge management, such as engineering and quality data, SOPs, electronic user manuals, and P&IDs. All data could be front-loaded into the model, either as individual items or imported in bulk *via* Excel or other spreadsheets/databases. The data was structured and presented as discussed throughout this article and Figure 1 displays a screen shot of a typical system, a bioreactor.

This overall plant model has been successfully deployed on several real life projects and one of the objectives of this research was to demonstrate that a modular approach to plant design is equally applicable on behalf of process. In other words, we wanted to evaluate the models ability to facilitate connectivity between the two layers, particularly in regard to the assignation of criticality, as in "this parameter is measured by this instrument, are they compatible?" We were confident that both challenges would be answered in the affirmative.

Aims

The overall aim of the project was to collate and model detailed plant and process information relevant to biopharmaceutical processing. The initial step in the development of such model was to outline the aims of the biopharmaceutical knowledge model.[8] Firstly, the aim was to provide a common description of the biopharmaceutical production process that could be clearly understood by a variety of users: production, quality, engineering, and technical services personnel. The second step was to determine the overall scope of the model. It was deemed that this model would contain all the essential plant and process information. Common unit operations were broken down into smaller, more specific process steps and plant equipment used within each of these steps, was subsequently modelled in detail.

Thirdly, we aimed to design a reusable database of centralized, multidisciplinary plant and process information to sufficiently model[8] a biopharmaceutical production environment. The final aim was to develop a glossary of terms used within the database.

Methodology

An iterative top-down, bottom-up model and review approach[8] was undertaken using the modelling and validation software, Avenio. The overall hierarchal structure of the model was decided upon initially (top-down method). This consisted of typical unit operations containing the relevant plant systems and process steps, placed in appropriate plant and process folders for clarity. These systems and steps were then filled with the relevant minor components (bottom-up method). The basic procedure for entering a typical item, a unit operation, plant system, or process step was as follows. The software allowed us to select a symbol to represent the desired item, e.g., a bioreactor, which was then identified, using a name or code and a title and displayed on the left hand side of the screen. Each entered item was subsequently characterized in detail on the right hand side and all characterization items were conveniently stored in hierarchical background libraries to allow for single entry, multiple use. Once all the required items, such as plant equipment, instruments, and process parameters had been entered, identified, characterized, connected, and reviewed their respective target values were assigned. These target values could then be compared with the actual attained values for these systems, components, and processes in question to verify their capability to meet the required values. The structure, components, and characterization were then reviewed for suitability and coherency by Subject Matter Experts (SMEs), recommended changes were implemented, and the model was again reviewed (iterative review). Figure 1 displays a screen shot of the database, specifically a bioreactor, with equipment parts and instruments visible on the top left of the screen. The alarms monitoring the relevant critical process parameters for this process step are visible on the bottom left. The detailed information required to characterize a bioreactor is visible on the top right. A procedure for performing an installation qualification on the bioreactor is visible on the bottom right. For the purposes of this research project, only a limited amount of target or actual values were entered into the model, owing to the substantial range of possible assignable values.

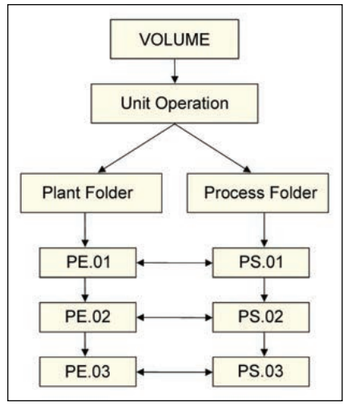

Figure 2. A schematic of the overall hierarchy.

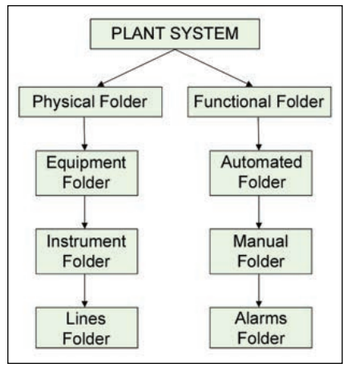

Figure 3. A schematic of the plant system hierarchy.

Naming Conventions

Suitable naming or tagging conventions were established for distinguishing systems and components of the model. These unique names or tags consisted of capitalized alpha-numerics with a period between the alpha and numeric section, e.g., Process Step No. 1 (PS.01). Contextualized titles that were highly descriptive and distinct were given to all items to provide further information; for example, a sampling port on bioreactor would be called: P.01 Seed Bioreactor Sampling Port.

Overall Hierarchy

To begin with, for the process or volume of interest, a generic biopharmaceutical process 'train' was determined. This was accomplished *via* consultation with Subject Matter Experts (SMEs), ISPE and other regulatory guidelines,[9-14] Piping and Instrument Diagrams (P&IDs), and site visits to relevant production facilities.

Ultimately, this process resulted in the development of a process flow diagram. This process flow diagram was then used to sub-divide the process into the relevant unit operations, process steps, and plant systems. Unit operations refer to the basic steps that carry out one function in a multiple operation process. Following this, plant systems, consisting of high level equipment and also equivalent minor process steps were identified and located in the relevant unit operation. For example, the plant system, production bioreactor, and process step (main fermentation) were located in the unit operation (fermentation).

To generate the hierarchy, firstly the numerous, constituent unit operations for the particular biopharmaceutical volume or process were entered into the database. Each unit operation contained a plant and process folder as shown in Figure 2. Each process folder consisted of any number of smaller Process Steps (abbreviated PS), such as PS.01, PS.02, and PS.03. In parallel with each of these process steps, each plant folder contained an equal number of equivalent Plant Equipment systems (abbreviated PE), such as PE.01, PE.02, and PE.03. For example: PE.01 refers to Plant Equipment No. 1 and PS.01 refers to Process Step No. 1.

Plant System Hierarchy

Within each of the individual plant systems, folders were created to provide useful groupings of the various items or components comprising the system.

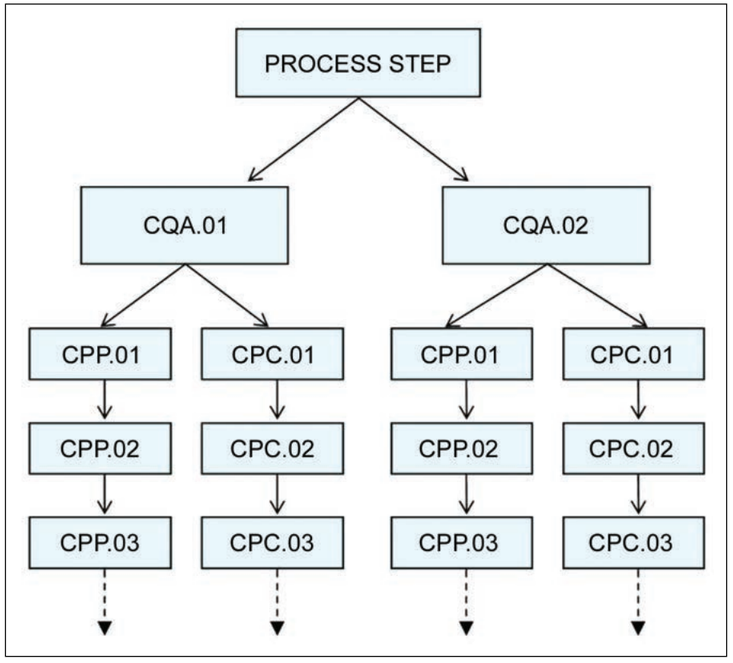

Figure 4. A schematic of the process step hierarchy.

Each system was first split into physical and functional folders, as shown in Figure 3. The physical folder was further divided into equipment, instruments and lines folders, populated with the relevant components, such as equipment parts, attached instruments, and utility lines. The functional folder also was further broken down into three specific types of functions: automated functions, manual functions, and alarms - *Figure 3*. Each of these individual items also could be assigned a criticality level if required; for example, high, medium, or low.

Process Step Hierarchy

The process model was characterized using three types of critical components. The first, Critical Quality Attributes (CQAs), were defined as physical, chemical, or microbiological properties or characteristics that need to be controlled (directly or indirectly) to ensure product quality.[14] For example, biological purity would be a CQA in a filtration step of any typical biotechnology process. Each critical quality attribute was linked to any relevant Critical Process Parameters (CPPs) and Critical Process Controls (CPCs) that could potentially influence it. Critical process parameters are defined as process parameters whose variability impact quality attributes and therefore, need to be controlled to ensure the process produces a product of the desired quality.[14] To take the previous example of an ultra-filtration step, temperature would be considered a critical process parameter, as it may influence the stability or biological structure of the biopharmaceutical product.

For the scope of this project, we have defined critical process controls as critical parameters that cannot be directly measured by an instrument during processing, but can be monitored or tested for before, during, and/or after a process is carried out to ensure the process is/was under control. To provide structure for these components, a subfolder is created to contain the relevant CQAs within each particular process step. For each CQA, the CPPs known to directly impact it, and the CPCs associated with it were identified, as illustrated in Figure 4. Relevant CQAs, CPPs, and critical CPCs were determined for each process step utilizing risk based methods.[2,15] Finally, each CPP was connected via a relationship to the test or procedure used to verify it. These tests could be carried out at any stage of the process, during start up, in-process, or as part of finished product testing and are categorized as such. For example, following a typical biotech process step, such as ultra-filtration, a variety of bioassays would be carried out to check biological purity of the protein.

Classifications

Classifications are the characterization mechanism employed to attach a multitude of information to individual items, such as plant systems, unit operations, instruments, or critical quality attributes.

The information attached using this feature can take a number of forms; for example, instructions, operating procedures, documentation, images, and attributes, as shown in Figure 5.

Items were initially created at 'higher level' (e.g., plant systems and process steps) and subsequently filled with relevant 'lower level' components (i.e., equipment parts and critical process parameters) and characterization could occur at each of these levels. Therefore, each plant system and process step was characterized using a system or step level class. Accordingly, items were characterized at component level, using component level classes. For example, physical and functional components, such as instruments and alarms of plant systems and lower level components of process steps, such as CQAs, CPPs, and CPCs, were characterized at this level. To facilitate the generation of validation documentation, various verification milestones involved in the lifecycle of a typical product were created within the model, such as Design Qualification (DQ), Installation Qualification (IQ), and Operational Qualification (OQ). Using the software platform, it was then possible to 'disable,' i.e., switch off or hide from screen and document view any un-required information attached to items, for each of these various lifecycle phases. For example, during an OQ of a bioreactor vessel, it would be unnecessary to verify the surface finish of the vessel, as this would have been confirmed during DQ; therefore, the attribute, surface finish was disabled for the OQ phase.

All classifications thus created were stored in a central library, therein facilitating a single entry – multiple use

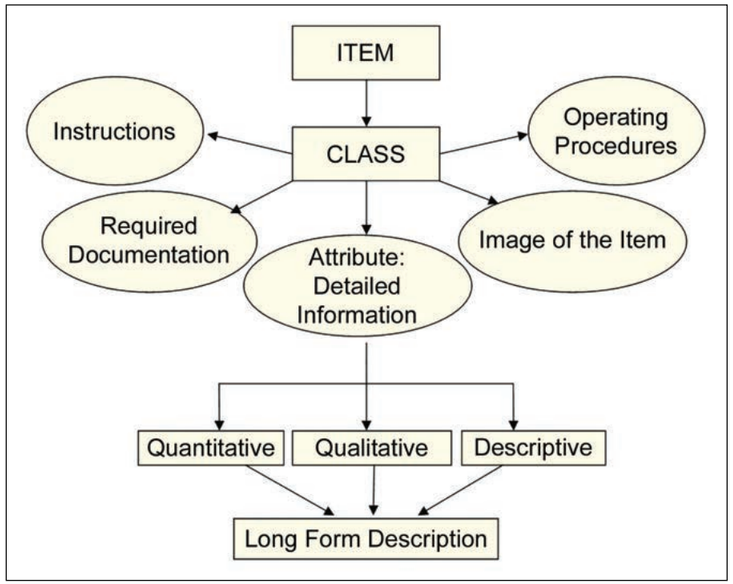

Figure 5. The structure of the classification of items.

concept. This eliminated unnecessary duplication of data and effort. During the population of the database, whenever a plant system, process step, or component was repeated in the model, the original classification stored in the central library could be attached. For example, within the biopharmaceutical process modelled, each time a pressure gauge was required, instead of generating another pressure gauge classification and associated information to be attached to it, the classification stored in the library could be connected. As each classification could be attached to an indefinite amount of relevant items, it was crucial that each classification contained only the essential attributes that provided the information or specifications to adequately detail the component or function in question. For instances of equipment and instrument components, where classifications used often contained large numbers of attributes (i.e., >20), up to two additional classes were attached to the main class. It was determined that each class layer would only contain attributes of a similar level of generality; as a result, classes were created on three tiers: General, Specific, and Detailed. For example, a diaphragm pump was classified and assigned attributes in the following manner:

1. The general class equipment, containing the attributes pertaining to all pieces of equipment; for example, manufacturer, model number, etc.

2. The specific class pump, containing all attributes applicable to pumps; for example, weight and material of construction etc.

3. The detailed class vacuum, containing the relevant attributes to describe vacuum pumps in particular; for example, ultimate vacuum.

Attributes

Of the various types of information that can be attached to the class of an item, attributes warrant specific attention. The attachment of attributes to items *via* their class provided more detailed information (qualitative, quantitative, or descriptive) regarding items.

For example, the class bioreactor, contained the qualitative attribute: Material of Construction, the quantitative attribute: Capacity, and the descriptive attribute: Manufacturer. As required, attributes could be assigned an appropriate target value and continuing on the previous example: the target values for Material of Construction, Capacity, and Manufacturer would be 316L SS, 500, and BioEng Ltd., respectively. Further text, such as descriptive information or prior knowledge, could be attached to each attribute as necessary. The attributes in each general class are inherited by each specific or detailed class. As the attributes of the general class, Equipment, were attached to all manner of equipment regardless of the function, caution was used when determining suitable attributes for this class. It was essential to ensure they were entirely applicable to each equipment sub-class (bioreactor, pump, valve, pressure gauge, etc.). When classifying non-equipment components of the plant system, such as lines, functions (automated, manual, and alarms), and of the process steps (CQAs, CPPs, and CPCs), it was found that one level of classification (general) was sufficient to contain the essential attributes.

For the process steps, all CPPs were assigned the CPP class which contained the attributes Target, Hi Limit, and Lo Limit. Also attached to all CPPs was a risk assessment class, containing relevant risk assessment attributes divided between two folders, Risk Assessment I and II. To perform the risk assessment, we utilized a multidisciplinary group of SMEs, in conjunction with a Failure Modes and Effects Analysis (FMEA) method to evaluate the probability, severity, and detectability of each possible failure mode.[2,15] Risk Assessment I contained the attributes probability and severity, while Risk Assessment II was assigned the attributes detectability and risk priority ranking. The combination of these classes and attributes provided the platform for risk assessment within the model.

Class	Attribute	Target Value
CPP	Target	121.0°C
CPP	Hi Limit	121.1°C
CPP	Lo Limit	120.9°C
Risk Assessment (Folder I)	Probability	Low
Risk Assessment (Folder I)	Severity	High
Risk Assessment (Folder II)	Detectability	High
Risk Assessment (Folder II)	Risk Priority Ranking (RPR)	Medium

Table A. Calculating the risk priority ranking for a variation in sterilization temperature of a vessel outside of the acceptable range.

Table A shows an example of how values assigned to these attributes were used to calculate the risk associated with a variation in sterilization temperature for a vessel outside of the acceptable range.

Connectivity

To provide even greater connectivity between the plant components, functions, and process systems, a series of relationships or 'connections' were created. Within each plant system, instruments were connected to their associated alarms. These alarms were then connected to the CPP that they monitor within the equivalent process step. CPCs were then connected to the particular test used to monitor it. A schematic of the overall hierarchy and connectivity can be seen in Figure 6. As a result of the parallel modelling of the plant systems and process steps, a platform for risk assessment was enabled. Our system could be used to identify CPPs or CPCs in an existing process that are not monitored by instruments or in-process tests that could potentially introduce risk into the process, by comparing it against our model. The screen shot of the database as seen

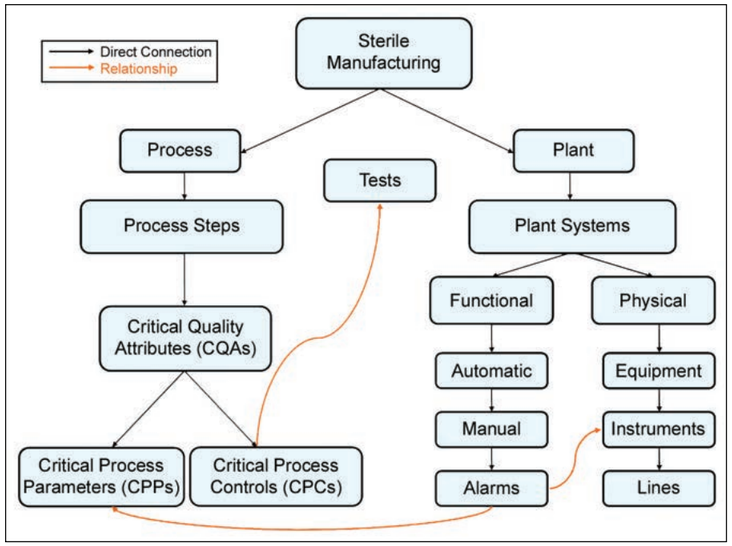

Figure 6. Overall structure of the ontology.

in Figure 1 illustrates a plant system with component parts and attached attributes, relationships, and procedures. The capacity for connectivity between components and their relevant classes, attributes, functions, and procedures is clearly illustrated.

Use

The overall model and software serves as an excellent knowledge management tool and validation documentation generator. With detailed technical and engineering data available immediately, in a concise, useful format, issues such as part or instrument replacement are much simplified and quickly resolved. While the model does not feed from real time, in process information, it can be invaluable in process deviation investigation or Corrective Action and Preventative Action (CAPA). Current approaches to identifying the root cause of a deviation can often be arbitrary and the model assists in streamlining the decision making process. For example, if having sterilized a seed bioreactor, testing revealed the presence of contamination, the model could be used to determine which CQA was affected and provide direction as to which CPP was inadequately controlled and may have led to the unwanted issue. This would result in more efficient and rapid deviation resolution. The software also has several functionalities, which would allow the deviation and resolution to be recorded in a number of formats and attached to the appropriate items at any level.

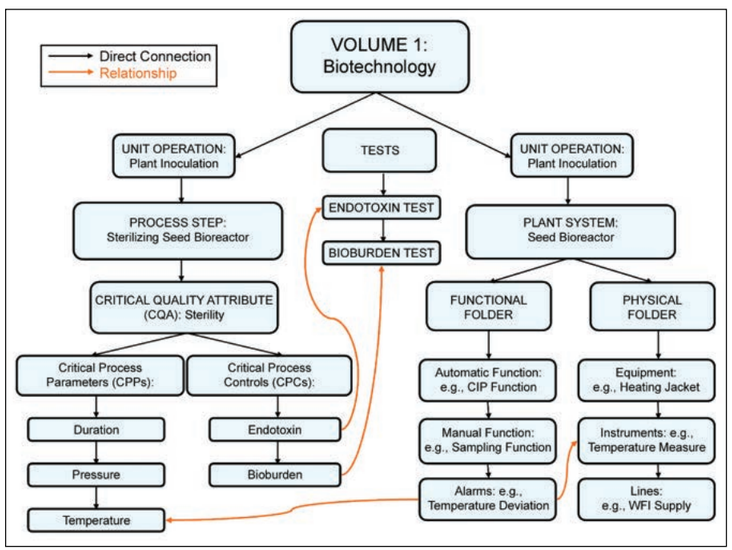

Figure 7. Schematic of a system, the seed bioreactor, and its equivalent process step.

Conclusions

The work performed during this project has resulted in the formation of a novel methodology, which can be used to successfully and explicitly model a variety of biopharmaceutical processes. The methodology illustrates the benefits of structured and reusable multidisciplinary data, information, and knowledge stored in one centralized location. The modelling of the process, in parallel with the plant, allowed for the risk-based determination of the relevant CQAs, CPPs, and CPCs, thereby leading to greater process understanding.

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An Exhausting Solution for Fermentors

by Ernest L. Stadler

This article provides various solutions from simple to complex that deal with the removal of water vapor, liquid particles, and solid particles that can escape a fermentor exhaust nozzle and clog the sterile exhaust filter.

Introduction

All processes are generally "debottlenecked" to optimize productivity. Process improvement in microbial fermentation is no different. Batches are often "pushed" to achieve higher cell densities. This will increase productivity by improving product yield; however, it does require an increase in the cultivation time since the organism doubling time is fixed by the organism being used. Also, similar trends exist to achieve higher cell densities in cell culture bioreactors. The length of a fermentation batch is usually limited by depletion of a growth component or lack of oxygen or lack of cooling. One very troublesome limitation that can lead to ending a batch prematurely occurs when the sterile exhaust filter becomes clogged from "wetting out" and/or "solids loading" on its surface. Loss of air flow brings about a quick end to respiration and the cells will begin to die. The proper choice of exhaust pathway components can deal with the variety of factors that tend to foul the exhaust filter element. The principles discussed here apply to both microbial fermentors and cell culture bioreactors; however, microbial fermentations will be severely limited, due to relatively higher gas flows when exhaust path design is not given proper consideration.

In general, the achievement of higher cell density will require more oxygen mass transfer for aerobic fermentations. This drives the need for higher aeration rates as well as higher agitation rates. In microbial fermentors, this can place a demand on the hydrophobic sanitary exhaust filter elements requiring them to remain unclogged for the duration of the batch. Extended operation will allow even the very last organism doubling to take place as the maximum cultivation time is achieved.

Exhaust Filter Elements

The customary material for sterilizing grade exhaust gas aseptic processing filter elements are 0.2 micron membranes comprised of expanded polytetrafluoroethylene (ePTFE) commonly referred to as teflon based on Gore™ material. An integrity test correlated to ASTM F838-83 bacterial challenge test would demonstrate the validity of the rating. The 0.2 micron rating refers to a membrane whereby validation testing has proven the filter as being capable of withstanding a microbial challenge. The challenge would demonstrate the membrane as being capable of withstanding 1×10^7 *B. diminuta* organisms per square centimeter of membrane surface area.

This size exclusion is meant to prevent external adventitious organisms larger than 0.2 micron from entering the sterile boundary where they could establish themselves and contaminate a batch of potentially high dollar value product. Similarly, the exhaust filter is expected to keep the microbes of interest inside the fermentor sterile boundary to protect the external environment. However, it should be noted that a limited group of bacterial spores and viruses can be smaller than 0.2 micron. There has been some thinking that the size exclusion should be lowered to 0.1 micron, but excess pressure drop and a propensity to clog quicker

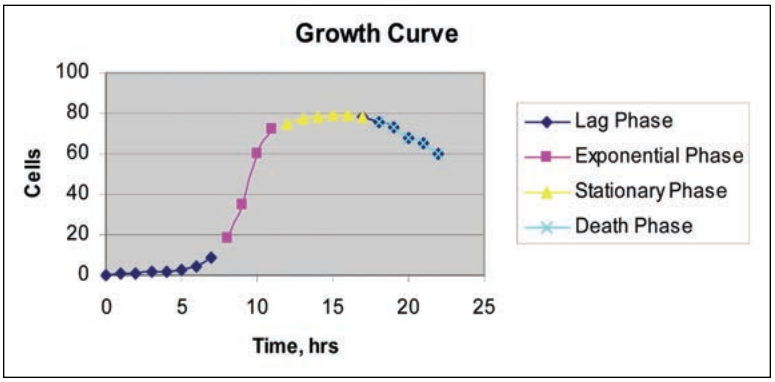

Figure 1. Typical growth profile.

have deterred most users from specifying a membrane with a rating lower than 0.2 micron.

Now, due to the hydrophobicity of this filter element material, i.e., it resists wetting by water, the element itself has a finite operating time when it is presented with a very wet gas stream comprised of liquid fines and small solid particles. Herein lies the challenge when debating the correct treatment of exhaust gas leaving the fermentor. Remember that the exhaust gas is heavily saturated with moisture and is at or near 100 percent relative humidity. It is important to think about all of these effects with respect to where the culture is in its growth kinetics.

We commonly think of the batch as existing in one of four stages of growth,[1] i.e., lag phase, exponential growth phase, stationary phase, and death phase. The following typical chart represents these phases over time in a growth curve having no specific quantification of number of cells:

The exhaust velocity is highest near the end of the batch since oxygen demands and sparge gas flow are greatest at this point of maximum cell density. Exhaust gas at this high velocity will most likely have a high percentage of fine liquid particles as well as solids. Where do these particles come from?

Source of Particulates

A few common sources are:

- Sparge gas bubbles breaking the surface interact with proteins in the broth and create foam at the surface. Foam bubbles at the upper most layer break open and discharge wet particles containing solid material carried up in the foam layer. High sparge gas flow rates exacerbate this problem, but are necessary to support oxygen mass transfer.
- High mixing speed contributes to an "agitated" liquid surface area. Aggressive mixing will cause splashing on the baffles and general surface vortexing all of which contribute to creating of liquid fines in the headspace. Often the surface of a highly aerated and agitated fermentation will appear to be boiling with the surface surging up and down in a seemingly random pattern.
- Droplets of moisture dripping down from the top head and addition port dip tubes or other internal pipes act as small implosions when they hit the liquid surface level of the broth. Each droplet has an almost equal reaction in that a jet of liquid is sent up from the liquid level creating liquid fines as it breaks up. These small particles can be carried out through the exhaust in the high velocity gas stream.
- Liquids that condense in the exhaust pathway and reflux back to the fermentor must flow against the exhaust gas stream and eventually drip back into the headspace and onto the broth surface.

Vessel Head Space and Foam

It is not recommended to increase the working volume of a fermentor in an effort to gain higher productivity. The first consideration to deal with the myriad of liquid and solid fine particles generated is to have a vessel geometry with ample freeboard head space above the fully gassed liquid level. A good rule of thumb is to allow 25% of the total vessel volume dedicated to freeboard headspace above the unaerated liquid working level. This may need to be even higher in processes where very high aeration will greatly expand the working volume height. This "free" volume of space allows particle conglomeration by impingement and de-entrainment by settling. Many particles will drop back to the surface if they are in relatively low upward velocity zone. Ample freeboard space above the working level also is necessary to deal with the formation of foam from the process. Foam level control is a very important first step to ensure long cultivation time. There are a variety of foam breaking techniques that will cut the foam layer and keep it from escaping the exhaust nozzle where the liquid and solid particles can very quickly clog the exhaust filter bringing the batch to a screeching halt. These include the spurious addition of antifoam agents to the batch, addition of electro-mechanical foam breakers (slingers or disk stacks), or addition of external foam separation devices.

Foam breakers can be installed in the headspace to collect the foam and direct it back to the vessel side walls where the liquid will run back down the vessel wall into the liquid broth. The function of these electro-mechanical devices is to protect the fermentor vessel exhaust nozzle from being filled with a slug of foam. Foam is the single largest contributor to rapid clogging of the exhaust filter element with resultant loss of gas flow. Another type of device that can be considered is an external vortex style separator to obtain a relatively moisture free gas stream leading to the exhaust filter.

The Great Debate

The most debated area and one where experience brings a variety of solutions is how the exhaust path piping and components are treated between the fermentor broth surface level and the inlet of the exhaust filter housing. As in all engineering design, first principles must apply and the simplest solution that will do the job is usually the most effective. However, sometimes complexity must increase when pushing the limits of conventional practice. The resultant productivity improvements can only be achieved by proper application of additional components. Let's start by building a simple system and establishing a path that will allow successively longer cultivation times to understand how the complexity can increase.

Batch: Simple Aeration: Low Agitation: Normal Foam: Low

A simple batch could be as short as 18 hours to 24 hours so there is no extended operating time necessary to achieve high cell densities. A simple batch fermentation is one with traditional Optical Densities (OD_{600}) of 20 to 60 Absorbance Unit (AU) measure OD at 600 nm wavelength and Oxygen Transfer Rate (OTR) in the area of 100 to 120 mMol O2/L/hr. A typically accepted rule of thumb is that 1 AU equates to 1 gm/L dry weight of cells in the broth. This is a very easy target for simple microbial fermentations that will yield acceptable performance. Gassing rates could be as low as 0.5

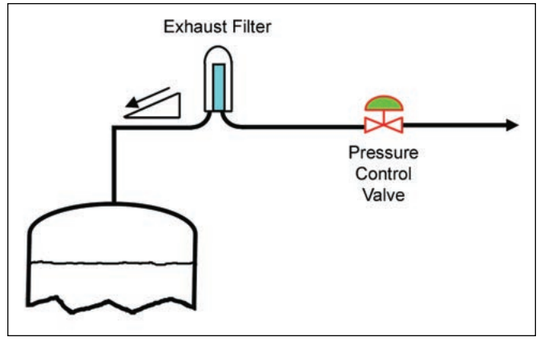

Figure 2. Simple exhaust path.

Vessel Volumes per Minute (VVM). If foam is not a problem, a very simple exhaust path sloped back to the vessel with an exhaust filter and backpressure control valve will do the job as shown in Figure 2.

Note: For purposes of explaining the effects of droplet re-entrainment, we should visualize the liquid condensate running down the vertical exhaust pipe and dripping (refluxing) back into the fermentor flowing against the normal exhaust velocity of gas escaping up through the exhaust pipe.

Batch: Simple Aeration: Medium Agitation: Normal

A simple batch could be as extended from 24 hours to 30 plus hours to achieve higher cell densities by virtue of supporting additional microbe doublings. In this case, the optical densities could be in the range of 80 to 160 AU (OD_{600}) and Oxygen Transfer Rate (OTR) in the area of 200 to 300 mMol O2/L/hr are not uncommon. The air flow rate will typically be at least 1.0 VVM during maximum metabolism of cell mass. Foam will most likely become a problem and clogging of the exhaust filter must be prevented. A typical first step to control foam in the headspace is to provide for a control loop to add liquid antifoam when the foam has reached a predetermined level. The addition is generally introduced via a "J" tube or straight inlet tube each of which rely on mixing to disperse the antifoam agent. Antifoam acts as a surfactant and various types are used. Polyethylene glycol is one example. Some

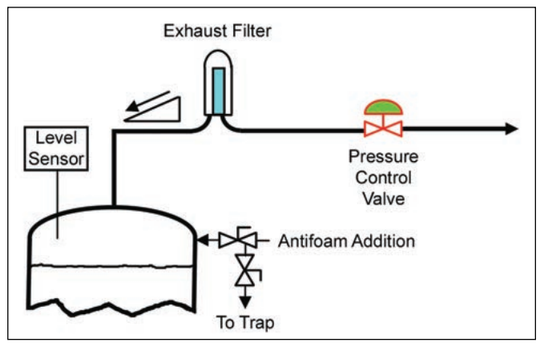

Figure 3. Foam level control.

applications have used to varying degrees of success a spray type nozzle to disperse the antifoam agent across the surface layer of foam for quick reduction.

Now with foam under control, there is still the issue of liquid fines in the headspace generated when gas bubbles burst at the liquid surface.[2] The following schematic represents the stages of bubble bursting that will form film drops and jet drops.

The reduced surface tension created by the antifoam agent also can influence the dynamics of bubble bursting. The general effect is to both assuage and exacerbate the droplet formation during bursting thereby affecting the carryover that might be expected to exit the exhaust nozzle. The opposing forces are that lower surface tension creates fewer fluid film particles as the rising bubble overcomes the liquid surface tension; however, the lower surface tension also releases more energy when the liquid jet and the jet droplets eject upon bubble collapse. It is hard to say which effect dominates; however, it can be assumed that the larger size jet droplets may settle back to the surface whereby the smaller surface film droplets may carry into the exhaust gas stream. Some solid particles can be carried over as well.

Batch: Simple Aeration: High Agitation: High Foam: Normal

In this case, one is seeking extremely high cell densities and the optical densities could be in the range of 200 to 400 AU (OD_{600}) with Oxygen Transfer Rate (OTR) in the area of 500 to 600 mMol O2/L/hr during the end of the exponential growth phase and subsequent stationary phase. The gassing rates can be as high as 2.0 VVM. In addition, there will almost certainly be the need for oxygen enrichment of the inlet gas stream. The supplemental oxygen can have a positive effect of lowering the gas flow, while permitting higher OTR. This is one sure way to reduce foaming if it is available and the equipment is capable of measuring and controlling multiple gas flows. However, if oxygen is not used and the gas flow is approaching 2 VVM, foam will most likely become a problem and clogging of the exhaust filter must be prevented. In addition, the combined effect at the liquid surface from high gas flow as well as extreme agitation will increase the quantity of liquid/solid fines being propelled into the headspace.

Liquid particles are generated in a variety of ways during periods of extreme agitation. In this fermentation mode, it

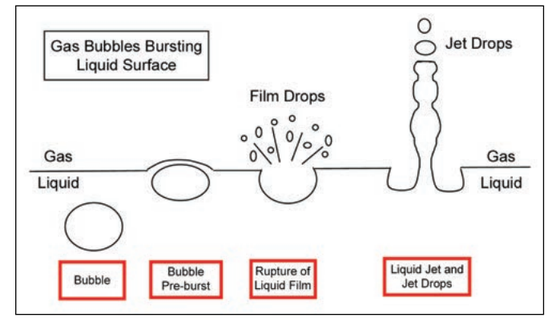

Figure 4. Dynamics of bubble bursting.

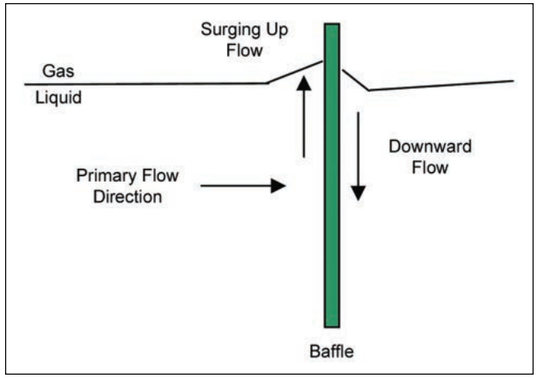

Figure 5. Liquid surge at baffles.

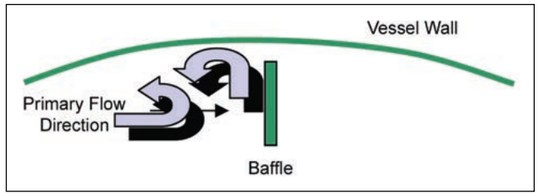

Figure 6. Formation of baffle vortexes.

is a gross error to assume the liquid surface is a quiescent level pool. It is in fact quite the opposite appearing much like a boiling cauldron without the high temperature.

For proper agitation to obtain a well mixed homogenous broth as well as to enhance effective mass transfer of oxygen, vessel baffles[3] are used in combination with radial pumping turbine impellers. Typically, the vessel will have four baffles running the length of the side wall from the bottom tangent line to either just below the working level or in some cases to above the working level. Figure 5 (side view) and Figure 6 (top view) illustrate typical flow patterns at baffles. The baffles extended above the working level can enhance mixing when there is high gas flow and large holdup volume, due to the higher void fraction from the gas bubbles. This author prefers baffles submerged just below the static liquid volume to avoid splashing and simplify cleaning. Baffles extended above the liquid surface are prone to spray, splashing, vortex formation, as well as vortex collisions, up pumping and down pumping effects as shown in Figures 5 and 6. During periods of high aeration and high agitation, these factors will contribute to putting more liquid fines in the headspace.

An additional effect during extreme agitation can be the creation of a central down pumping unstable vortex from the top radial pumping turbine impeller. This vortex has a tendency as all other vortexes to be unstable both forming and collapsing over time. During each collapse cycle, liquid droplets can be flung into the headspace as yet another source of moisture that can carry liquid toward the exhaust nozzle.

Occasionally, the top impeller in a fermentor may be an axial down pumping design to enhance batch homogeneity by superimposing a top to bottom mixing pattern over the radial pumping turbine impellers. These impellers are notorious for forming a large, but stable vortex that in a small way may be useful in pulling the foam into the broth and refolding it back into solution. This is mostly effective only in the early stages of foam formation and is not a panacea for dealing with greater foaming processes.

Exhaust Cooling

As a minimum step to retain as much liquid in the batch as possible, it becomes imperative to add an exhaust condenser to the vessel exhaust nozzle. It also is recommended to increase the surface area of the exhaust filter. In most cases, the same filter base can be used and a longer element put in its place. This also involves changing to a taller filter housing so overhead clearance must be considered. Typical, filter elements come in 5", 10", 20", and 30" sizes. Beyond that, a larger housing with multi-round filter element arrangement may become necessary particularly on larger size fermentors (greater than 2000 L).

Remember that exhaust condensers come in a variety of designs, some being more effective than others. For small fermentors (less than 200 L), a simple shell and coil condenser may do the job. These can drop the exhaust gas temperature below the dew point, but have no directional flow paths and are therefore somewhat inefficient. For larger fermentors, a sanitary vapor in tube design will be more effective in condensing a high percentage of liquid to reflux into the fermentor vessel. This can maintain batch volume with minimum loss of moisture leaving the exhaust as uncondensed vapor that can pass through the exhaust filter element.

A few points to remember in placement and application of shell and tube condensers:

1. Surface area and cooling fluid temperature will determine the maximum capability to condense liquid.
2. The optimal location would be locating the condenser directly on the exhaust nozzle. Other arrangements are possible with caution to avoid "flooding" at the tube sheet gas inlet[4] or in the piping.

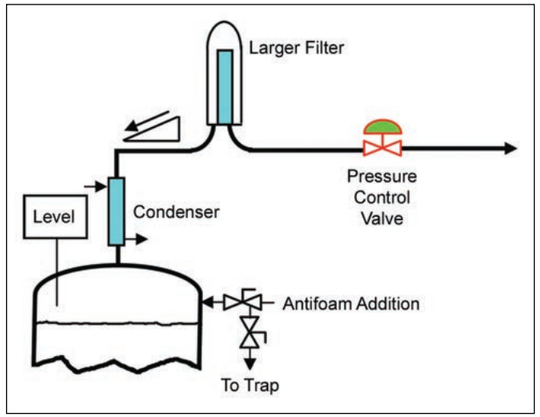

Figure 7. Condenser and larger filter area.

3. It is recommended that vapor in tube condensers be oriented in the vertical direction with cooling flow counter current to the gas flow. Gravity is a prime helper to get the liquid to flow against the gas velocity and reflux back into the vessel. Sloping the condenser can have a large negative impact on ability to reflux properly.
4. A proper design minimizes the re-entrainment of liquid refluxing into the fermentor. Critical upward gas velocity must be less than the liquid downward velocity (Flooding Velocity) to prevent flooding. Flooding velocity can be exceeded if sparge gas flows are pushed beyond the limits of design.
5. Condensers are not perfect and do not remove all of the exhaust moisture. It is important to understand the performance with respect to condensable and non-condensable vapors.
6. These devices are inside the sterile boundary being upstream of the exhaust filter so materials of construction, surface finish, and design for sterility are an important consideration.
7. Exhaust condensers are problematic when considering CIP for a validated licensed facility, due to difficulty assuring equal velocity and cleaning in all tubes. A proper cleaning program sequence for exhaust piping will be necessary.[5]

Figure 8 is a typical exhaust condenser internal tube bundle that also shows the internal baffles to obtain effective cooling fluid flow path.

Exhaust Heating

Another line of defense against exhaust filter wetting out is to include an exhaust gas heater between the condenser and the filter housing. These are generally concentric tube devices to allow ease of SIP and CIP since the internal surface is merely a continuation of the exhaust gas piping and at the same diameter. The outer tube is sealed against the inner tube and steam inlet and outlet nozzles are attached. A low pressure source (regulator recommended) of plant steam is sufficient to raise the temperature a few degrees above the dew point to re-volatilize any liquid fines that pass through the condenser. The resultant gas stream going through the filter element will contain more condensable liquid vapor; however, this is a means of reducing the liquid and possibly solid loading on the filter surface to extend its operating life.

Remember to consider where further condensate might collect in the facility exhaust system pathway. Better to deal with it as part of the facility design to avoid blocking the exit path with a liquid slug. Figure 10 illustrates an actual pathway represented in the above schematic. Note the amount of vertical and horizontal space necessary to accommodate these items. As always, accessibility for maintenance access is of paramount importance.

Figure 10 is less than optimum in that the condenser is offset from the exhaust nozzle on the manway. It is connected by a flex hose since the vessel is on load cells. The gas travels from condenser outlet down to a horizontal exhaust heater then into the Tee style exhaust filter. All three components were placed to be accessible from a platform accessing the top head of the fermentor. An optimum arrangement would be to locate the condenser on the exhaust nozzle and keep the exhaust heater at a high point, then into the filter with slope back to the condenser; however, one can see how this would have required extremely high elevation and would have made the heat and filter housing quite inaccessible from the platform. This is a good example of the layout compromises that can occur when form out-weights function. Proof of concept is verified when the exhaust filter has an acceptable life and the system can be sterilized and cleaned properly.

Figure 8. Condenser shell baffles.

Another popular way to reheat the exhaust gas prior to passing through the sterile filter element is to utilize an exhaust filter housing that includes a heating jacket. Low pressure regulated plant steam can be sent to the upper nozzle on the jacket with condensate routed away from the jacket via the lower nozzle. The warming of the housing will reduce condensate formation; however, long term operation can have a slightly negative effect on filter element life particularly if the element is not replaced until after many use cycles. The number of useful cycles for the exhaust filter element will vary from user to user with some applications even replacing the element between each batch.

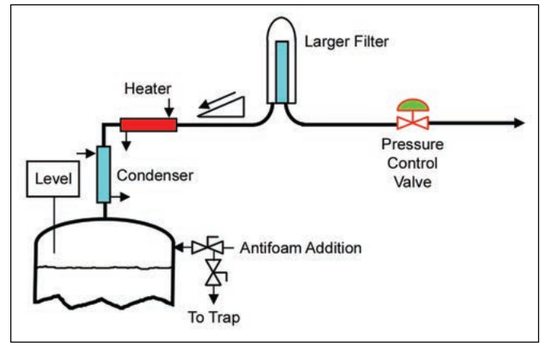

Figure 9. Exhaust heater.

Figure 10. Example exhaust pathway.

Finally, it is possible to use electric heat tracing on the exhaust piping to test the benefit of heating upstream of the filter housing. Electric heat tracing is commonly available with a built in thermostat and is relatively inexpensive. Although it may be fine in a pilot plant, it is not recommended as a permanent fix in a production environment as it can be subject to damage over the long term. Specifically, it may present a safety hazard in the event it requires frequent connect and disconnect as in the case wrapped around an exhaust filter housing.

Batch: Simple Aeration: High Agitation: High Foam: High

Taking one more step in complexity, one must consider the day to day treatment of highly foaming processes where foam is known to form regularly. This is particularly problematic if the foam layer is heavy, stable, and laden with proteinaceous material. One solution is to incorporate an electro mechanical foam breaker in the headspace.

Foam Breakers

The slinger style impeller is a good first choice. This design

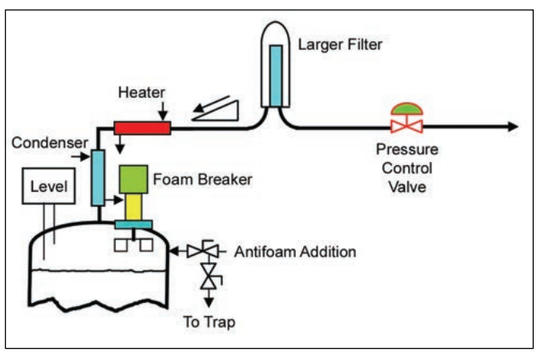

Figure 12. Slinger style foam breaker.

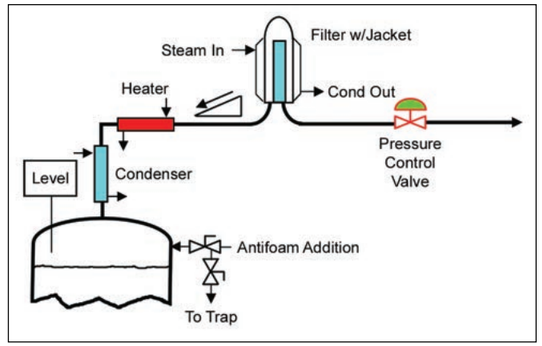

Figure 11. Exhaust filter with jacket.

uses a fairly simple impeller that will pull a vacuum in the impeller eye and direct the liquid horizontally out toward the vessel wall. This device creates an additional complication for sterilization as well as cleaning and it will require routine maintenance. The foam level control can incorporate two different length sensors such that the longer sensor will cause the addition of antifoam agent. Then the shorter sensor in turn brings on the foam breaker for a preset (operator adjustable) period of time after which it stops rotating and awaits a high foam signal again when it turns on for its next cycle. This cyclic operation saves on wear and tear to extend operating life.

Another type of electro mechanical foam breaking device that can be installed in the head space is a multi disk stack centrifuge type of impeller that collects liquid on its upper surfaces, while allowing liquid free exhaust gas to pass through the disks and out of an integral exhaust connector. These devices are designed to be operated continuously throughout the entire batch and are extremely effective in removing entrained liquid particles as well as preventing "foam out." In fact, once foam production is accepted and dealt with, the need for antifoam addition and level control may no longer be needed.

This device like the slinger style foam breaker must survive repeated SIP and CIP cycles and it also is an electro mechanical item requiring preventative maintenance of seals and bearings.

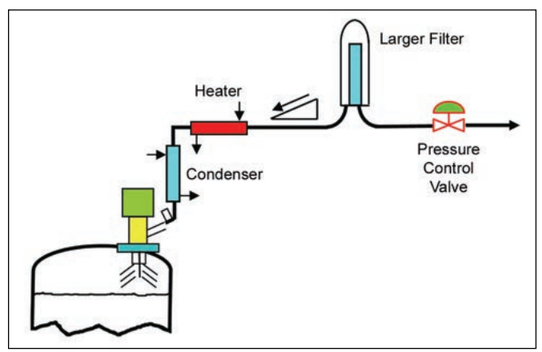

Figure 13. Disk stack style foam separator.

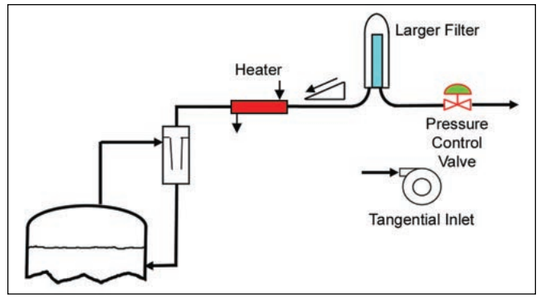

Figure 14. Vortex style foam separator.

A nice side effect of utilizing this type of continuously operating device is that traditional addition of antifoam agent could possibly be eliminated. Excessive use of antifoam agent can have a negative effect on dissolved oxygen control and further it is an additive that must be removed during downstream processing. An additional consideration is that the fermentor may be operated at higher than normal levels if the foam and liquid fines are under control through the entire batch. This translates to an improvement in productivity whenever more product can be squeezed from each batch. It might be possible to operate the fermentor at 85 to 90 percent aerated level rather than the typical 70 to 75 percent level.

Vortex Separators

Another method to deal with capture of foam and liquid fines is to install a vortex separator. This is an external device that mounts on the fermentor top head directly in the exhaust stream leaving the vessel.

The tangential inlet nozzle on the separator creates a swirling gas flow effect around the shell. This throws the liquid particles against the vertical walls where they coalesce and run down the side walls to collect at the bottom and be routed to a subsurface port on the vessel. The liquid free gas stream then passes down the shell to the inlet of the upward flow draft tube to route it to the top outlet nozzle.

Fed-Batch or Continuous Culture

Everything presented in this article may apply equally well to fed-batch and continuous cultures. These modes of operation are inherently designed to achieve higher productivity compared to batch fermentation. However, they also are susceptible to the same limitations of operating time based on airflow, foam, moisture, and solid particle entrainment, all of which can cause early clogging of the exhaust filter. In some cases, multiple exhaust filters mounted in parallel can be strategically important to allow one filter to have an in-run isolation, decontamination, change-out, and resterilization, while the back-up filter keeps the process going.

Conclusion

Cost, complexity, and expected degree of success must always be carefully weighed to properly match the exhaust path design and components to the process need. Sometimes this is difficult to do early in the design when all process conditions are not yet fully understood. It is a good idea to plan ahead with piping spool pieces that are easily removed for replacement in the future with condensers and/or heaters. In some cases, perhaps the vessel could be outfitted with a spare blind port for future addition of a foam breaker device. When in doubt, err on the side of prudence to avoid field retrofits when on-stream time is critical for success.

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Guide for using Open Source Software (OSS) in Regulated Industries based on GAMP

This article demonstrates the benefits of employing Open Source Software (OSS) in compliance with GAMP for the validation of computerized pharmaceutical applications.

by Markus Kaufmann, Marcus Ciolkowski, Andreas Hengstberger, Till Jostes, Erwin Kruschitz, Thomas Makait, Karl-Heinz Menges, Stefan Münch, and Martín Soto

Introduction

Differences between Open Source Software (OSS) and Commercial-Off-The-Shelf (COTS) software are smaller than many stakeholders perceive. This article outlines the benefits of free and Open Source Software (OSS) in contrast to commercial software and the resulting approach to qualification and operation of OSS in GxP-regulated areas.

Commercial software is generally assumed to be traditionally developed and marketed by a company and often requires royalties. Typically, source code is not disclosed and the customer has no right to modify the software.

Free and open source software are terms for software which comes with certain rights or freedoms for the user. The rights vary dependent on the chosen license. They typically allow access to and modification of source code and free redistribution.

One main driver for using OSS is the reduction of business risk, due to the open nature of the software; all details of a system can be verified and reviewed in detail. On the other hand, today's validation methods need to be adapted to address aspects such as:

- Communities are not conventional (commercial) business partners. Communication and ways of working may be different, e.g., service level agreements are not available or the community might not want to work with you for some reason.
- As conventional supplier audits cannot be performed on OSS communities, other methods for vendor evaluations must be applied.

Free and open source software is already an essential part of today's software industry. Many business critical applications already exist, continuously gaining momentum. However, most installations of software systems containing OSS to a certain degree, use it as part of "Infrastructure software" (as per GAMP 5). They consist in part or in its entirety of OSS (OSS Applications) by using LINUX and MYSQL databases. Especially for such infrastructure software, there is a high potential for economic savings.

International regulatory bodies generally do not distinguish between commercial software and OSS;[2] therefore, companies are free to choose either one. All GxP regulated computerized systems must be validated prior to use to show that the system is fit for the intended purpose. Decisions on data integrity controls and the extent of validation should be based on a documented and justified risk assessment. Impact on patient safety and product quality as well as data integrity/availability should be evaluated during this process. Clear acceptance criteria should be defined based on this risk assessment and documented in the validation plan.

Specific Nature of Open Source Software

One common misconception about OSS is that it is produced exclusively by altruistic individuals and that, consequently, it should always be free of cost. However, both the development and the deployment of OSS involve significant effort investments that cannot be reasonably ignored. Understanding the business and license model, development processes, and support structure is fundamental to make appropriate business

decisions regarding OSS. Parties involved include OSS communities, commercial software firms, system integrators, consultants, users/health care industries, and regulators.

The Business Models

"How are those developers supposed to earn money?" – Just like any other software development project, an OSS project requires effort directly related to the size and complexity of the intended product. In commercial software endeavors, the work is done by paid developers with financial resources being provided by customers through a direct development contract or some sort of licensing model.

In the case of OSS projects, development effort is mainly contributed by:

- Individuals who spend part of their free time working on the project.
- Companies and other organizations that directly or indirectly commit paid programmers or other professionals to work on the project.

The motivation for individuals in the first group can vary widely and range from being excited by technical challenges over having altruistic motives (e.g., OSS may help combat poverty and inequality) to attempting to build their personal reputation as developers by making valuable contributions to a visible project. Companies and freelance professionals, on the other hand, are rather interested in developing new business opportunities around their OSS involvement. A number of business models are possible:

- Extending or improving OSS and contributing back to the corresponding project as a cost-effective make or buy alternative.
- Offering paid services for an OSS product. This may include enhancing or correcting the product on a contractual basis for customers.
- Turning a commercial product into OSS. This can increase product adoption, creating new business opportunities for the company.
- Offering a product under dual licenses. In such cases, a product is made available under a commercial license and as OSS. The OSS license is typically restrictive in some aspects (e.g., it does not allow integration of the product into commercial products) while the commercial license lifts these restrictions. This way, the company can exploit the benefits of a community (e.g., external contributions, large user base) and still provide some additional paid services.

In summary, many OSS projects are motivated by business considerations at least to a certain extent. This trend is likely to continue in the following years, underpinning the increasing interest in OSS.

Legal Aspects

OSS is free of (license) costs, but not free of any liabilities. Therefore, legal aspects need to be considered when deploying OSS. When discussing legal aspects, we need to strictly differentiate the contractual side (e.g., warranty) from the intellectual property (copyright) side of the subject.

Let us first take the perspective of a typical software user: in case the intended use of OSS is acquiring, installing, and running (typically the case for Linux, MySQL, or Apache) without changing the software, the legal situation is not much different compared to the situation of buying commercial software. Even if the source code of the software will be changed in order to adapt the software functionality to the requirements there are normally no legal implications, as long as it is not distributed to others. However, the user should be aware that with using OSS, a contractual relationship is potentially entered that may encompass contractual and copyright aspects. As with commercial software, the purchaser should ensure that the supplier grants software to be free of rights of third parties.

The perspective of a software supplier or integrator is, compared to a normal OSS user, more complex: OSS license conditions and additional country-specific legislation need to be considered when OSS software is used as a basis for developing new software which is being distributed later. Depending on the OSS license model, the distributor is subject to some OSS specific obligations. For example, the BSD-type licenses (e.g., Apache Server) allow modifications of the OSS software and commercial distribution without disclosure of the source code. On the other hand, the GNU General Public License requires the (modified) source code to be published. It also requires that the source code of software, which has been combined with OSS – Software, needs to be published. In case of doubt, professional advice should be taken into account.

Development Process

The typical OSS development process involves a group of loosely coordinated developers, who work in parallel on new features or corrections. In many cases, a versioning system (such as CVS or Subversion) is used to manage the product's source code. Usually, only a small number of trusted developers (called *maintainers*) have write access to the source code repository, being able to make changes to the main development line. However, other contributors can make a copy of the code (for example, through public, read-only access to the repository) and develop their own contributions based on those copies. They submit a file containing their changes (*patch file*) to the maintainers, who review it, and if deemed adequate, integrate it to the main code branch.

Branching may lead to separate development streams. Those may later be merged again to the main development line or may lead to a split of the project (*forking*).

Mature OSS projects often have a number of processes in place that support activities, such as requirement management, release management, issue reporting and tracking, software distribution, software testing, and as mentioned before, version and configuration management. These processes are usually enforced by a combination of software tools

and community activities. Openness and transparency of the community are key factors.

Support and Maintenance

An active community around an OSS product also increases the chance of obtaining free support for that product. In many cases, users of an OSS product can submit questions to open mailing lists or Internet forums related to the product. Also many projects provide an issue tracking system that everyone can use to report problems or suggest enhancements. However, it must be taken into account that these free support channels are not guaranteed to work. A question sent to a mailing list may not be answered or a reported problem may remain unsolved for a long time. Reasons include that knowledgeable people do not answer, nobody in the community knows the solution, or the request or problem is not even considered to be relevant. Even in a project with a large, active community, such a situation may still occur.

For organizations requiring guaranteed support, there are options, such as contracting a company or freelance developers or providing in-house support by hiring experienced developers and system administrators.

Customer–Supplier Relationship

In contrast to the well-known customer–supplier relationship of commercial software, OSS offers several ways of interacting with a community or supplier. The list below shows typical scenarios.

- Scenario (a): customer downloads, installs, and uses OSS application "as is," the application is not changed by customer or customer's IT. In this scenario, the customer is not part of the community.
- Scenario (b): application is supported and maintained (and may be customized) by a system integrator or other supplier. Depending on the license model, the integrator or supplier may be part of the community by contributing code.
- Scenario (c): as (b), but customer's IT department acts as facilitator and supports and maintains the application, customer or customer's IT may change code. Here, depending on the license model, even the customer may become part of the community.

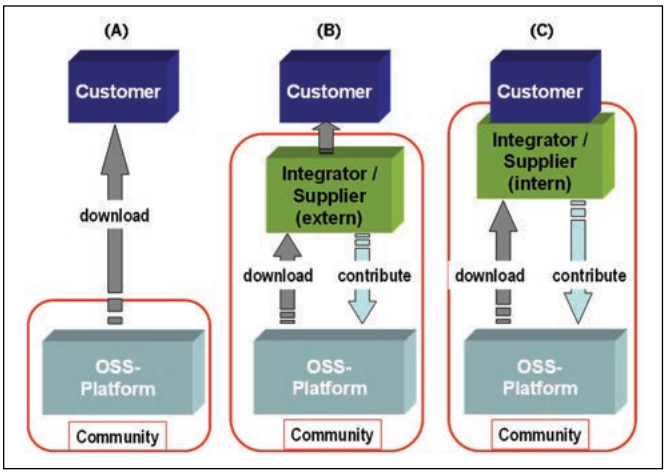

Figure 1. Typical scenarios for Customer-Supplier Relationships.

These three scenarios are prototypical; in real life, different variations and combinations can be found.

The selection and institutionalization of one of the above-mentioned scenarios is of major importance, as they have implications on the role of the OSS customer. For example, if removing defects and adding features is critical to the application of the OSS software, it may be advisable to hire an external supplier (scenario b) or contribute internal developers to the project (scenario c) in order to guarantee quick resolution of issues. Furthermore, if the modified OSS product is given to third parties (e.g., as part of an embedded system), it may even be necessary to contribute the changes to the community, depending on the OSS license. Although it may seem strange on first sight to invest into something that potentially benefits other companies, the support and product improvements received from the OSS community can still pay off.

Distribution Channels

For distribution, several channels are available to OSS developers.

The most common ones include:

- *Direct Internet download.* In some cases, OSS projects provide and manage their own internet servers (often with financial support from company contributors). Many projects, though, rely on Web sites offering generic services for OSS projects, such as SourceForge or Launchpad. Software distributed through such generic channels is often only available in source code form.
- *Operating System Distributions.* Distributions combine an operating system kernel (such as Linux or BSD) with utility and application software to produce a usable, integrated system. Since distribution developers (operating system distributions are OSS projects by themselves) normally put effort into making the various components work together, distributions are often the most convenient way to install Open Source products. Also, in most cases, distributions provide precompiled, ready-to-run code for popular hardware architectures. Examples of (Linux) system distributions are Fedora, SUSE Enterprise Linux, and Ubuntu.
- *Software Download Web sites.* Web sites specializing in (often commercial) software downloads (e.g., Tucows), are offering a continuously growing selection of OSS.
- *Software Collections.* Software collections, such as those often distributed by computer related magazines, often contain OSS.

The main risk associated with such distribution channels is that of inadvertently downloading versions of the OSS product that have been modified by malicious third parties. This risk can be minimized by using the "official" community server or platform, as the download is in many cases secured by checksums and/or digital signatures to verify its authenticity.

Lifecycle Approach for OSS Systems Based on GAMP

The same regulatory expectations apply to software in the GxP environment regardless of whether that software is commercial or OSS.

Achieving and maintaining compliance of GxP regulated systems containing OSS components can be *generally* performed according to GAMP Guidance in the same way as commercial software. The differences and the adaptation of the life cycle approach for OSS will be described in this section. The generic project life cycle described in GAMP 5 is applied as a general framework.

Table A lists GAMP 5 categories and gives examples for OSS applications. In the rightmost column, recommendations for life cycle activities are presented. Some suggestions for different life cycle approaches strategies also have been outlined in Table A.

Concept Phase

The purpose of the concept phase is to prepare the project to have the appropriate resources in place.

Project/Validation Plan

The project plan defines work products to be developed; life cycle model and approach to be used; customer requirements related to project management; tasks to be accomplished; task ownership; project resources; schedules, milestones, and target dates; estimates; and quality criteria. In addition, the plan identifies critical dependencies; required work products; project risks and risk mitigation plan; and contingency actions for non-completed tasks.

As for any validation project, the validation plan should include at least significant background information, the objectives of the project, the responsible personnel, description of SOPs to be followed, standards and criteria for the relevant processes; and predetermined acceptance criteria for drawing conclusions.

Requirements/Specifications

Depending on the development lifecycle used for the software, specifications are handled in different ways. Sufficiently defined requirement specifications should be available. Specifications should describe the process supported by the software with inputs and outcomes. Of course, the level of detail also depends on the GAMP category as well as risk, complexity, and novelty. Technical specifications like functional specifications or design specifications have to be in line with the chosen lifecycle model.

Project Phase

Vendor/Supplier Evaluation

Due to the specific nature of OSS and the different customer–supplier relationship, the vendor and supplier evaluation is probably the most challenging task with major differences to commercial software.

For low risk applications, a supplier evaluation is not required. For medium to high risk applications, scenarios (b) or (c) are recommended, because a service organization – whether internal or external – will reduce the uncertainties and risks of support and maintenance by a community.

For scenario (b), the vendor evaluation is the same as for commercial products. For scenario (c), internal quality standards apply, and the internal supplier needs to evaluate the community according to scenario (a). The rigor of evaluation should be commensurate with the risk priority.

Category	Software Type	Examples	Life Cycle Approach
1	Infrastructure	Core system and utilities of major commercial Linux distributions like embedded systems (e.g., firmware, networking software, Linux, BSD operation system, Apache HTTP Server, MySQL), and established layered software (e.g. OpenOffice, Firefox, DIA)	Standard GAMP approach, provided that a legal entity exists to maintain the software, i.e., providing services along the SDLC that can be considered a supplier in terms of the GAMP guidance.
2	N/A	N/A (Formerly firmware, obsolete since GAMP 5.)	N/A
3	Non-configured	RANDI2	Standard GAMP approach, provided that a legal entity exists to maintain the software, i.e., providing services along the SDLC that can be considered a supplier in terms of the GAMP guideline. Depending on the risk, vendor evaluation may be different, see section 3.3.
4	Configured	Alfresco (CMS), Compiere (CRM/ERP)	Standard GAMP approach, provided that a legal entity exists to maintain the software, i.e., providing services along the SDLC that can be considered a supplier in terms of the GAMP Guidance. Supplier audit against the criteria laid out for OSS. The scope and depth would be dependent on the intended use of the product.
5	Custom	The authors currently do not know of custom software directly supporting pharmaceutical processes that were released as OSS. Custom parts added in the course of a project should be regarded as custom code. If such software would be released as part of an OSS product after initial testing and verification, the category would decrease as a consequence.	The standard GAMP approach for validation of OSS applications should be applied.

Table A. Life cycle approach.

If a community is selected as a direct source (scenario (a)), suitable quality criteria to measure the stability and quality of a community have to be applied. A general assessment checklist for OSS is provided by GAMP 5, accompanying material (Example Checklists and Questionnaires).

The sustainability of an OSS community can be evaluated using the following common criteria, which shall be considered when conducting a supplier assessment.[4] The selection of criteria is case-dependent and should be documented.

- Activity of the community:
  - Number of downloads
  - Number of developers
  - Number of contributions
  - Activity of mailing lists and discussion forums

- Personal profiles:
  - Experience of key developers/maintainers (an important motivation for OSS developers is earning acceptance by the Community)

- Communication:
  - Mailing lists
  - News groups

- Organizational structures within the community,[1] such as:
  - Project management
  - Definition of a core team
  - Maintainers of subprojects

- Configuration Management:
  - Definition of the process of review of contributions and integration into main branch
  - Definition of the process for forking off stable releases
  - Version control
  - System and release documentation

Additional criteria can be found e.g., at FlossQuality.[14]

Development Standards

Development standards appear to be a major challenge for OSS, but in fact many communities have standards in place. Depending on the license model, following standards is imperative for reusing and modifying the code. This should be a criterion for the vendor evaluation.

Traceability

Relations between URS, FS, development specification, and tests should be traceable. For example, if you hire parts of a community to extend or build an application, either you or the hired contractors from the community have to provide traceability as described in GAMP 5.

Risk Assessment

Risk assessments can be performed on various levels. A high level general risk assessment may take system complexity and risk as basic inputs for a life cycle activities strategy.

In case of complex systems, a detailed risk assessment on function level that includes configuration and coding might be useful to target or reduce testing effort. As a means to a risk assessment, EN 60812 (which describes Failure Mode and Effects Analysis (FMEA) and Failure Mode, Effects, and Criticality Analysis (FMECA)), and GAMP 5, which also applies functional risk assessment approach may be applied, but fault tree analysis and other methods (e.g., refer to ICH Q9) are acceptable as well. However, remember that the overall idea is not to measure risk, but to identify and manage risk.

Also, keep in mind that the methods for the risk assessment of commercial software and OSS are the same – and so is the consequence of a failure – but the mitigation methods covered later on by the risk management process are slightly different. For example, for OSS additional code review is a mitigation method that usually cannot be applied to commercial software, whereas additional testing for highly critical functions can be used for either system.

Implementation

The purpose of the implementation phase is to build the system; therefore, this phase applies to SW of category 4 and 5 only. Here, the difference between commercial software and OSS is obvious and the different license models (see section 0) need to be taken into account:

- If you use the SW directly as provided by the community (scenario a), it will most likely not be SW category 5. With respect to accountability and liability, additional risks may apply.
- If you purchase the OSS through a supplier (scenario b), maybe including source code or configuration changes supplied by the community, you should expect the same processes and tests like for commercial software.
- If you change or configure the SW by your own (scenario c), you may be (or become) part of the community when distributing your software to others (Copyleft). If you use the SW for your own purposes only, Copyleft does not apply. In the first case, you have to follow the community's rules, in any case, you should define your own internal processes and tests for your own work. This may include raising staff awareness of OSS license issues (see section 2.2) and maintaining appropriate license documentation. It is advised to check whether a change, extension, and/or redistribution of the software is planned. This is particularly important with software components under GPL-style licenses.

Depth and rigor of testing should be commensurate with the identified risk.

Installation

The installation process comprises more activities than the Installation Qualification (IQ): you have to have a description for the installation process with prerequisites and, e.g., hard-

ware requirements in place. The IQ might follow this process and documents, proving that it is performed appropriately alike for all other software, too.

Acceptance Testing

Regardless whether you follow the V-model or any other type of development model, acceptance testing is a must for all SW categories other than 1, hence for OSS, too. The same methods to perform and document acceptance testing for commercial software can be applied to OSS as well.

Training

Like for all systems, users and system administrators have to be trained to be fit to use the system. The recommendation is to use internal or external training resources to perform the required training activities.

Validation Report

At the end of the project, the system has to be handed over to operations. Both parties have to agree about the status and the acceptance of the system as it is. The appropriate activity to document project closure is the validation report. The validation report defines the end of the project from a quality point of view and releases the system for use. Prerequisites for the release are the successfully performed activities defined in the validation plan. The validation report for OSS does not differ from validation reports of other systems.

Operation Phase

The purpose for the system operation phase is to supply a system for the users.

Service Desk and Incidents

For all applications, including OSS, a responsible person or organization as single point of contact should be defined. Similar for commercial software, this person/organization manages incidents. Since a community has not the required availability and may even disappear in the future, a community based services desk poses additional risks. Therefore, internal resources or a supplier with a binding contract need to be in place.

For systems with high GAMP categories and high risk, suppliers with a legal binding contract (SLA) should be the way of choice. Systems with very low risk may be used without a defined service from a GMP point of view. For systems in between, the service might be based on communities without legal binding contract, but with an evaluation of the community.

Contracts such as SLAs should be in line with given standards such as COBIT and not differ from those used for commercial software.

Deviations/Problem Management

A process for deviation and problem management should be defined. Although communities may provide these problem solving services, the management of tracking and classifying incidents can be done on the vendor's side only. As before, it is recommended to set up internal resources or establish a binding contract with a supplier.

When working with a community, a bug tracking system as well as a feature and support request page should be available. These communication mechanisms must be integrated in the processes of your internal or external service supplier.

Change and Configuration Management

Change and configuration management takes place at two sides:

- Customer/user: Like for other applications, the regulated company has to implement a change management system for OSS applications.
- Vendor/community: The vendor or community need to provide sufficient underpinning/detailed data to allow change management on the customer/user side and allow changes to the software to be tracked. Depending on the complexity of the system, the methods may differ, e.g., release notes on patches and/or source code commenting are sufficient. Own the change management process to manage and control changes.

The service organization, whether internal or external, has to monitor the activities of the community. Bug fixes and releases have to be evaluated and implemented if appropriate. So the general approach is not different when compared to commercial software, but OSS updates may come with more details, thereby supporting risk assessments.

Maintaining the Validated State

In general, there are two kinds of evaluation:

- After changes to the system: As integral part of the change control process, impact and risk of every change needs to be identified, evaluated, and managed.
- Periodic review to ensure the current capability of the system.

Like with all other systems, frequency and extent of periodic reviews should be determined by a risk-based approach and a review of historical data.

Retirement Phase

Again, system retirement is nothing specific to OSS. The most important requirement is to manage and provide the data throughout the retention period. For OSS, data formats and algorithms are available and may support data analysis and migration.

Summary and Future Trends

While Open Source Software is often perceived as being completely different from traditional commercial software, the consequences for regulated industries turn out to be rather minor. The differences affect the licensing models and development processes, and may in turn influence vendor selection and service processes. However, the life cycle activities remain

basically the same, and the risk-based approach promoted by GAMP 5 is still applicable.

Consequently, there is no reason to generally exclude usage of OSS in regulated industries. Increasingly, OSS applications emerge that can be an alternative to commercial software. As an example, the Open Document Format (ISO/IEC 26300) provides a format independent from applications, and is an excellent solution for documents which have to be archived or exchanged between different systems. Up to now, only Open Source applications are supporting this format.

Other regulated industries like aerospace companies are far ahead, already using OSS even in critical areas.

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Successful Use of Simulation as a Tool in a Lean Six Sigma Program

by Bruce Sawyer, Johnny Muñoz, and Jim Curry

This article presents the role of simulation in Johnson & Johnson's process excellence program. It uses a case study of a large pharmaceutical plant to describe how simulation evolved from improvement and capacity projects to the ongoing planning and management process.

Introduction

Simulation is growing in popularity as a best practice tool for lean six sigma programs that allows companies to move to the next stage of optimization of the supply chain and manufacturing environment. It is partly due to the sophistication and robustness of the tools available, as well as the need to optimize operations in response to changing market needs and financial pressures.

As lean and six sigma methodologies coalesced, simulation has become recognized as a tool for effective testing and implementation of process improvement in any manufacturing environment. Simulation tools have been available for 40 years, but advances in computer technology have now made them truly practical for widespread use in operations.

A simulation based planning system has a variety of uses within a plant for lean teams, six sigma experts, planners and schedulers, buyers, and plant management. This article describes the experiences and learnings from the use of simulation over the past four years in a complex plant campus that produces different finished product types in several manufacturing streams.

Focus

An accepted truism is that to be successful, a lean operations excellence program needs to have sustainable continuous improvement capability built in. It is easier said than done. One-time analysis projects are not enough to sustain process changes and continue to adapt to changing business needs. Simulation helps to provide this continuous capability in several ways.

1. First, there is a need to understand real capacity. What is the plant capable of producing with the given set of demands in a timeframe? Typically, you would get different answers from the functional areas involved, depending on the assumptions that they make and definition of metrics.

2. Second, it is a useful tool for the different functional areas to assess impacts on overall company objectives, as well as the departmental impacts. An operations excellence program needs to integrate lean six sigma analysts, manufacturing work-centers, capacity and inventory planning, and quality assurance functions.

3. Lastly, a full function simulation-based planning system provides a single strategic tool set for assessing and improving processes, evaluating capacity investment, and testing alternative scheduling methods for the operation. It also provides the ongoing tool for "what-if" evaluations as potential changes in the demand volume or mix arise, and their impacts on the business.

History

The J&J Global Pharmaceutical Supply Group (GPSG) Process Excellence organization had been interested in using simulation for a number of years, and the company had licensed some off-the-shelf simulation tools, but had not been successful in deploying a tool that could have broader use throughout the organization.

It was difficult for people to develop models that reflected the real issues of manufacturing and supply chain, due to the complexity of the processes. It also was found that if people had the knowledge to develop the detailed models, it was difficult to devote the time required for model building and upgrades that would provide enough flexibility.

These early attempts with general purpose simulation didn't take into account the training

required or the complexity of the processes. It also was found that people in different locations and organizations could "reinvent the wheel" even for similar processes.

In 2005, J&J began using OpStat's pre-configured models at the Alza site in Vacaville, California that had the underlying structure to simulate all finished products types, e.g., tablets, liquids, transdermals, parenterals, specialized delivery, etc., as well as API manufacturing, and that accommodated all the processes at the site.

Table A includes definitions related to lean, six sigma, and simulation terminology that are used throughout the article.

Critical Management Success Factors

Successful use of any technology requires a tool that has the required functionality, but also requires management planning and continued support, critical success factors for the lean six sigma program.

There needs to be an underlying management vision recognizing the importance of the supply chain in a lean manufacturing program. The scope needs to be broader than just manufacturing work-centers. Organizationally, six sigma black belts were assigned responsibility for supply chains for an entire processing stream from raw materials procurement through finished product delivery. Metrics were developed to reflect this end to end scope.

Black Belt – A process improvement specialist trained in Six Sigma methodology who works projects between business functions. A Master Black Belt also trains Black Belts and Green Belts.[1]

Constant Work In Process (CONWIP) – releases production orders to maintain a level of N jobs in the system at all times.[2]

Every Part Every Interval (EPEI) – is the time period over which every member of the product family can be produced, including the changeover between products.[3]

Kaizen – the Japanese term for improvement; continuing improvement. A kaizen blitz or event refers to the rapid improvement of a limited process area, for example, a production cell, within a short period of time.[4]

Kanban – a method of Just-in-Time production that uses standard containers or lot sizes with a single card attached to each. It is a pull system in which work centers signal with a card that they wish to withdraw parts from feeding operations or suppliers.[5]

OEE – Overall Equipment Effectiveness is a measure of Total Productive Maintenance, calculated as Availability x Performance Efficiency x Quality Rate.[6]

Postponement – a product design strategy that shifts product differentiation closer to the consumer by postponing identity changes, such as assembly or packaging, to the last possible supply chain location.[7]

Rhythm or Rotation Cycle – sequences production orders in a repetitive pattern of quantities for a mix of products within the overall EPEI. Also referred to as "level schedule" or heijunka.[8]

Simulation – is a computer model that represents a system as it evolves over time, such as a conveyor system in a factory. A simulation model is numerically exercised for a set of inputs to see how they affect the outputs of performance, i.e., "what-ifs".[9]

Takt Time – sets the pace of production to match the rate of customer demand and becomes the heartbeat of any lean production system. It is computed as the available production time divided by the rate of customer demand. Takt rate is the inverse of takt time.[10]

Value Stream Mapping – identification of all the specific activities occurring along a value stream for a product or product family.[8]

Table A. Definitions.

Setup and use of the pre-configured models involved the multi-discipline views and inputs from the different functional organizations at the site. The combined teams had been working at lean improvements for some time, and had developed value-stream maps for each of the three processing streams at the site. When model setup was initiated, the multi-discipline input included:

- Master black belts provided valuable inputs on how the model could be useful to them so the "what-if" capability could be most useful.
- Work center staff provided the day-to-day details of operational steps, which added specifics to documented requirements, such as validated paths for products.
- Planners and schedulers provided the coordination link between demand and supply.
- Finance staff also provided an important input – the product, work center, and project coding used in internal systems, which need to be linked.

The initial focus of the team was to set up the model for each manufacturing stream and evaluate the best alternative scheduling and replenishment techniques that should apply to each work-center within each stream. This analysis was led by the master black belt after first validating the model vs. historical demand and production patterns.

Training on the model was provided to representatives from each of the functions involved. This consisted of model configuration using Excel spreadsheet parameter input, which all analysts were familiar with already. The historical baseline was used, supplemented by exercises in changing business assumptions.

Ownership of the model for ongoing use needs to be transitioned from the Process Excellence group to an operational department where the tool can be made part of the normal management process. In Alza's case, this was the planning group which had responsibility for capacity utilization, demand/supply balancing, and raw material acquisition.

Given the same training, individuals within a group will demonstrate different levels of proficiency in the use of any tool. In this case, an individual in the planning group became the super-user for the model, and provided guidance to others as they each used it for different purposes.

The ownership and super-user in the planning group also facilitated the necessary data management for the campus. A standard set of model scenarios were maintained and provided to the various users via a shared server so that the analyses considered were based on agreed underlying data.

Once the initial analyses gave credibility to the use of the model, plant management depended on it for decision-making, particularly for decision-making on capacity related questions. The model became part of the standard management process.

Value-Add of Simulation

A successful lean program ultimately strives to increase throughput and reduces cycle time and inventory for a supply chain. In biopharmaceutical operations, that supply chain includes manufacturing, but also must address interaction with quality processes for both laboratory testing and documentation for raw materials, in-process and final release.

A comprehensive simulation tool to support this effort to optimize the operation will incorporate lean techniques that can be evaluated as needed and configured by operations staff without IT project budgeting. It adds value in several respects:

- It expands value stream maps beyond a static representation to use actual operational detailed data, for variability analysis rather than averages, and reflects the actual operational environment. Static value stream mapping has significant shortcomings, based on our experience of implementing changes that did not provide the expected benefit.
- Product mix and sourcing changes are a big factor. A full-function model provides a way to evaluate impacts of projected changes in both since the cleaning/changeover and validation rules are incorporated. Lean teams sometimes focus on the high volume products, easier to address in kaizens, but usually not where the issues are.
- A model also provides a way to validate project opportunities and test any change before implementing in the work-centers. Lean replenishment and scheduling changes, such as kanbans, rhythm cycles, constant work-in-process, and postponement, can all be simulated with actual as well as statistical variability.

Simulation is an ideal way to get your arms around the entire process with the full product mix of demand and validate opportunities not possible with a static map so that changes that do not result in the benefit expected are prevented.

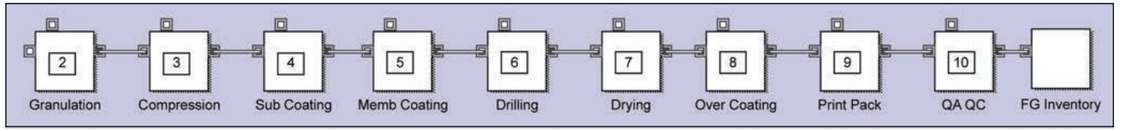

Figure 1. Production flow for tablet products.

How the Model was used Initially

Several production work-streams were set up on the model at the Alza site, including those for a multi-layer tablet, a transdermal consumer product, a controlled substance transdermal requiring recyclable shared containers, and an electronic delivery implant. The tablet production is explained here in more detail to illustrate how a model can support the traditional lean improvement process.

The production line is used for eight products totaling 20 different strengths and varieties. The process includes a sequence of processes beginning with granulation, then compression, and several coating, drilling, and drying operations. Tablet printing followed by QA release is the final step in this facility. The model was set up for nine operations, including the final release. Of the nine, three were coating operations and used shared coaters in a single work center. Figure 1 depicts the production flow for the operation.

There are a total of 35 individual sets of equipment spread over the operations. Each product/strength can be made using specified sets of equipment in the overall flow across the eight producing work centers, i.e., the validated paths. Cleaning rules specify when different levels of cleaning procedures need to be followed before/after a set of equipment is used. Table B shows the equipment validated by operation.

Initially, the short term business needs for the facility were how to handle projected growth in the drugs made in this work-stream over the next several years. The work plan for the lean team focused first on defining the true current capacity, determining an optimal schedule, and then on identifying potential alternatives for improvement.

The capacity question must always address the instantaneous machine capacity assumptions, and then the assumptions about campaign/lot sizes and related lost time, due to changeovers/cleanouts. Determining the facts and assumptions from planners/schedulers and work center operating staff can take several iterations. Loading the simulation model with these inputs provides immediate benefits by identifying disconnects, e.g., total time accounted for does not add to that available. Variability in processes, cleaning, and downtimes

Operation/Equip	2 Granulators	3 Compression	4 Sub Coat	5 Mem Coat	6 Drill	7 Dry	8 Overcoat	9 Print and Pack	10 QA Release
1	Gran 1	Press 1			Drill 1	Dryer 1	Coat 1	Printer 1	
2	Gran 2	Press 2	Coat 2		Drill 2	Dryer 2	Coat 2	Printer 2	
3	Gran 3	Press 3	Coat 3		Drill 3	Dryer 3	Coat 3	Printer 3	
4		Press 4		Coat 4	Drill 4	Dryer 4			
5		Press 5		Coat 5	Drill 5	Dryer 5			
6		Press 6		Coat 6	Drill 6	Dryer 6			
7		Press 7	Coat 7	Coat 7		Dryer 7	Coat 7		
8		Press 8	Coat 8	Coat 8			Coat 8		
9									
10									

Table B. Equipment validated by operation input to model.

New Schedule Indicator (auto generated)	Turn On/Off 0 = Off, 1 = Use Rhythm, 2 = Start When Not Busy	Operation	Op Nbr	Equipment	Equip Code	Lots per Camp	Rhythm Cycle Days	Day in Cycle	Lot Size Units (if applicable)	Bulk Code	Prod Code
Start Sched	**1**	**Granulation**	**2**	**Gran 3**	**3**	**5**	**38**	**1**		**12345**	
	1	Granulation	2		3	5	38	2		23456	
	1	Granulation	2		3	5	38	3		12345	
	1	Granulation	2		3	18	38	4		34567	
	1	Granulation	2		3	1	38	5		56789	
	1	Granulation	2		3	2	38	6		78901	
	1	Granulation	2		3	1	38	7		67890	
	1	Granulation	2		3	1	38	8		45678	
	1	Granulation	2		3	4	38	10		12345	
	1	Granulation	2		3	4	38	15		12345	
Start Sched	**1**	**Compression**	**3**	**Press 3**	**5**	**45**	**87**	**1**			**98765**
	1	Compression	3		5	4	87	2			87654
	1	Compression	3		5	3	87	3			76543
	1	Compression	3		5	3	87	4			87654
	1	Compression	3		5	4	87	5			76543
Start Sched	**1**	**Compression**	**3**	**Press 4**	**6**	**2**	**87**	**1**			**65432**
	1	Compression	3		6	2	87	2			65432
	1	Compression	3		6	8	87	3			54321
	1	Compression	3		6	2	87	4			65432
	1	Compression	3		6	30	87	5			98765
Start Sched	**1**	**Compression**	**3**	**Press 5**	**7**	**12**	**87**	**1**			**54321**
	1	Compression	3		7	12	87	12			54321
Start Sched	**1**	**Compression**	**3**	**Press 6**	**8**	**5**	**87**	**1**			**43210**
	1	Compression	3		8	3	87	2			32109
	1	Compression	3		8	20	87	5			98765
	1	Compression	3		8	8	87	6			54321
	1	Compression	3		8	20	87	45			98765
	1	Compression	3		8	3	87	46			32109

Table C. Rhythm schedule input to model.

also comes to light fairly quickly. This had not been monitored closely prior to this so some simplifying assumptions were made initially.

Scheduling mechanisms used have an impact on determining the throughput capacity of an operation. The model allows each work center to be scheduled independently to evaluate the optimal combination. Since it contains all of the lean replenishment techniques as options, kanbans, rhythm (Every Product Every Interval) cycles, Constant Work in Progress (CONWIP), and postponement may be turned on or off for each work center.

Depending on the product, the recipe (bill of material) required up to three different granulations for each finished product with up to five granulation lots input to tablet compression for a production lot of tablets. Later in the stream, the production lot sizes changed depending on the equipment, e.g., how many lots could be included in the dryers. These unit conversions were part of the rules entered into the source spreadsheets that feed the model.

The model showed fairly quickly that balanced rhythm cycles in granulation and compression were the only way to deal with the initial critical constraint in the process, which was granulation. Table C shows a portion of the schedule feeds to the model. Initially, historical monthly demands dictated

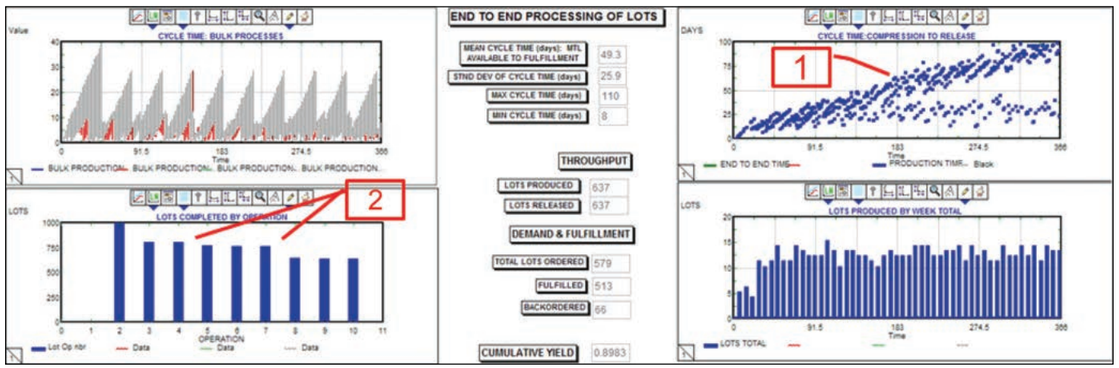

Figure 2. Summary outputs of model run.

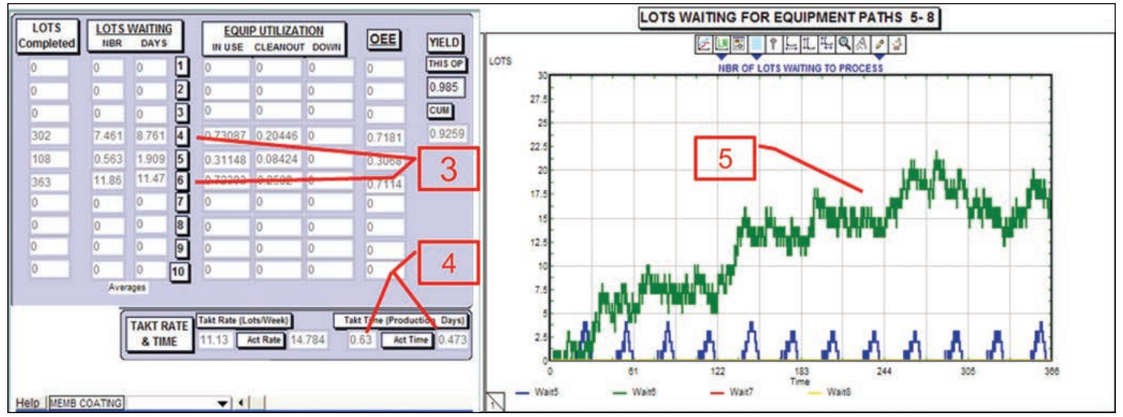

Figure 3. Detailed metrics by operation.

how much of each product was required, and the analysis focused on alternative balanced cycles for each of the three granulators and six compressors. The following two features of the model were used to optimize the balanced schedules:

1. An automated startup of a rhythm cycle – used in granulation to eliminate any gaps in the schedule for each set of equipment.

2. A combination rhythm and kanban check – used in compression to produce in a given cycle only if a kanban at the final released inventory needed to be replenished.

The result of this initial work was a series of scenarios to relieve the constraint in granulation. The option selected was to both validate one of the existing granulators for an additional key product, and also to bring additional granulated drug from another validated facility. This would allow better utilization of the less constrained downstream operations at the Alza facility.

As in any production process, constraints may change depending on the product mix, and when a constraint is relieved, other constraints may become critical. Figures 2 and 3 depict a drill-down capability from summary level to details by equipment, used to identify and analyze performance issues. Figure 2 is a summary graphic output of the model with one year runs (365 days on the x axis) of projected demand requirements for all products. Callout 1 highlights the steadily increasing cycle time from Compression to Release, which showed that all work centers in the manufacturing process were not keeping up with the demand rate pacing the production starts. Callout 2 shows two drop-offs in volume in downstream operations – Membrane Coating (Op # 5) and Over Coating (Op # 8), which should have kept up with the Compression rate.

Drilling down to the work center and then equipment level shows additional detail about these coating constraints. Figure 3 shows some detail for the Membrane Coating operation. Callout 3 shows that Coaters 4 and 6 have an excessive average number of lots waiting and days waiting to process. In addition, Callout 4 shows that the takt time and takt rate in this operation is not keeping pace with the required demand. That is, the required time per lot is .473 days, and the Coating performance is .63 days. Note that the demand rate may be fed by actual historical demand or projected volume requirements as it was in this case.

Callout 5 in the Lots Waiting for Equipment shows how the lots have built up for Coater 6 (in green) over the 365 day period. It also shows Coater 5 (in blue) with lower activity; which reflects that few products were validated for this coater.

Next Use of the Simulation

A series of scenarios were next developed and evaluated to propose a time-phased upgrade to the facility. In the initial and follow-on use of the model to consider alternatives, each scenario was developed with a set of operating assumptions. In this case, some of those assumptions included:

Scenario #	Ramp Up Assumptions	Simulation Assumptions
Scenario 1	Status Quo	Each Scenario Run:
Scenario 2	Third Granulator Validated for a Major Active, New Moisture Analyzer, and New Rhythms in Granulation	- With/Without Downtime Variability
Scenario 3	Compressing Improvements, An Existing Coater Validated for Another Product, and New Laser in Drilling	- Full/Reduced Staff Resources
Scenario 4	New Coater Added and Validated for use in Sub, Membrane, and Over Coating	- Full/Reduced Staff Resources
Scenario 5	Cycle Time Improvements in all the work centers by Kaizen Teams	- Full/Reduced Staff Resources
Scenario 6	Coating a Major Product Offsite	- With/Without Validation Batches
Scenario 7	New Projected Product Volumes	- With PM Scheduled

Table D. Scenarios planned and run for evaluation of improvements.

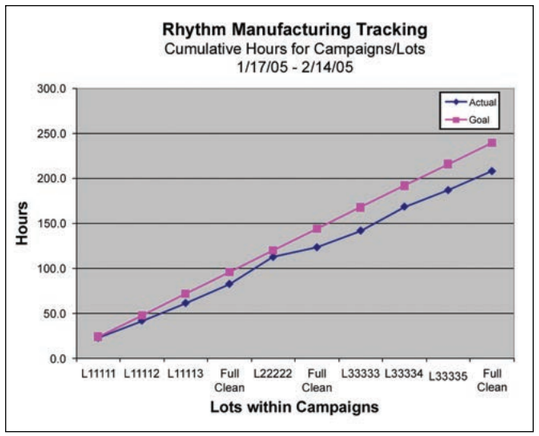

Figure 4. Tracking actual rhythm performance for a resource.

- Availability of equipment – whether there was statistical unplanned downtime introduced into the model, and whether planned preventive maintenance was included.
- Use of equipment for validation batches – whether volumes for technology transfer and FDA validation runs were included in the mix of demands.
- Staffing levels – whether full crews or probabilistic absenteeism was used.

Four additional proposed progressive steps were developed and costed to increase throughput. These included:

- cycle time improvements in all work centers from kaizen teams
- compressing improvements
- additional drilling equipment
- a series of changes in the coating operations, which was the next major constraint

The simulation model was an ideal tool for evaluating the coaters, used in three different steps, and with different products validated on different sets of equipment. Table D shows the planned runs of scenarios that were evaluated. The finalized plan included two separate validation changes to increase throughput, as well as outsourcing coating for one of the products to another J&J site.

It should be noted that the model was used tactically to evaluate the throughput impacts of validating additional equipment for certain operations, but the requirements for validation process itself with the FDA did not change.

Institutionalized Use of the Model

The simulation was not intended to be a one-time project, but rather a short/mid/long term capacity planning and continuous improvement tool. Over the next three years, as in most facilities, options were continually being considered for the supply chain network. This work stream is one of the largest for this technology in the J&J network and is usually key to

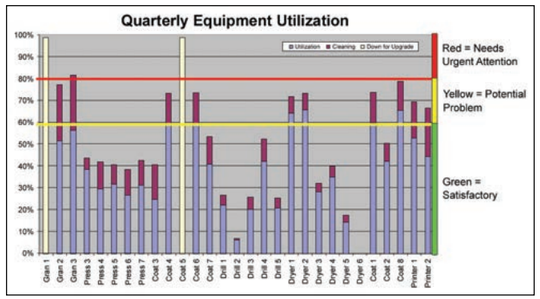

Figure 5. Tracking overall utilization.

any network decisions.

The model had the option to run with flexible time horizons, e.g., from three months for some analyses to 84 months for longer term projections. Key metrics were developed to track actual to planned performance. Figure 3 shows how some key OEE and takt time projections in one of the constrained coating operations are depicted. Note that the example used did not include downtime so the OEE calculation is not complete. When used with actual and statistically projected downtimes, the monte carlo simulation capability shows ranges of outputs. Figure 4 is an actual to planned rhythm cycle.

New product introductions in particular, always affect the demand volumes for a given facility. The model became central to plant management decision-making. With the ownership in the planning group, changing requirements over time were evaluated. Scenarios were developed to:

- develop the annual plans quarter by quarter
- respond to volume and mix changes
- address sourcing strategic changes for API and finishing
- change procurement patterns for raw materials

Engineers in the operating department also began to use the model for tactical analyses of more detailed scheduling and improvements in the work-centers, such as recyclable resources, staffing, and continued cycle time improvements. Figure 5 shows a utilization reporting graphic that was output and used to project available capacity.

Summary of Model Requirements

The simulation must have the capabilities to reflect the realities of the pharmaceutical processes in order to be a credible tool. The pre-configured model reflected the differences among product/process types and included all the lean replenishment techniques to evaluate impacts on throughput, capacity, staffing, and inventories.

For example, while it had the same look and feel for the lean six sigma analysts, one process stream had nine work-centers and others had four or five. Also, the production authorization mechanism for each work center could be different; one might be triggered by kanbans, another by a rhythm cycle, or first come first served, etc.

A value stream map is a good start to set up a model. It

provides the physical flow and basic data requirements to get started. The simulation shows both the material flows through the process, but actually operates based on the information flows and triggering mechanisms set up. In animation mode, lots can be seen moving through the model, which has a positive effect for management presentations and workshops since everyone can see immediate impacts of "what-if" changes.

The model needs to be robust enough to handle the volume and complex rules that underlie the processes. Some basic requirements are:

1. Rules specifying validated paths, changeovers and cleanouts, pre-sterilization of suites and equipment, and the ability to vary the associated choice of path based on product.
2. Lean techniques for authorizing production and the inventory through the process. Each work center is managed differently depending on the process. Triggering mechanisms include kanbans linked to any downstream work center, EPE rhythm cycles, CONWIP to prevent a constrained resource from being starved, postponement of final configuration.
3. Variable batch sizes, bill of material relationships, and yield as the form of the drug product changes through the process from API to packaged form.
4. Shared equipment, containers, suites used for multiple operations.
5. Staff sizes and work schedules by work center, e.g., 7/24 in one, five day in another, etc.
6. Ability to easily change to evaluate all the "what-ifs" possible and store the desired scenarios.

The combination of these real parameters makes it difficult for someone to envision the combined system without a tool like this. As an example, in a one year run for this operation, the simulation tracked over 400,000 events throughout all the operations.

Data Management and Integration

Spreadsheet integration is an important feature to make a tool useable in a reasonable amount of time. People are used to them, and it makes it easier to import or export information. It also allows the model to be set up without IT support for system changes. Most operational systems already have some extract capability that can be used to feed a model.

In the longer term, as models are institutionalized, a database capability also is necessary, but it should not be a requirement initially.

Models also should be set up to use standard coding schemes used in operational systems in the company. Product coding is a good example. Typically, there are codes representing each product in the ERP, procurement, and MES systems, as well as higher level product type codes in the financial systems.

Organizational Evolution Over Time

Participants	Project Work				Base Business		
	Data Collection		Model Validation	Training			
Plant Management	Identified critical issues				New management process/metrics: cycle times, throughput, inventory	Ongoing capacity evaluations	
Process Excellence - black belt for each of 3 manufacturing streams	Value-stream maps	Cleanouts and downtimes	Initial model setup done by outside trained resource	Each black belt trained on setup	Modeled new scheduling mechanisms	Alternative supply chain sourcing	
Planning Group - planner for each manufacturing stream		Product/ equipment validation matrices	Checked baseline model outputs using actual history	Selected planners based on interest and ability	Modeled new forecast scenarios Designated "super-user" for the campus	Established centralized data management Additional manufacturing stream setup	Integrated with procurement and laboratory processes
Operating Work Centers - supervisors and lead personnel		Production Times		Selected engineers based on interest and ability		Detailed work center analysis	

Span of approximately 1 year

Process Excellence, Planning Group, and Work Center personnel worked on each activity. Those identified were led by the group specified.

Figure 6. Project evolution, roles, and responsibilities.

These should be incorporated in the model's master tables to get the most benefit and reduce confusion.

For example, the first step should always be a validation of the models using actual data and historical metrics. The history from the internal systems provides the actual demand, production work orders, and downtimes. After validation, the model logic and metrics are credible for projected scenarios. Periodic extracts of updated history are then needed for the continuous improvement program.

Lastly, a data management requirement is the actual handling of the files used in the model. A common repository and owner is necessary to maintain change control over the system. A shared server with the base assumptions for a given period, e.g., the latest plan, is a good solution to use as a starting point for people using the model to download to their own computers.

Project Organization, People, and Training

Plant management originally recognized the need to improve performance and charged the staff with that objective. As mentioned earlier, the Process Excellence Team, Planning Group and operating Work Centers worked together to analyze the current operations and develop solutions. Figure 6 provides a summary of the continuum as the project evolved and the solutions became part of the base business processes.

The pre-configured model meant that analysts and engineers could focus on the process, rather than learning the details of programming a simulation software package. The process is still complex and time must be devoted to learning how to use any sophisticated tool, but the time to full productivity with it is in months rather than years.

The total time commitment for the effort during the project work phase consisted of the three Process Excellence black belts who were assigned close to full time for several months, three Planners, about 20% of their time, and Work Center staff 5 to 10% of their time. After training and analyses outlined in Figure 6, as part of the ongoing base business process, the management of model in the Planning Group and Work Centers centered on one super-user about 75% and another about 25%.

People's skills and backgrounds obviously have a lot to do with how long it takes an individual to be productive vs. another person. Those with good Excel experience, engineering/science academic backgrounds, and six sigma black belts all have a set of skills that seem to minimize the learning curve.

Therefore, the time to productivity will be a variable, but also will depend on how much else a person has within their job description. There needs to be some percent of a person's job devoted to learning a model and how to use it fully, and then an ongoing percent of their time to actually using it on an ongoing basis. These skills need some reinforcement over time, i.e., "use it or lose it."

Our experience provides some estimates of training requirements. The learning curve differs depending on the person and background:

- upfront formal classroom training time – 8 to 30 hours
- on-the-job use with a model already set up and in use – 20 to 60 hours with guidance from an experienced person
- After that on the job training period, an analyst should be able to add equipment, change process parameters, perform analyses, develop plans, and answer "what-ifs" for management.
- Those individuals who required the least training tended to become the "super-users" who added things to the models, such as new output graphics, used them for different analyses, and added detailed operations to the manufacturing streams.

Setting up a new manufacturing process from scratch was done by two of the super-users over a period of time. This last category also requires interviewing, analysis, and data collection experience beyond using a model. These might be the skills of black belts and engineers used to studying and improving processes. One of the benefits of the model is that it can be configured using higher level data for simplification and then adding more detail later when data are available. The setup person needs the judgment and experience to be able to differentiate when it is important to drill into detail and when a more simplified approach will be adequate.

The training program also needs to be institutionalized to be both reinforced and introduced to new people as promotions and rotations to different jobs occur. As lean and six sigma training has been institutionalized in many organizations, simulation needs to be a tool in the toolbox of lean six sigma analysts and needs to have the same emphasis to receive the benefits.

Summary of Learnings and Benefits

A full-functioned simulation model as we have described provides immediate and longer term benefits to an organization. It is a multifaceted tool:

- that provides end to end visibility of constrained work centers and can be a dynamic value stream map providing common information to all functions and levels in an organization
- for strategic capacity planning, evaluation of manufacturing scenario planning, and capital investment evaluations over an 84 month horizon
- that can be utilized to validate the impact of cycle time reduction projects on manufacturing throughput, before the projects are initiated, minimizing the non-value work associated with the execution of sub-optimal efforts
- that can be used to optimize plant performance, material flow, and resource utilization based on current and projected future work center metrics, staffing, product mix, and volume

We experienced significant benefits in delivering positive change, in three related areas:

1. Better utilization of our project and base business personnel by not squandering their time on projects that did not deliver the expected results. Without adding staff, this was a case of "working smarter" by using the tool to pre-test the process changes.
2. Accelerated the delivery of value-added projects that improved cycle time, throughput, and inventory by selecting the right lean techniques and parameters, such as kanban levels, to get to the optimum solutions across the combined upstream and downstream operations.
3. Improved the accuracy and timeliness of planning information for plant and supply chain management to evaluate options for sourcing and capacity within the plant and across the supply chain.

There is an obvious opportunity for use of this technology in other types of operations and industries. As changing business needs require operations managers to respond with flexible solutions, simulation provides another step forward in the toolset for improvement.

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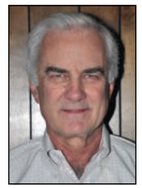

Jim Curry is the CEO and founder of OpStat Group Inc. He has been advising pharmaceutical and biological companies on process design and improvement for more than 20 years. He has led the development of simulation models for manufacturing, supply chain, and laboratory operations to test process and configuration changes in equipment, staffing, and schedules. He also has developed and utilized a methodology for lean improvement for several major global companies. Prior to forming the company in 1986, he was responsible for IT system development for Seagram. He is a member of the Steering Committee for ISPE's Operations Management Community of Practice. He also currently chairs the Simulation Tech Group for the Society of Manufacturing Engineers (SME), and is an adjunct professor in the graduate engineering program of Fairfield University in Connecticut. He can be contacted by telephone: +1-203-431-3905 or email: JimCurry@OpStat.com.

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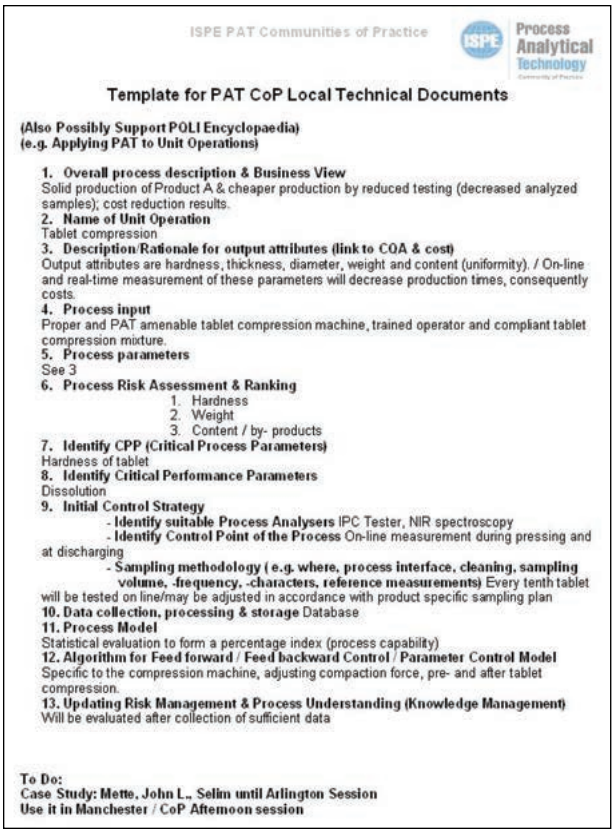
A Simplified Statistical Model to Assess Product Capability

by Selim Seyhan, Tolga Özcan, and Merve Öktem

This article presents a simplified model that can be used after future refinements to identify the specific process capability in pharmaceutical manufacturing. Data for a concrete production stage of a solid product is presented. Technologies, present and future, are identified.

Introduction

There is a distinct trend today with regard to validating manufacturing processes, which is different than from the long accepted notion that validated processes remain constant. We now know that starting materials and equipment undergo difficult to detect changes over time, which necessitates subsequent modifications in the "classical" sense of validation processes. The latter had been "frozen" according to the currently accepted validation concept. Product quality had been related solely to specifications, resulting in process understanding assuming a secondary role. As a result, the FDA published important guidance addressing this issue.[1] Much publicized in the ensuing four years, many companies around the globe accepted the ideas promulgated in this document, such as Process Analytical Technology, Quality by Design, and Parametric Release as a way of understanding their processes; however, there has been little progress in obtaining concrete results. This also is evident by the relatively few number of products, which have been approved to be released parametrically. This article presents a simple model that was developed at a manufacturing facility, PharmaVision, Istanbul, Turkey, which is currently being tested for a number of products manufactured by various member companies of the ISPE Turkey PAT COP.



ISPE PAT Communities of Practice

Process Analytical Technology

Template for PAT CoP Local Technical Documents

(Also Possibly Support POLI Encyclopaedia)
(e.g. Applying PAT to Unit Operations)

1. **Overall process description & Business View**
Solid production of Product A & cheaper production by reduced testing (decreased analyzed samples); cost reduction results.
2. **Name of Unit Operation**
Tablet compression
3. **Description/Rationale for output attributes (link to CQA & cost)**
Output attributes are hardness, thickness, diameter, weight and content (uniformity). / On-line and real-time measurement of these parameters will decrease production times, consequently costs.
4. **Process input**
Proper and PAT amenable tablet compression machine, trained operator and compliant tablet compression mixture.
5. **Process parameters**
See 3
6. **Process Risk Assessment & Ranking**
   1. Hardness
   2. Weight
   3. Content / by- products
7. **Identify CPP (Critical Process Parameters)**
Hardness of tablet
8. **Identify Critical Performance Parameters**
Dissolution
9. **Initial Control Strategy**
   - **Identify suitable Process Analysers** IPC Tester, NIR spectroscopy
   - **Identify Control Point of the Process** On-line measurement during pressing and at discharging
   - **Sampling methodology (e.g. where, process interface, cleaning, sampling volume, -frequency, -characters, reference measurements)** Every tenth tablet will be tested on line/may be adjusted in accordance with product specific sampling plan
10. **Data collection, processing & storage** Database
11. **Process Model**
Statistical evaluation to form a percentage index (process capability)
12. **Algorithm for Feed forward / Feed backward Control / Parameter Control Model**
Specific to the compression machine, adjusting compaction force, pre- and after tablet compression.
13. **Updating Risk Management & Process Understanding (Knowledge Management)**
Will be evaluated after collection of sufficient data

To Do:
Case Study: Mette, John L., Selim until Arlington Session
Use it in Manchester / CoP Afternoon session

Figure 1. Filled for Tablet A, compression stage.

The Model

In line with the PAT Template (Figure 1) developed by the ISPE Turkey PAT COP, manufacturing processes were dissected into distinct unit operations, such as compression, coating, and packaging in order to monitor the process and establish a standard to compare production processes.

The process for tablet compression was selected for the model, because of its simplicity. Almost every In-Process Control (IPC) laboratory takes samples to test various parameters, usually every hour or half an hour from this process; therefore, enough data is accumulated to analyze this process.

Critical Quality Attributes (CQA) for the particular product demonstrated in Figure 1 are hardness, thickness, diameter, weight, and content (uniformity) for the tablet compression process.

Critical Process Parameters (CPP) influencing such attributes, on the other hand, are compression force, homogeneity

Factor for Control Limits			
n	X Chart	n	X Chart
	A_2		A_2
2	1.880	8	0.373
3	1.023	9	0.337
4	0.729	10	0.308
5	0.577	11	0.285
6	0.483	12	0.266
7	0.419		

Table A. Factors for constructing variables control charts.

and flow rate of the powder, and speed of the compression machine.

In the current actual situation, the IPC laboratory takes samples at regular intervals, per specifications of the particular product, from the tablet compression process and measures their hardness, weight, diameter, and thickness.

There are warning (alert) and action limits for the weight. For manual operations, when the warning limits are exceeded, IPC warns the compression operator and the operator makes the necessary adjustments.

However, when the action limits are exceeded, the machine is stopped and the collected product further examined. This standard in-process procedure applies in all tablet compression operations. With automated systems employing feed-forward capabilities, such adjustments can be done without stopping the equipment. Yet, the basic principle remains the same, i.e., from accumulating live data, a meaningful and simple to comprehend number should emerge, which will give the operator an indication of process robustness and control. Following is the statistical background and justification for arriving at such an index, which will be referred to as "robustness index."

Statistical Justification

In order to find an index for a product (Tablet A), the weight, hardness, and disintegration and assay data for a minimum of 30 batches was collected. The first step required was to check whether the process was in control or not.

$\overline{X}$ Control Charts

In any work environment, no matter how well a process is designed or maintained, there will be a certain amount of inherent or natural differences in the parts, services, or process settings. This natural variation is the cumulative effect of many small and sometimes uncontrollable causes, for instance, the floor shaking, the air circulating, air pressure changing, and so on. As long as these differences remain small, they are considered acceptable for the process. In fact, from a process control point of view, this variation is often called a "stable system of chance causes" or "common variation." A process that is operating with only this common variation present is said to be in statistical control.[2]

Control charts also may be used to estimate the parameters of a production process and through this information, to determine the capability of meeting process specifications. The control chart also can provide information that is useful in improving the process. Finally, remember that the eventual goal of statistical process control is the elimination of variability in the process. Although it may not be possible to eliminate variability completely, the control chart helps reduce it as much as possible.[3]

In order to draw $\bar{X}$ control chart, the following calculations must be performed: mean of every sample ($\bar{X}$), average of the sample means ($\bar{\bar{X}}$), mean range of the samples ($\bar{R}$), Upper Control Limit (UCL), and Lower Control Limit (LCL).

$$\bar{X} = \frac{x_1 + x_2 + \ldots + x_n}{n} = \frac{\sum_{i=1}^{n} x_i}{n} \quad \text{(sample mean formula)}$$

i is the number of samples (i = 1, 2, 3, ... n)

$$\bar{\bar{X}} = \frac{1}{m}\sum_{j=1}^{m} \bar{X}_j$$

$$\bar{R} = \frac{1}{m}\sum_{j=1}^{m} R_j$$

j is the number of batches (j = 1, 2, 3, ... m)

Upper Action Line = $\bar{\bar{X}} + A_2\bar{R}$ (for $\bar{X}$ chart)
Lower Action Line = $\bar{\bar{X}} - A_2\bar{R}$ (for $\bar{X}$ chart)
Upper Warning Line = $\bar{\bar{X}} + 2/3\ A_2\bar{R}$ (for $\bar{X}$ chart)
Lower Warning Line = $\bar{\bar{X}} - 2/3\ A_2\bar{R}$ (for $\bar{X}$ chart)

Equation 1

where n is the sample size, m is the number of samples, and A_2 is constant that is tabulated for various sample sizes in Table A.

Upper Action Lines (UAL) and Lower Action Lines (LAL) are known as action lines, because beyond this point, an action should be taken. There also are warning lines, which are two thirds of the distance between the control limit and action lines. These lines are illustrated in Figure 2.

From this data, $\bar{X}$ control chart can be established. The observations of weight are in Table B.

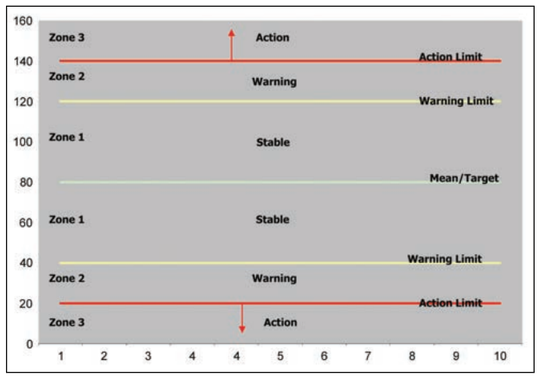


Figure 2. Zones on the control charts.

No.	1	2	3	4	5	6	7	8	9	10	$\bar{X}$	R
1	641.6	644.0	658.7	649.7	632.4	641.1	664.2	661.3	671.1	653.9	651.8	38.7
2	663.4	651.7	652.2	634.7	653.7	624.2	648.4	646.5	647.6	646.3	646.9	39.2
3	654.7	655.7	651.4	648.3	649.6	642.4	646.8	629.5	649.0	644.5	647.2	26.2
...	...	...	...	...	...	...	...	...	...	...	...	...
28	657.2	649.2	651.5	659.0	658.5	629.4	653.6	643.4	645.8	648.7	649.6	29.6
29	651.6	635.0	655.4	622.2	665.7	659.8	668.5	667.3	656.6	666.5	654.9	46.3
30	654.4	658.1	659.5	662.9	654.2	653.2	646.1	652.6	659.4	653.7	655.4	16.8

Table B. The observations of weight attribute.

The parameters for weight attribute are calculated according to the formulas in Equation 1.

$$\bar{\bar{X}} = \frac{651.8 + 646.9 + \ldots + 654.9 + 655.4}{30} = 651.6$$

$$\bar{R} = \frac{38.7 + 39.2 + \ldots + 46.3 + 16.8}{30} = 28.3$$

UAL = 651.6 + 0.308 X 28.3 = 660.3 (Upper action line for $\bar{X}$ chart)

UWL = 651.6 + 0308 X 28.3 X (2/3) = 657.4 (Upper warning line for $\bar{X}$ chart)

LAL = 651.6 – 0.308 X 28.3 = 642.9 (Lower action line for $\bar{X}$ chart)

LWL = 651.6 – 0.308 X 28.3 X (2/3) = 645.8 (Lower warning line for $\bar{X}$ chart)

The resulting chart is as follows - *Figure 3*.

Before the control charts are used or the process capability is assessed, it is important to confirm that when the samples were taken, the process was indeed 'in statistical control,' i.e., the distribution of individual items was reasonably stable.

If the process from which the data was collected is in statistical control, there will be:

- no mean or range values, which lie outside the action limits (Figure 2, Zone 3)
- no more than about one in 40 values between the warning and action limits (Figure 2, Zone 2)
- no incidence of two consecutive mean or range values, which lie outside the same warning limit on either the mean or the range chart (Figure 2, Zone 2)
- no run or trend of five or more, which also infringes a warning or action limit (Figure 2, Zone 2 or 3)
- no runs of more than six sample means, which lie either above or below the grand mean (Figure 2, Zone 1)
- no trends of more than six values of the sample means that are either rising or falling (Figure 2, Zone 1).[4]

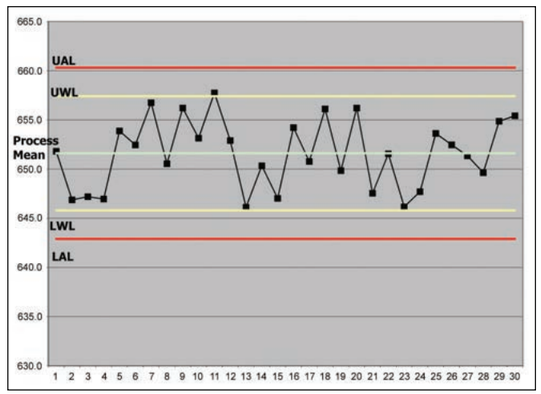


Figure 3. Chart for weight attribute.

Process Capability

After assessing the state of the control, the process capability can be calculated. Lower Specification Limits (LSL) and Upper Specification Limits (USL) of critical attributes are taken - *Table C*.

For each batch, sample mean and standard deviation of each attribute is calculated ($\bar{X}$, s) according to the following formulas.

$$\bar{X} = \frac{x_1 + x_2 + \ldots + x_n}{n} = \frac{\sum_{i=1}^{n} x_i}{n} \quad \text{(sample mean formula)}$$

$$S = \sqrt{\frac{\sum_{i=1}^{n} (x_i - \bar{x})^2}{n - 1}} \quad \text{(sample standard deviation formula)}$$

where n is the sample size and x_is are the readings of attributes.

Equation 2

There are some assumptions made for some of the calculations. For example, in the case of assay, this parameter is only measured once in every batch and it is assumed that this measured value is taken as sample mean of this batch. Similarly, the standard deviation for 30 batches is assumed constant for that parameter.

The mean of the batches are listed in Table D. The standard deviations of the batches are listed in Table E.

A process capability index is a measure relating the actual performance of a process to its specified performance, where processes are considered to be a combination of the plant or

Attribute Name	LSL	Target	USL	Unit
Weight	617.50	650.00	682.50	Mg.
Hardness		Min. 70		N
Assay	475.00	500.00	525.00	Mg.

Table C. Specification limits of Tablet A.

Batch No.	Weight	Hardness	Assay
1	651.8	99.5	503.4
2	646.9	97.6	511.0
3	647.2	91.7	496.0
...	...	...	...
28	649.6	87.8	508.5
29	654.9	91.9	503.5
30	655.4	89.1	502.7

Table D. Mean of the batches.

Batch No.	Weight	Hardness	Assay
1	12.15	8.97	4.32
2	10.73	9.20	4.32
3	7.45	9.19	4.32
...	...	...	...
28	8.86	10.44	4.32
29	15.25	12.08	4.32
30	4.72	9.44	4.32

Table E. Standard deviations of the batches.

equipment, the method itself, the people, the materials, and the environment.

In order to manufacture within a specification, the difference between the USL and the LSL must be less than the total process variation. So a comparison of 6σ with (USL - LSL) gives an obvious process capability index, known as the C_p of the process:

$$C_p = \frac{USL - LSL}{6\sigma}$$

where σ is the short-term process standard deviation, USL is the Upper Specification Limit, and LSL is the Lower Specification Limit.

Clearly, any value of C_p below 1 means that the process variation is greater than the specified tolerance band so the process is incapable. For increasing values of C_p, the process becomes increasingly capable.

The process width denominator is chosen as 6 standard deviations, because this is deemed to be a reasonable representation of the width of the process (99.73% of data points lie between ±3 standard deviations in any normally distributed data).[5]

C_p index gives no indication as to process centering, but it is a simple comparison between the variation and specification limits.

C_{pK} represents the distance of the center of the process to the nearest specification limit in units of process width. Therefore, it shows the amount of variation and the centering of the process. C_{pK} is calculated according to the Equation 3.

$$C_{pL} = \frac{\bar{X} - LSL}{3\sigma} \qquad C_{pU} = \frac{USL - \bar{X}}{3\sigma} \qquad C_{pK} = \min\{C_{pL}, C_{pU}\}$$

Equation 3 – Capability Index

In the model, for each batch, process capability (C_{pK}) of each attribute is calculated.

Batch No.	Weight	Hardness	Assay
1	0.8	1.1	1.7
2	0.9	1.0	1.1
3	1.3	0.8	1.6
...	...	...	...
28	1.2	0.6	1.3
29	0.6	0.6	1.7
30	1.9	0.7	1.7

Table F. C_{pK} values.

CpK Range	Score Range
$0 < C_{pK} \leq 1$	0 – 25
$1 < C_{pK} \leq 1.33$	25 – 50
$1.33 < C_{pK} \leq 1.67$	50 – 75
$C_{pK} > 1,67$	75 – 100

Table G. C_{pK} vs. model index.

The C_{pK} values of each attribute for every batch is listed in Table F.

We would like to simplify the above detailed theoretical background to a less sophisticated model and numerical value, which the operator will understand as the process takes place and can react upon. The latter will actually happen in the future, when relevant PAT technology is available and is implemented, such that measurements will be made on-line and adjustments (within design space) completed as the manufacturing progresses. C_{pK}, we thought, is a statistical term, too specific for an operator to react to; what would a number of 1.33 mean to direct line operator?

A 0 to 100 scale index, we thought would be more practical and easier to understand. Also, to assign a C_{pK} value to a process (or even a unit operation) is extremely difficult and very susceptible to manipulation. Obviously, QA personnel and engineers also will benefit from the model, even in the shorter term, as they are the ones to design the system and technology for process understanding before handing over to the operator level. C_{pK} and robustness Index conversion is shown in Table G.

A C_{pK} value of less than 1.0 means that the result is out of specification and unacceptable accordingly. Since the process has to prove capable of producing aimed results directly related to pharmaceutical product quality, C_{pK}=1.33 and higher is the desired state. The values in 1.0 to 1.33 range indicate the need for improvement. Commonly, $C_{pK} > 1.67$ is needed for running critical processes or setting targets during design stage. C_{pK} equal or higher than 2 reminds us of six sigma studies and according to the model's calculation method, such values are given the highest score.

Table H shows the model index values after the conversion of C_{pK} to Model index values.

In order to compare the batches and the other products tablet compression process, a percentage was assigned to each attribute.

We don't want to overstate the score of products; therefore, we give low percentages to attributes, which have relatively high scores. Percentage determination procedure is given as follows:

Batch No.	Weight	Hardness	Assay
1	21	32	75
2	23	25	31
3	50	20	72
...	...	...	...
28	41	14	45
29	15	15	74
30	93	17	79
Score Mean	41	20	73

Table H. Model index values.

$$\text{Score Mean of the } k^{th} \text{ attribute} = \overline{SM}_k = \frac{\sum_{j=1}^{m} Z_{jk}}{m}$$

(m is the total number of batches, Z_{jk} is the score of k^{th} attribute in the j^{th} batch)

$$\text{Percentage of } k^{th} \text{ attribute} = yk = \frac{1/\overline{SM}_k}{\sum_{k=1}^{p} 1/\overline{SM}_k}$$

(p is the total number of attributes, $\overline{SM}_k$ is the score mean of k^{th} attribute)

Equation 4 – Attribute Percentage Calculation

Using the formulas in Equation 4, the percentages of the attributes are calculated.

$$\text{Percentage of weight attribute} = \frac{1/41}{1/41 + 1/20 + 1/73} = 32\%$$

The other percentages are calculated and listed in Table I.

After determination of percentages, batch total scores and product scores can be calculated.

$$\text{Batch Score} = \sum_{k=1}^{l} Z_{jk} y_k$$

(Z_{jk} is the score of k^{th} attribute in j^{th} batch, y_k is the percentage of k^{th} attribute)

$$\text{Product Score} = \frac{\sum_{j=1}^{m}\sum_{k=1}^{l} Z_{jk} y_k}{m}$$

For the Tablet A example, batch and product score are shown in Table J.

$$\text{Tablet A score} = \frac{35 + 25 + \ldots + 23 + 50}{30} = 34$$

Conclusion and Future Work

The methodology listed above is admittedly in its development stage and will need further refinement. Yet, the preliminary scores received for various products indicate a fairly good correlation between this score, the robustness index, and the retrospective assessment of the product, such as Annual Product Review (APR) results, complaint history, deviation data, etc. This is certainly an improvement over the present state, where 'validated' processes do not necessarily deliver compliant products, as evidenced by huge expenditures associated with not right-first-time productions.

We anticipate that in the current year, together with other member companies of ISPE Turkey PAT COP, we will be testing this model with selected products from our manufacturing lines as a comparative backup to our ongoing regular release procedures. At that stage, we plan to reassess the correlation between the robustness index predicted by the model described in this article with the current specification based release parameters. It is neither practical, nor intended in the short term to replace release criteria for established processes, where testing methods are already well defined and implemented. This exercise is rather to contribute to the ongoing culture change emphasizing process understanding in lieu of off-line testing. It will take time, data from various manufacturing sites, and more sophisticated data processing and statistical evaluation, as well as regulatory permissions, before such a model to replace or supplement the current specification based lot release criteria.

Weight	Hardness	Assay
32 %	54 %	14 %

Table I. Percentages of attributes.

Batch No.	Batch Score
1	35
2	25
3	36
...	...
28	27
29	23
30	50

Table J. Tablet A, batch and product score.

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This article presents the process for leveraging supplier knowledge and documentation in the context of applying a risk-based approach to compliant commissioning and qualification programs.

Systems Turnover Coordination: Effective Application and Integration of the Supplier-Provided Engineering Turnover Package (ETOP)

by Carol Susla

Introduction – Leveraging Vendor/ Supplier Involvement

The recurring theme of leveraging supplier knowledge and documentation continues to surface through the discussion of current pharmaceutical industry trends in the context of applying a risk-based approach to compliant commissioning and qualification programs. GAMP® 5 dedicates a full section of the Guide to Supplier Activities, Section 7, in which good practice activities are described as applicable to product and application development and support for GxP computerized systems.[1] The decision to leverage supplier knowledge, documentation, and testing is driven by the objective of eliminating the duplication of effort and time such that the defined programs and contributions of the supplier are directly applied to the end-user commissioning and qualification programs.

As a precursor to capitalizing on the involvement of the supplier and leveraging supplier provided documentation, a formalized supplier assessment program must be established. This prerequisite assessment is detailed in GAMP 5 and reinforced in a broader manner through Sub-Practice 2: Supplier Audit Plan of the ISPE Good Practice Guide: Good Engineering Practice, in which the need for a Supplier Audit Plan is reiterated.[2] The ASTM Standard E2500-07 expands on supplier management systems, under the Quality Risk Management discussion in which "the risks pertaining to delivery including supplier or construction risk,…should be considered relative to their ultimate impact on product quality and patient safety."[3] Once supplier capability has been fully determined, and the documented assessment provides sufficient evidence of supplier accreditation, capability, and adequacy of quality management systems, the opportunity exists to truly capitalize on maximizing supplier involvement through the lifecycle of the equipment or system.

This discussion specifically details the steps to effectively apply supplier involvement and leverage the supplier role on the project team to support the Engineering Turnover Package. There are two primary objectives in transforming from a traditionally based equipment/system delivery and turnover process to a supplier leveraged process:

- Reduce efforts, cost, and scheduling overruns caused by the duplicity of testing, documentation generation, and compilation.
- Increase resource capacity for the project lifecycle by applying supplier knowledge, in-house expertise, and experience. Establish capable suppliers as direct contributors to the project deliverables and documentation systems.

The Role of the Systems Turnover Coordinator

The concept and necessity of the Engineering Turnover Package (ETOP) has been widely accepted in support of the overall commissioning and qualification program within the pharmaceutical manufacturing arena. In a brief sojourn into the history of the ETOP, the *Pharmaceutical Engineering* article published in March/April 1996, authored by Mr. Daniel Dunbar, presented

a "Systems Approach to Mechanical Construction." In the referenced article, turnover packages are described to "contain all the documentation required to show the facility has been built per the construction documents in a high quality manner."[4] This concept has since been applied beyond the historical context of facility construction, extending to the full scope of pharmaceutical systems. Two definitions of "system" serve to define the broader perspective, including:

System – an organization of engineering components which have a defined operational function, e.g., piping, instrumentation, equipment, facilities, computer hardware, computer software.[5]

Manufacturing Systems – elements of pharmaceutical and biopharmaceutical manufacturing capability, including manufacturing systems, facility equipment, process equipment, supporting utilities, associated process monitoring and control systems, and automation systems that have the potential to affect product quality and patient safety.[3]

In the contemporary context, the requirements of the Systems Turnover Coordinator are established with the following functions:

- Provide start-up/commissioning/turnover package management.
- Maintain the Commissioning and Qualification program standards to ensure the effective compilation of all system related engineering documentation.
- Ensure construction to commissioning turnover documentation integrity.
- Develop and extend the interfaces between the owner and all responsible parties (supplier and sub-contractors) to ensure that all construction and equipment design/fabrication/assembly/testing documentation is reviewed, retained, and consistent with pre-determined documentation practices and site-specific Good Engineering Practices.
- Implement effective communication channels between the owner representatives, supplier, and (sub)-contractors to monitor progress of the generation of the ETOP.
- Define the ETOP infrastructure to ensure that all compliance requirements for the system turnover process are met.
- Deliver the enhanced turnover package without incurring delays or rework (due to incomplete or missed documentation).

This listing of accountabilities mirrors a job description, because it is intended to capture the key accountabilities that can be transferred to the supplier. With effective planning, defined requirements, and a formal assessment of capabilities, this role may be effectively held, entirely or in part by an accredited pharmaceutical supplier. This article further serves to delineate the steps to transfer partial or complete accountability of the ETOP from the in-house Engineering staff at the pharmaceutical manufacturing facility to a supplier-coordinated initiative. Table A summarizes the six essential steps needed to facilitate the application and integration of the supplier-provided turnover package.

A Six Step Process for the Supplier-Coordinated ETOP

Step 1: Formally Assess Supplier Competence and Quality Capability

The criticality of the supplier assessment process is underscored as the evaluation of supplier capability serves to support the basis and extent of involvement of each key supplier through the specification, design, and verification process. The structure of the supplier assessment program and strategy thereof is best detailed in a high level procedure or policy document. Alternatively, the supplier assessment strategy can be presented within the context of the Validation Master Plan.

The key prerequisites are reinforced:

Step	Process Step	Rationale
1	Formally assess supplier competence and quality capability.	Supplier assessment is a prerequisite to the application of the supplier-provided turnover package.
2	Develop the ETOP requirements as an input to the Requirements Phase of the Specification, Design, and Verification Process.	Provides for consistency in the delivery of the Engineering Turnover Package. Requirements are provided as an input to the specification and design phases.
3	Build the ETOP infrastructure: procedures/work instructions, checklists, and the ETOP matrix.	The overall strategy is identified in Step 2; the development of the ETOP is facilitated in this step. Provides for the supporting documentation to facilitate the process.
4	Integrate the ETOP matrix requirements with the system/equipment specification. Leverage the procurement process.	Through the issuance of the equipment specification (purchase specification) to the supplier, the ETOP documentation requirements, and timelines are clarified.
5	Define and standardize good documentation practices for engineering documentation; download to supplier quality representatives.	Communication of the documentation requirements early in the process will reinforce expectations and mitigate delays at the later stages of the project.
6	Establish the turnover schedule, communication channels, and issue resolution process.	By ensuring that conformance to the turnover schedule is monitored and communicated, visibility to the timeline is maintained through the duration of the project.

Table A. Six steps toward integration of a supplier-generated turnover package.

Leveraging Supplier Knowledge

- Define the supplier assessment process.
- Establish a project specific approach.
- Communicate the approach and expectations to the key suppliers supporting the project as soon as practically possible, such that potential gaps are addressed prior to the procurement phase of the project.

It is critical that the assessment process incorporate the quality requirements defined by the supplier management program. As such, the sub-team responsible for the implementation of the supplier assessment strategy typically includes membership from quality assurance, engineering, and site procurement/purchasing, at a minimum. It is recommended that the supplier assessment sub-team members be provided directly from the project execution team, as the overall project plan, commissioning and qualification objectives are best represented by the cross-functional members involved in the execution of the project.

The Good Engineering Practice Guide provides both a supplier audit template and supplier quality questionnaire as reference documents which serve as good starting points to support the development of the supplier assessment process. From an OEM perspective, supplier quality questionnaires to gather baseline data are becoming increasingly accepted as the basis for the evaluation. In addition to the questions provided with the sample quality questionnaire areas outlined in the Guide, we've recently seen the following questions posed as an OEM serving the pharmaceutical and biotechnology sectors:

- Company Details:
  - Company history, cumulative projects completed in healthcare/pharmaceutical applications; participation/revenue by industry sector and by application (custom build/automation system/system type).
- Quality Management System:
  - Request for a summary of the professional development and training programs in place, training hours/employee per annum.
  - Request for breakdown of staffing utilizing a recognized professional job classification/coding system.
  - Number of professional societies represented and number of members.
  - Summary skill matrix, including staff members with cleanroom application; microbiology, pharmaceutical formulation/filling/inspection/packaging experience. Detailed skill matrix for control, automation system, and MES expertise.
- Listing of all calibrated equipment and instrument available onsite; summary of all associated calibration procedures.
- Deliverables:
  - Along with providing a listing of standard documentation, include a listing of all standard protocol templates/forms and document templates.
  - Request for additional details regarding drawing standards and in-house standards library.

The collection of the baseline data through the Supplier Quality Questionnaire provides the basis for the audit process conducted at the vendor's site and provides added insight into the level of direct supplier involvement anticipated through the execution of the project.

In addition to the seven audit areas presented in the Good Engineering Practice Guide, end-user review of the supplier change control system and non-conformance/deviation management system is considered essential. From the perspective of the supplier, the review of these two key quality systems ensures that there is an alignment of expectations on the reporting requirements, and a process for addressing system changes or deviations incurred during fabrication and assembly of equipment. The supplier audit visit provides the ideal opportunity to establish the guidelines and expectations regarding change control and deviation handling, while formalizing the communication and escalation processes from both the supplier and end-user perspective.

Step 2: Develop the ETOP Requirements as an Input to the Requirements Phase of the Specification, Design, and Verification Process

As defined in the ISPE Baseline® Guide, Volume 5, Commissioning and Qualification, First Edition, the project turnover strategy is "a plan for hand-over or transfer of responsibility of the project."[6] The Engineering Turnover Package serves as a compilation and collection of all engineering documentation generated through the design, procurement, construction, and installation phases of the project. The ETOP compilation is the repository for all associated engineering documentation. The ETOP compilation furnishes, in part, the technical document package for commissioning and qualification of the manufacturing system.

By defining the process of developing and compiling the ETOP through a formalized procedure, and providing reference thereof in the system/project specific Commissioning Plan and Validation Plans, the requirements of the ETOP and overall responsibilities for the documentation across the life cycle of the manufacturing system are clearly delineated. In a 2008/2009 pharmaceutical capital expansion project for which the concept and design phases have been recently completed, the engineering and quality team members developed Commissioning Standards, re-defined local Good Engineering Practices, and formalized the requirements for the Engineering Turnover Package, through the issuance of updated and enhanced Commissioning Procedures.

The Commissioning Program, as defined in the associated site standard operating procedures, includes the following provisions:

- Definition of the ETOP and ETOP matrix. Specifically, the matrix provides a summary of the document types provided as part of the overall turnover package. The matrix serves as a guideline and is customized based on the manufacturing system impacted, constructed, or modified within the scope of the project. A sample ETOP matrix is provided in Table B.

- Outlined responsibilities for the development and compilation of the ETOP. More specifically, the responsibilities of the Commissioning Team are detailed to ensure that ownership and maintenance of the ETOP are clearly defined.
- Recommendation that the intended level of supplier/contractor documentation support and ETOP coordination be reviewed at the early phases of the project, namely the requirements and design phases to ensure alignment of engineering and quality.
- Reference to the supplier assessment process and prerequisites to implementing a supplier coordinated turnover package.

As a project specific document, the Commissioning Plan references the ETOP requirements prescribed by the site specific SOPs, while further establishing the ETOP matrix for the specific manufacturing systems and presenting detailed turnover schedules.

Document Type	Responsibility	Approval Sign-off	Approval Sign-off
System General Information:			
System Description			
Engineering Calculations Examples: Pressure relief, pump and tank sizing, performance curves; system capacity calculations			
Purchase Order Specification History including Addenda, Change Orders			
Change Documentation			
Drawings:			
Vendor's List of Drawings, Catalogues, and Documents			
General Arrangement, Outline Drawings			
P&ID's			
Assembly Drawings			
Fabrication Drawings			
Motor Drawings			
Certified Drawings			
Name Plate Details			
Major Components List			
Detailed Parts List, Bill of Materials, Fabrication Documentation			
Warranty			
All related material certification documents: - Mill Certificates - Material Certificates			
Code Certificates: - ASME - Seismic - NEC			

Table B. Example ETOP matrix.

Step 3: Build the Documentation Infrastructure: Procedures/Work Instructions, Checklists, and Define the ETOP Matrix

In the 2001 Baseline Guide for Commissioning and Qualification, the Guide states that "strategies for turnover should be determined early in the planning stages of the project Commissioning Plan." Within the last eight year period, the infrastructure has evolved from a description of intent and strategy in the Commissioning Plan document to the development of the following procedures and related controlled documents:

- Commissioning Program Procedure – a high level procedure under the ownership of engineering detailing the key elements of the end-user program, prerequisites for supplier involvement, overview for the development and compilation of the ETOP.
- Turnover Procedure – detailing the steps required to develop and compile the ETOP, including two primary engineering responsibilities: identification of the documentation deliverables required to support the turnover process; definition and communication of the requirements related to document scope and content, timing, format, layout, numbering, and identification. Document maintenance and specific storage/retention requirements through the system/equipment lifecycle may be specified.
- ETOP Matrix – serves to record all required contents of the Engineering Turnover Package, presented in Table B. The ETOP matrix provides a summary of the document types provided as part of the overall turnover package. This matrix serves as a guideline and is customized based on the manufacturing systems impacted, constructed, or modified within the scope of the project. A master ETOP matrix is used to tabulate all documentation deliverables for projects involving multiple manufacturing systems.
- The Turnover Checklist is project specific and provides for review by the contractor/supplier designee with end-user Engineering final approval.
- The ETOP Manual table of contents identifies the order and sequencing of the turnover package documentation set for ease of reference

Step 4: Integrate the ETOP Matrix Requirements with the System/Equipment Specification. Leverage the Procurement Process.

Through effective navigation of the procurement process and with a skillful oversight of the contractors and companies supplying the manufacturing systems and engineering services, greater economic value can be achieved. By integrating the engineering documentation deliverables into the overall purchasing specification, the procurement process:

- captures the needs of the ETOP implementation strategy
- allows for the opportunity of leveraging supplier capability for documentation
- provides for a contracting/procurement model, which adapts to the project specific economies
- builds a provision to extend engineering resource capacity, by capitalizing and leveraging the capabilities of the supplier based engineering personnel

By defining the ETOP requirements at the onset of the procurement phase, there is a greater transparency in the procurement process, which ensures a "level playing field" in the bid review process. Additionally, the potential for incremental hidden costs associated with the generation of compliant engineering documentation is minimized. An example of the Equipment Specification Document Deliverables matrix is presented in Table C.

This tool serves to identify each document deliverable, the prescribed format/style/identifiers, number of copies (hard/soft), and target delivery date. Utilizing a pharmaceutical filling system as an example, the detailed mechanical drawings are identified as deliverables; the drawing format is specified to be either AutoCAD or SolidWorks, the sheet format for the mechanical drawings is based on the ASME Y14.100 title block and drawing numbering is based on the customer provided format. Similarly, detailed electrical drawings are also identified as a document deliverable with the same drawing format, same title block and numbering requirements, symbology identified as IEEE 315 (ANSI Y32.2), and a drawing layout on D-size (plotted, A – size landscape).

In both cases, the document deliverables matrix identifies the number of soft and hard copies. It is essential that the purchasing specification identifies the soft copy requirement prior to finalization of the purchasing agreement, in order to secure electronic versions of the drawings, essential for ease of documenting future changes at the manufacturing facility without reliance on supplier-sourced drawing updates, necessitated to support change control.

For both deliverables, the delivery time frame has been specified to ensure issuance of the initial P&ID following the issuance of the purchase order, drawing approval during the design phase with final versions available at a defined time point prior to the Factory Acceptance Testing (FAT), supplemented with drawing verification at FAT in order to support commissioning and qualification.

With the first steps toward a complete and compliant ETOP taken in the early phases of the project, the pharmaceutical supplier is better equipped to collaborate through the execution phases of the project.

Prior to engaging formally in the quality partnership and as a prerequisite to the integration of supplier-coordinated turnover packages, the supplier must be assessed to establish ability to handle the requirements and scale of the project.

Step 5: Define and Standardize Good Documentation Practices for Engineering Documentation; Download to Supplier Quality Representatives

Establishing the documentation standards and formally communicating the expectations regarding good documentation practices are value-added activities, which serve to prevent documentation delays in the latter stages of project execution. It is essential that the documentation requirements be presented to the supplier prior to the development of the engineering documentation. Suppliers are often prepared to supplement in-house training programs for documentation practices for their key engineering staff to underscore the needs of a pharmaceutical client and to further customize practices to the pharmaceutical customer's standards. The

	Deliverable	Format		Copies		Target Delivery Timeframe		
				Soft	Hard	For Approval	Pre-FAT Requirement	For C&Q
1	Detailed Electrical Drawings	Drawing Format to be provided	AutoCAD/Solid Works	2	3	Design Phase	6 weeks prior to FAT	Verify at FAT
		Symbology	IEEE 315 (ANSI Y32.2)*					
		Title Block	Vendor provided format					
		Drawing Layout	D-size (plotted - A-size landscape)					
		Numbering	Vendor provided format					
2	Detailed Mechanical Drawings	Drawing Format to be provided	AutoCAD/Solid Works	2	3	Design Phase Initial P&ID Submitted 1 week after P.O.	6 weeks prior to FAT	Verify at FAT
		Sheet Format	Based on ASME Y14.100** (B, D, and E sheet sizes)					
		Title Block	Vendor provided format					
		Numbering	Specified by end-use SOP - #####					

* IEEE 315 (ANSI Y32.2), Graphic Symbols for Electrical and Electronics Diagrams (Including Reference Designation Class Designation Letters), The Institute of Electrical and Electronics Engineers, Inc., September 1975, Reaffirmed 1993.
** ASME Y14.100-2004, Engineering Drawing Practices, American Society of Mechanical Engineers, September 2005.

Table C. Equipment specification document deliverables matrix.

End-User Benefits	Supplier Benefits
• Fully defined expectations; formalized process for generating the ETOP. • A detailed ETOP timeline with clear deliverables, leveraging the procurement process. • An efficiency gain by utilizing the engineering resource pool at the OEM. • The elimination of duplicity of efforts in document generation and testing by capitalizing on supplier capabilities and contributions.	• Fully defined expectations from the end-user customer. • A detailed ETOP timeline with clear deliverables. • A competitive advantage to those suppliers equipped with the infrastructure, resources and systems to satisfy the needs of the pharmaceutical industry. • The ability to leverage in-house expertise and provide a value added service to the end-user customer.

Table D. The advantages of supplier-leveraged turnover packages.

key to ensuring that engineering documentation is clear, concise, consistent, and compliant is early expectation sharing combined with on-going reinforcement of the standards.

Step 6: Establish the Turnover Schedule, Communication Channels, and Issue Resolution Process

A turnover schedule ensures that all deliverables are tracked through completion and that adherence to the turnover timelines is measured. The point at which to define and align to requirements for supplier and contractor turnover packages is the procurement stage (Step 4) concurrent with the negotiation of terms of the agreement and equipment/system delivery schedules.

By having defined responsibilities and timelines incorporated into the contract documents, the end-user is provided with added leverage, and the supplier is provided with clearly delineated expectations in the early stages of the project plan. In addition to the document deliverables identified in the ETOP matrix, timing for the final punch lists, system walkdowns, as built drawings, and system turnover are specified in the turnover schedule.

Defined communication channels facilitate the management of the turnover plan/schedule, and for larger scale projects, it has been recommended that ETOP meetings be scheduled on a weekly basis through design and fabrication phases to ensure continuity in the review of deliverables and to address any potential issues related to testing/verification as they occur. Near real-time review of any potential changes during the early stages of the project execution plan limits the impact to the schedule rather than resolution at the formal factory acceptance testing stage.

Conclusions

The six step process supports the overall objective of effective application and integration of the supplier provided ETOP. There are four key benefits - *Table D.*

It is important to note that the supplier-leveraged turnover package reduces, but does not fully eliminate effort and coordination needed by the engineering team. More specifically, engineering is responsible for identifying the documentation deliverables required from the supplier, along with communicating the expectations and standards related to document requirements, content, timing, format, layout, nomenclature, and identification. With a well-defined process, the supplier can assume the responsibilities of coordinating the document generation process, and ensuring a "real-time" adherence to documentation standards. This additional support by the supplier reduces the potential of rework once the ETOP is reviewed by the engineering project team as part of the documentation verification phase of the installation.

The upfront planning effort lays the groundwork for the transition from the more traditional approach of ETOP generation. With the development of a formal process, which serves to leverage supplier involvement, the supplier-provided turnover package can be fully integrated as part of the overall project plan.

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About the Author

Carol Susla authored this article during her tenure as a Senior Consultant with ATS Automation Tooling Systems Inc. and has extensive quality and validation management experience in the pharmaceutical industry. She has acquired more than 20 years of quality management experience, having worked with multinationals in both the United States and Canada. While working directly in the pharmaceutical industry, Susla has spent the last 12 years focused on parenteral drug manufacturing. Susla gained a degree in chemical engineering from the University of Waterloo, has been a licensed engineer with PEO since 1990, and joined ISPE in 1998. Susla currently holds the position of Senior Director, Quality at Cangene Corporation, a biopharmaceutical company that develops, manufacturers, and markets specialty plasma products with headquarters in Winnipeg, Manitoba, Canada. She can be contacted by telephone: +1-204-261-8055 or by email: casusla@yahoo.ca.

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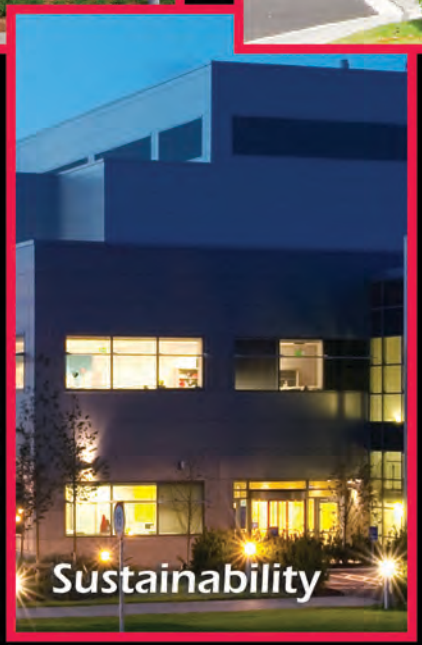
Supplement to

PHARMACEUTICAL ENGINEERING

2010

Facility of the Year Awards
CATEGORY WINNERS

Facility of the Year Awards
CATEGORY WINNERS



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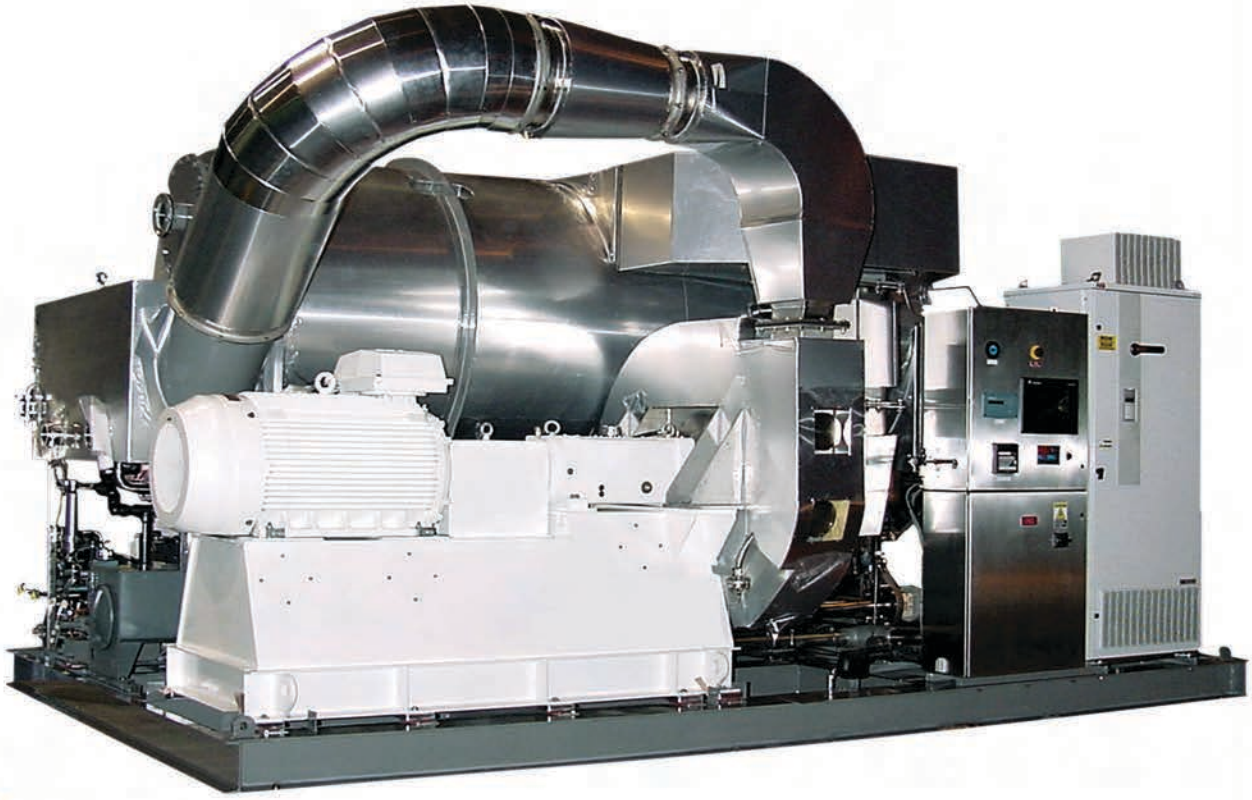

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2010 Facility of the Year Awards Program:
Honoring Innovation in Pharmaceutical Manufacturing

The Facility of the Year Awards program recognizes state-of-the-art pharmaceutical manufacturing projects that utilize new and innovative technologies to enhance the delivery of a quality project, as well as reduce the cost of producing high-quality medicines. Now in its sixth year, the awards program effectively spotlights the accomplishments, shared commitment, and dedication of individuals in companies worldwide to innovate and advance pharmaceutical manufacturing technology for the benefit of all global consumers.

Five pharmaceutical manufacturing facilities constructed in Singapore, Ireland, and the USA were selected as Category Winners in the sixth annual Facility of the Year Awards (FOYA) program sponsored by ISPE, INTERPHEX, and *Pharmaceutical Processing* magazine. The winning companies and respective award categories are:

- **Biogen Idec**, winner of the **Facility of the Year Award for Operational Excellence** for its **Large-scale Manufacturing (LSM) Technology Map Project** in Research Triangle Park, North Carolina, USA
- **Genentech**, winner of the **Facility of the Year Award for Project Execution** for its **ECP-1 Bacterial Manufacturing Facility** in Tuas, Singapore
- **MannKind Corporation**, winner of the **Facility of the Year Award for both Equipment Innovation and Process Innovation** for its **Technosphere® Insulin Manufacturing Facility** in Connecticut, USA
- **Pfizer Biotechnology Ireland**, winner of the **Facility of the Year Award for Sustainability** for its **Monoclonal Antibodies (MAbs) Small-scale Facility** in County Cork, Ireland

Biogen Idec: bioreactor buffer tank.

Genentech: fermentation suite.

- **Pfizer Ireland Pharmaceuticals**, winner of the **Facility of the Year Award for Facility Integration** for its **Aseptic Facility Expansion Project** in Dublin, Ireland

The Facility of the Year Awards program is truly global, as submissions over the past six years have been received from more than 25 different countries and territories. Each of the submissions was reviewed by an independent, blue-ribbon judging panel of global representatives from the pharmaceutical design, construction, and manufacturing sectors. These industry professionals included:

- **Chaz Calitri, *Judging Panel Chairman***
  Vice President, Global Engineering, Pfizer Global Engineering
- **Jim Breen**
  Vice President, Project Management, Worldwide Engineering & Real Estate, Johnson and Johnson
- **Steve Dreamer**
  Head of Global Pharma Engineering & Operational Excellence, TechOps, Novartis Pharma AG
- **Brian Lange**
  Director, Quality Services, West Point Quality Operations, Merck & Co.
- **Geoff Monk**
  Vice President, Global Engineering Services, Schering Plough
- **Shinichi Osada**
  General Manager, Biopharm, Industrial & Logistics Systems Division, Hitachi, Ltd.

MannKind Corporation: centrifugal chillers and distribution piping in the CUB.

- **Andy Skibo**
  Senior Vice President, Global Engineering, MedImmune
- **Ron Trudeau**
  Vice President, Facilities Engineering Services, Baxter Healthcare

2010 Facility of the Year Events

There will be several opportunities to meet the 2010 Facility of the Year Award Winners and learn first-hand about the facilities being honored as "best in their class." These events include:

- **INTERPHEX2010** – The Facility of the Year Awards Display Area is located at booth number 1059 in the exhibit hall of the Jacob K. Javits Convention Center, where during 20 to 22 April, Category Winners discuss the success stories associated with these pharmaceutical manufacturing facilities. For more information, visit www.interphex.com.
- **ISPE 2010 Annual Meeting** – Learn first-hand who the Overall Winner of the coveted 2010 Facility of the Year Award is during ISPE's 2010 Annual Meeting, 7-10 November in Orlando, Florida, USA. For more information, visit www.ISPE.org.

At each event, a Facility of the Year Awards display will feature the 2010 Category Award Winners.

Pfizer Biotechnology Ireland: media preparation.

Visit www.FacilityOfTheYear.org for more information about the awards program and detailed information about each Category Winner's project participants.

About ISPE

ISPE, the International Society for Pharmaceutical Engineering, is the Society of choice for 24,000 technical professionals working in or serving the manufacturing sector or drug development in the pharmaceutical industry in 90 countries. ISPE aims to be the catalyst for "Engineering Pharmaceutical Innovation" by providing Members with opportunities to develop their technical knowledge, exchange practical experience within their community, enhance their professional skills, and collaborate with global regulatory agencies and industry leaders. Founded in 1980, ISPE offers online learning opportunities for a global audience and has its worldwide headquarters in Tampa, Florida, USA; its European office in Brussels, Belgium; an Asia Pacific office in Singapore; and its newest office in Shanghai, China. Visit www.ISPE.org for additional Society news and information.

Pfizer Ireland Pharmaceuticals: in-line inspection machine.

About INTERPHEX

Now in its 31st year, INTERPHEX is the world's most trusted source for leading-edge technology, education, and sourcing of the products and services that drive scientific innovation for Life Sciences manufacturing from drug development to market – accelerating regulated products for patient care globally. Held 20 to 22 April at the Jacob K. Javits Convention Center in New York City, New York, USA, the 2010 exhibition features more than 950 exhibitors, an expanded conference program, and a high-profile roster of industry professionals and speakers. For information, visit www.interphex.com.

About *Pharmaceutical Processing*

Pharmaceutical Processing magazine is the pharmaceutical industry's leading information provider, reporting on a full range of innovative new products, equipment, technology and trends for 31,000 engineers and managers responsible for the development, manufacture, validation and packaging of pharmaceuticals. An official sponsor of INTERPHEX, Pharmaceutical Processing distributes critical information to these professionals in a timely manner through a full range of print, electronic and online media. For information, visit www.pharmpro.com.

Biogen Idec

Realizing the Value of Renovation

Introduction

To upgrade the infrastructure of the company's bulk biologics production facility and reduce challenges associated with downstream processing bottlenecks, Biogen Idec completed the largest renovation of a licensed manufacturing facility in the company's 30-year history: **Building 22 Large Scale Manufacturing (LSM) Technology Map** project at Research Triangle Park, North Carolina, USA.

Winner of the **2010 Facility of the Year Award (FOYA) for Operational Excellence**, the upgraded facility provides a better than 300% increase in yield over its previous production output by incorporating new technologies and de-bottlenecking operations at an existing site at a fraction of the cost of building new facilities. The resulting higher throughput comes, in part, from facility and equipment improvements that achieve faster and more streamlined technology transfers and process changeovers within the multi-product facility.

The project team successfully implemented and achieved this strategic upgrade utilizing exceptional up-front project planning and management; integrated, lean design and construction techniques; and rolling plant shut-downs at a scale that few, if any, have attempted to execute at one time.

Value Proposition

Biogen Idec's capabilities and capacity for protein manufacturing are world-class in quality and scale. Biogen Idec has expertise in protein expression in mammalian cells and process sciences capability for cell culture and downstream processing. Biogen Idec is one of a few biotechnology companies with three licensed and dedicated biological bulk-manufacturing facilities. One of these facilities includes a 250,000-square-foot LSM plant in Research Triangle Park (RTP), North Carolina.

Since 2000, when the LSM plant was designed and constructed, significant investments have been made in the biopharmaceutical supply chain across the industry. Improvements in media, process, and cell-line development are examples of methods that have significantly improved yields. This increase in titers and improved expression yields create pressure on downstream processing. This downstream processing bottleneck is consistently cited by pharmaceutical and biotechnology companies as one of the top three biomanufacturing challenges today.

Aerial view.

As part of a broader initiative to operate as effectively as possible, Biogen Idec developed a "Manufacturing Equipment and Facility Technology Map" for each of its manufacturing facilities and corresponding infrastructure, which considered the age of the facilities, advances in new equipment and technologies, raw materials, cell lines, and operational excellence. In support of this long-term corporate initiative and to reduce challenges associated with downstream processing bottlenecks, Biogen Idec renovated its existing LSM plant.

In comparing what it would cost to build a new 90,000 L LSM facility to deliver titers in the >3g/L range vs. renovate the existing 250,000-square-ft LSM facility and take it from 1g/L to >3g/L, there were significant time and capital savings with renovation. Based on industry averages, the equivalent capital outlay of a new LSM facility is in the range of approximately $500 million and would take at least 60 months to design/build/validate and license. In contrast, the renovation and upgrade of the LSM leveraged what was already operational and executed it in 18 months at a cost of $39.1 million.

Facility and Equipment Improvements

The Building 22 Large Scale Manufacturing (LSM) Technology Map project enabled Biogen Idec to significantly update and improve current and future manufacturing capabilities,

Continued on page 8.

Biogen Idec

Category Winner – Operational Excellence

Project: Building 22 Large-Scale Manufacturing (LSM) Technology Map
Location: Research Triangle Park, North Carolina, USA
Size: 50,000 sq. ft. (4,645 sq. m.)
Total Project Cost: $39,100,000
Duration of Construction: 4 months

Modular 1000 L to 4000 L buffer hold tanks.

capacities, and efficiencies. Biogen Idec completed the largest series of manufacturing renovations in its 30-year history and has created one of the largest state-of-the-art bulk biologics facilities in the world. Highlights in facility, equipment, and technology improvements include:

- robust tech transfer and product changeover processes
- flexible manufacturing platform consistent across sites
- increased overall efficiencies with maximized throughput
- consistency from early stage through commercial capabilities
- increased titer capabilities from 1 g/L to >3g/L (+300%)
- platforms that grow and facilitate partnerships/collaborations
- operations that perform with speed, excellence, and discipline: overall manufacturing operations efficiency

Nutrient feed tank area.

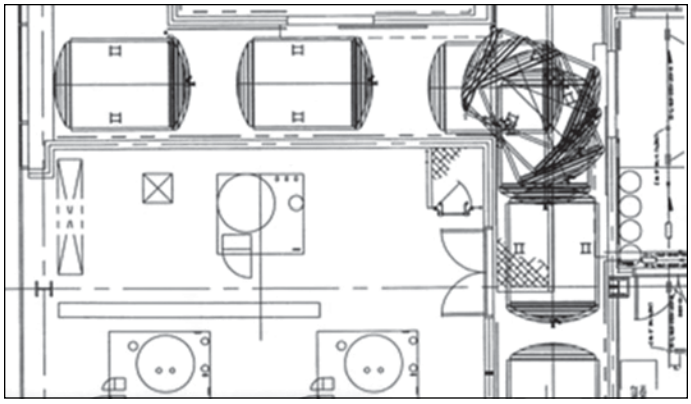
- avoidance of having to build new capacity to increase capacity
- increased SIP, CIP, Sampling and Addition Operations
- addition of large scale feed vessels – 3 × 6200 L and support infrastructure
- new mixing technology for media components
- replacement of 13 product hold vessels ranging in size from 2000 L to 9000 L utilizing modular construction for minimizing outages
- new final filtration (flat sheet) technologies

The following is a list of functional areas/systems that were modified:

- bioreactor vents and exhaust systems (new piping and filters)
- three new purification product hold arrays (three modules, nine vessels)
- purification hold array modifications
- two new 6000 L buffer prep vessel systems (stick-built)
- three new buffer hold vessels (two 6000 L, one 8000 L) (modular)
- two new 8000 L harvest buffer hold vessels (stick-built)
- three new 6000 L bioreactor feed vessels (stick-built)
- two new product hold nutrient vessels (stick-built)
- new lenticular depth filter systems for product isolation (modular)
- new "POD" filter (disposable technology) system
- modifications to four 20,000 L harvest and permeate tanks
- three heat transfer systems (skidded)
- utility upgrades

Notes from the Judging Panel – What Impressed Them

Their plan to deliver was what made this project so impressive. There is a lot here that big companies could learn from. Lots of skid-mounted equipment that equals a lot of scheduling issues.



Travel plan for 6000 L tank.

Unique Project Execution Strategy

The project execution strategy is unique due to the involvement of a building refurbishment, a conventional stick-build support facility, and modular process equipment, all at the same time. In addition, there were many constraints that impacted the project, such as limited windows for allowed shut-down (16 weeks) and the close tolerances for equipment access into the existing facility.

For a project with such limited execution time, the need to integrate the planning and work together was paramount. An integrated owner's team was established at the project inception and continually collaborated with all stakeholders.

Concludes on page 10.

Why Our Project Should Win

The following is an excerpt from Biogen Idec's submission, stating in their own words, the top reasons why their project should win the 2010 Facility of the Year Award:

- The facility, process, and equipment improvements deliver an increase in titer capabilities from 1 g/L to >3g/L. The result is a >300% increase over previous capacity.
- Value! In comparing what it would cost to build a new >3g/L facility vs. renovating LSM to deliver >3g/L, the equivalent capital outlay of the new facility would have been in the range of approximately $500 million and would take approximately 60 months to design, build, validate, and license. In contrast, this project leveraged what was already operational and executed it in 18 months (with only a four month shut-down) at a cost of US $39.1 million.
- The renovation also provides capability to establish late stage clinical/commercial capabilities and also provides harmonization between Biogen Idec's other global large scale manufacturing facilities.
- This lean transformation resulted in an overall increase in capacity by de-bottlenecking the process operations and addressed the downstream process operations and made significant efficiency improvements.
- The project incorporated lean project delivery methods utilizing 3D Building Information Modeling (BIM) of the process equipment layouts. The equipment was designed and modeled to within ¼" tolerance. The model was reviewed using real-time online software allowing stake holders in Denmark, Cambridge, Research Triangle Park, and Somerset, New Jersey to review for technical content, accessibility, ergonomics, and maintenance and operations.
- In addition, the "3D Model" was developed in conjunction with the equipment vendors and fabricators thus leveraging their expertise and eliminating duplication of efforts. The model was given to the contractors who then in turn utilized it to generate hundreds of isometric drawings saving several weeks of isometric submittal drawing time.
- Lean fabrication using modular skids and super skids were utilized. Components were assembled off site to speed installation, improve quality, and minimize environmental disruption.
- New technologies and increased capacity for mixing media components, additional large scale feed vessels (3 x 6200 L) with support and support infrastructure, replacements of 13 product hold vessels ranging in size from 2000 L to 9000 L utilizing modular construction speed installation, new final filtration (flat sheet) technologies and increased buffer preparation and hold capacities.
- Zero lost time accidents on more than 250,000 man hours logged.
- Utilizing a lean philosophy, the concept of "rolling shut-downs" reduced facility down time to a minimum. This optimized the production and eliminated the need to keep areas out of production when they didn't need to be.
- Excellent integrated collaboration among owner, architectural/engineering, and construction management project teams.

Modular skid.

Award Category – Operational Excellence

Winners in this category exemplify the application of modern management techniques aimed to improve operating efficiencies, promote excellent quality, consistency, and yield competitive cost of goods from existing and new facilities, processes, and manufacturing operations.

Since this project was very strategic in nature, considerable up front planning was undertaken. The early planning was embraced by all operational functions at the RTP facility and the ensuing comprehensive execution plan was compared with recent outages at other companies. The outcome, if successful, would indicate a clear, competitive advantage for Biogen Idec. During the early planning, the use of modular construction and the systematic approach to commissioning and validation would result in shorter facility outages by months or even quarters when compared with benchmarks from other companies.

As a result, the project execution plan was divided into seven project phases consisting of the feasibility study, conceptual design, preliminary engineering, preconstruction, construction, commissioning, and validation. This project required substantial overlap and coordination of activities among engineers, contractors, commissioning, validation, and quality teams.

A rolling shut-down approach was implemented to minimize duration of production outage, and construction and commissioning and qualification was integrated to effectively manage transition from construction to manufacturing. Rolling shut-downs and turnover included post campaign cleaning, GMP documentation close out (e.g. batch records), post use calibration, system decommissioning, and safety lockout. Additionally, all change control activities needed to be documented and approved prior to start of decommissioning activities.

Key Project Participants

Architect: Integrated Project Services (Lafayette Hill, Pennsylvania, USA) *(See ad on page 7)*
Design Manager/Engineer: Integrated Project Services (Lafayette Hill, Pennsylvania, USA) *(See ad on page 7)*
Construction Manager: Yonkers Industries (Cary, North Carolina, USA)

Successful Construction Approach

A lean design approach was developed that leveraged the capital project supply chain by integrating the A/E, CM, vendors, fabricators, owner, and key trades contractors. The integration was the key to developing the proper sequencing of work by selecting stick built and modular skids in anticipation of erection durations. In addition, maximizing off-site fabrication also was used to accelerate the schedule. Another technique essential to the construction sequence and meeting schedule was to perform as much of the work in the grey space boundary prior to production outage.

Conclusion

The renovation plan was designed to meet current and future manufacturing and clinical needs and comply with cGMP and regulatory requirements. By utilizing modular and stick built techniques, Biogen Idec was able to significantly compress the schedule – completed the construction within a four month shut-down – and reduce construction costs and speed products to market. Through exceptional up-front project planning and management; integrated, lean design, and construction techniques; and rolling plant shut-downs, the project resulted in:

- flexible manufacturing platform consistent across sites
- increased overall efficiencies with maximized throughput
- consistency from early stage through commercial capabilities
- increased titer capabilities from 1 g/L to >3g/L (+300%)
- platforms that facilitate and grow partnerships/collaborations
- operations that perform with speed, excellence, and discipline
- avoidance of having to build new capacity to process higher yields

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2010
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The Rockwell Automation EMEA Life Sciences team would like to congratulate Pfizer Ireland Pharmaceuticals on being awarded the 2010 Facility of the Year award for Facility Integration and we are delighted to be associated with the ISPE FOYA winning facility for the 2nd consecutive year.

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Genentech

Innovative Project Execution Outpaces Ambitious Schedule

Introduction

Genentech's **ECP-1 Bacterial Manufacturing Facility** was built in Tuas, Singapore to increase the production capacity of Lucentis® (ranibizumab injection), which is used to treat patients with wet age-related macular degeneration. Genentech established a highly ambitious schedule that would be the defining challenge: to take a project from engineering kick-off through initiation of GMP qualification batches in 24 months. Winner of the **2010 Facility of the Year Award (FOYA) for Project Execution**, the facility was initially developed by Genentech, a wholly owned member of the Roche Group, and is now operating as Roche Singapore Technical Operations.

Meeting an ultra-fast-track schedule on an international project required a collaborative team to develop and execute an innovative strategy. With its contractors Jacobs Engineering Group and Bovis Lend Lease Pharmaceutical, Genentech developed a strategy utilizing large-bay modules integrated with traditional stick-build construction. The team also developed a parallel work strategy that enabled a 90% overlap of design and construction efforts, leading to significant overall schedule savings.

As with any project of this size and complexity, the Genentech team encountered numerous challenges, but overcame each through outstanding project execution techniques. The team's planning, dedication, and innovation enabled delivery of a fully integrated, high-quality facility in record time.

Vision for an Unmet Medical Need

Wet Age-Related Macular Degeneration (AMD) is a retinal disease that causes irreversible vision loss and is one of the leading causes of blindness in people over 55 years of age. The 2006 FDA approval of Lucentis for the treatment of wet AMD was followed by rapidly escalating patient demand. Genentech elected to increase Lucentis manufacturing capacity by constructing a new production facility that could meet future business needs with ability to accommodate increased throughput and a changing product mix.

Genentech

Category Winner – Project Execution

Project: ECP-1 Bacterial Manufacturing Facility
Location: Tuas, Singapore
Size: 102,000 sq. ft. (9,476 sq. m.)
Total Project Cost: $194,000,000
Duration of Construction: 14 months

Aerial view of exterior.

A worldwide selection effort yielded a 30-acre greenfield site in Tuas, Singapore, because it offered a knowledgeable, highly supportive business environment, a modern infrastructure, and an improved cost structure. Additionally, Singapore houses a thriving pharmaceutical community, which enabled Genentech to draw from a deep regional talent pool.

The project comprises a total building area greater than 102,000 square feet, more than 30,000 square feet of which is manufacturing space on two levels. Production support areas, including administrative offices, a GMP warehouse, and a central utility building were stick-built on the site. Additional site scope included infrastructure, such as roads, main utility services, landscaping, and an electrical substation.

Module fabrication shop.

Continued on page 14.

Congratulations Genentech!

Winner of the 2010 ISPE Facility of the Year Award for Project Execution

Genentech Biologics Manufacturing Facility *Tuas, Singapore*

Bovis Lend Lease is proud of its partnership with Genentech and the exceptional team that helped deliver the design and challenging fast track execution of this facility.

Whether providing up front consultation or comprehensive EPCMV services, our goal is always the same – delivering safe, sustainable, innovative solutions with profitable outcomes for the life science industry.

Bovis Lend Lease: proud partner of ISPE's Facility of the Year Award recipient for Project Execution for the second consecutive year.

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Ocean transport of finished modules.

Accelerating the Schedule with Modular Construction

An early stage study indicated that a modular approach offered numerous advantages and concluded that it was the only viable method to meet the schedule requirements. Melding modular and stick-built construction, ECP-1 utilized 24 large bay structural modules measuring 25'W × 21'H × 45'L (as opposed to the standard module size of 14'W × 12'6"H × 45'L). One large bay module is equivalent in size to four standard modules. Utilizing modular construction shortened the duration for overall project execution because:

- Modular construction allowed for progression of significant structural, mechanical, electrical, and architectural works in parallel with Singapore site construction. Normally these occur in sequence.
- Experienced hygienic craft labor was available at Jacobs' module shop in Charleston, South Carolina, USA.
- Productivity benefited from the controlled environment in the shop, which also reduced the density of field craft in confined areas.
- Genentech was able to execute FAT and qualification in the same controlled module fabrication shop, prior to shipment.
- Charleston location facilitated Genentech involvement to resolve engineering and design issues and ensure quality control.

The total ocean transport time from Charleston, South Carolina to the site in Singapore was 45 days per shipment, which represented a significant block of time on the schedule's critical path. Planning for dedicated "last on, first off" ocean shipping and pre-approval of all permits and customs documents were keys to maintaining the planned project schedule.

Modules were moved after midnight with police escort on roads that were closed to other vehicles. In advance of the move, trees were trimmed, lights removed, and utility lines relocated.

The construction site was prepared for the modules by setting drain piping, base plates, rigging and soil compaction (for the crane), scaffolding and safety barriers. Upon arrival at the

Modules staged in final layout.

site, each module was carefully lifted and set in place with a 500 ton crane/220 foot boom, and a dedicated team of tradesmen under Bovis' direction. Temporary weather protection was applied until the modules were connected with each other and the site infrastructure.

The speed and flexibility of panel installation both in Charleston during primary fabrication and in Singapore during module interconnection, contributed to achieving the overall schedule targets. The quality and consistency of the panels and finishes was excellent, and they made the long ocean journey without a scratch.

Significant Contributions in Project Execution

Meeting an ultra fast track schedule on an international project required a collaborative team to develop and execute an innovative strategy, and Genentech found this team in Jacobs and Bovis.

A project execution plan was established prior to preliminary engineering that recognized each company's strengths and experience for each task. The plan called for Jacobs and Bovis to form two design build teams; Jacobs led the US-based design and construction of complete manufacturing area modules, while Bovis managed Singapore-based design-build of infrastructure and non-process areas, as well as module setting and hook up. This parallel work strategy enabled more than 90% overlap of design and construction efforts, resulting in significant overall schedule savings.

With design activity taking place in four locations spanning 12 time zones, the project team selected "typical" design tools and procedures to eliminate learning curves, and their online, real-time model allowed immediate design review and comment. This online, real-time data model allowed immediate design review and comment. This online process proved so effective that planned on-site reviews were greatly reduced, saving travel costs and time, as well as the lag between design and design approval.

Equipment and instrument procurement could not proceed quickly enough, which meant that critical vendor design data would not be available to support the design and module fabrication schedule.

Concludes on page 16.

Why Our Project Should Win

The following is an excerpt from Genentech's submission, stating in their own words, the top reasons why their project should win the 2010 Facility of the Year Award:

Outstanding Project Execution

- The project team successfully delivered a high quality E. coli drug substance facility in record time – preliminary engineering to initiation of GMP qualification batches in less than 24 months! This was the fastest schedule in Genentech history, and was more than 10 months faster than industry benchmarks.
- The project achieved a perfect safety record. Module fabrication and site construction utilized nearly two million man hours with zero lost time incidents and zero reportable accidents.
- The focus on quality engineering, quality construction, and team collaborations resulted in precise alignment between thousands of module connections at the Singapore site. In no case was there any connection misalignment greater than 3/8 of an inch.
- Modeling of the GMP process modules maximized use of Plant Design System (PDS®) 3D in Cincinnati to reduce obstacles and to ensure that field interconnections had proper alignment. The stick-build design was executed with AutoCAD 2D in Singapore.
- The project utilized large bay modules, a first for the pharmaceutical industry. The large bay modules resulted in a 75% reduction in the number of modules, further accelerating schedule completion.

Unique Project Challenges Overcome

- Two ocean shipments of oversized modules were each transported almost 14,000 miles, enduring weather, rough seas, and traffic logistics. All modules arrived fully intact and on schedule.
- Outstanding communications made this successful project possible, despite the team spanning 12 time zones with team members in Singapore, San Francisco, Cincinnati, Charleston, and various vendor shops.
- Nearly all acceptance testing and qualification work was executed before module shipment to the Singapore site, thus reducing the time to start up once the modules were installed at the ECP-1 site.
- The team drew strength from what could have been obstacles arising from the diversity of languages, customs, standards, and practices in this multinational project.
- The team surmounted labor availability issues in Singapore by leveraging pre-existing subcontractor relationships, while still maintaining cost effectiveness. All subcontracts were bid on a lump sum or unit price standard.

Exceptional Project Management

- The project set new standards for team collaboration, teamwork, and team leadership.
- From the outset, Jacobs, Bovis, and Genentech formed a seamless partnership without boundaries or corporate egos.
- The tone of the project was set early with each team member committed to providing any and all resources required in order to deliver this facility in record time.
- Decision making occurred quickly and at the lowest levels possible.
- Emphasis was placed on meeting post-construction, FDA licensure-critical compliance deliverables to assure the GMP Lucentis Qualification batch schedule.

Notes from the Judging Panel – What Impressed Them

The project execution was fantastic. Completion in 24 months! They had three geographic regions working on this project and they all came together with no items off more than three eighths of an inch. Good use of large box modules, done very well. They had some severe logistical challenges.

Award Category – Project Execution

Winners in this category exemplify the application of novel tools and approaches to delivering projects that improved efficiencies, overcame unusual challenges, promoted effectiveness, and organized stakeholders and project team participants in ways that led to successful outcomes.

The risk to the schedule of potential rework was mitigated through the development of a process that:

- established a design basis for each component (equipment/instrument) on the project
- tracked the vendor information for each component and its impact on design previously completed
- managed the impacts from a separate contingency fund established for this issue

A Unified Team Approach

The guiding principle throughout the project was the need to provide patients with products that addressed unmet medical needs, and the end users with facilities that were fit to operate.

Key Project Participants

Designer/Architect/Engineer: Jacobs Engineering Cincinnati (Cincinnati, Ohio, USA)

Construction Manager: Bovis Lend Lease Pharmaceutical Pte Ltd. (Singapore) *(See ad on page 13)*

Modules set on foundations.

Many design decisions were resolved by answering the question "what's best for the patient?" These simple, but powerful words had long been part of the Genentech culture and were immediately embraced and followed by the contract members of the team, as well.

Effective communication with open and honest discussion of issues and concerns among all parties was an obvious requirement for this project to succeed. The project management team established an atmosphere of trust early, thus ensuring that team members did not overreact when potential problems or bad news arose. This allowed the team to be informed about issues early, while options to mitigate the situation were still open.

Although the project was highly collaborative, Genentech was at the top of the organization chart and had ultimate responsibility for all strategic decisions. Effective decision making with a well defined process and clear accountabilities was another critical success factor that made it possible to attain the aggressive schedule.

Performance was measured daily and formally reported weekly to Genentech and the rest of the team. This report highlighted overall cost trends, schedule status, progress, and productivity by discipline/task/module, staffing, change management, and safety. Through timely analysis of this data, the team identified negative trends early enough to implement mitigation steps and effectively kept the project on its schedule and cost targets.

Conclusion

The business requirements of the ECP-1 project presented the project team with significant schedule, cost, and execution challenges. However, by committing to a modular approach from the beginning, along with an early focus on site issues, outstanding project planning, execution techniques, and team development, the project beat the aggressive schedule target of 24 months by two weeks and 10.5% under a $217 million budget. As a result, facility production capacity goals were met, delivering a high-quality, licensable manufacturing site to meet future Lucentis market demand.

Bayer AG
Pfizer
Lek Pharmaceuticals
GlaxoSmith Kline
Smithkline Beecham Pharmaceuticals
BRI
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Interbio
Sandoz
ARC International
Eden-Waren
TMI
Miles, Inc.
Biotechnikum
EuroCetus
Sclavo SpA
Pasteur Merieux Connaught
Gist-Brocades
Südzucker AG
Lonza AG
Genzyme Biochemicals
Lignozym
EBEWE Pharma GmbH
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AKZO Intervet International BV
Amgen, Inc.
Ciba-Geigy
Antibioticos
Werthenstein Chemie AG
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Astra Zenaca
Novartis Pharma AG
Tecnogen S.C.p.A.
LG Chem
Universiti Teknologi Malaysia
Sanofi-Aventis
DSM Biologics
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Allergan Pharmaceuticals, Inc.
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Regeneron Pharmaceuticals, Inc.
Avecia Ltd.
Laboratoires Serono SA
Cerbios-Pharma SA
GPO
Biovitrum AB
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CP Guojian Pharmaceutical Co. Ltd.
Celltrion, Inc.
Dongbao Enterprise Group Co. Ltd.
Suzhou Landing Biopharmaceutical Co. Ltd.
Zhejiang Hisun Pharmaceutical Co. Ltd.
Daiichi Suntory Pharma Co. Ltd.
Dr. Reddy's Laboratories Ltd.
Serum Insitute of India Ltd.
Center of Molecular Immunology
Phyton Biotech GmbH
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From small to large scale-bioreactors

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2009
Facility of the Year Awards
CATEGORY WINNER
Facility Integration • Supplier

MannKind Corporation

Changing the Face of Bulk Lyophilization

Introduction

MannKind Corporations' signature drug, an ultra rapid-acting insulin therapy, was developed to offer the millions of people suffering from diabetes a non-invasive treatment option. At the heart of the drug lies MannKind's proprietary Technosphere® molecule that can deliver not only insulin, but also a wide variety of other macromolecules into systemic circulation through the pulmonary route. The Technosphere particle and Technosphere® Insulin (TI) were so revolutionary and specialized that no existing facility in the world was capable of producing them. For this reason, the company designed and built its own **Technosphere Insulin Manufacturing Facility** in Danbury, Connecticut, USA.

It is the custom process line the facility houses that impressed the judging panel and inspired them to award this project the **2010 Facility of the Year Award for Process Innovation**. MannKind engineered an innovative manufacturing process line from start to finish and at every point in this process, designed new technology or applied innovative adaptations to existing technology to meet their needs.

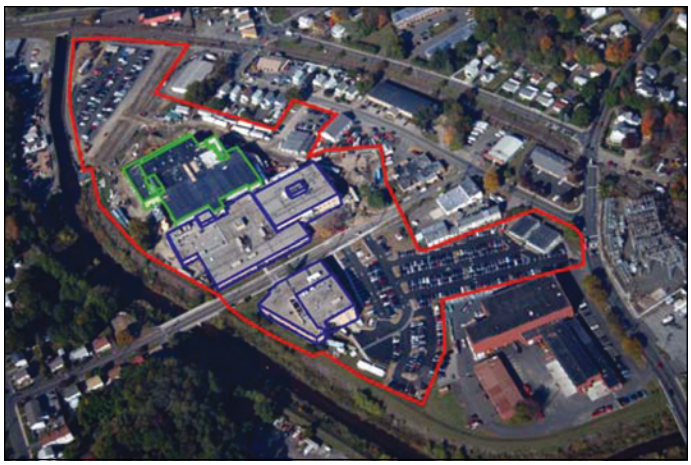
Yet another distinguishing feature of MannKind's facility is a first-ever solid-dosage pharmaceutical adaptation of a cryopelletizer for which the judges awarded the **2010 Facility of the Year for Equipment Innovation**. MannKind worked with Cryogenic Equipment Services to modify the cryopelletizer to create uniform pellets from the slurry so that the water could be removed quickly and consistently during the bulk lyophilization process. This revolutionary adaptation dramatically improved the quality of the drug and the efficiency of its production.

Innovation for a Top Priority

According to the Centers for Disease Control and Prevention, 7.8% of the U.S. population is afflicted with diabetes, as is a staggering 10.7% of Americans aged 20 or older. Diabetes costs our nation more than $170 billion annually, and more importantly, it is responsible for tens of thousands of premature deaths each year.

MannKind Corporation, a diversified biopharmaceutical company engaged in the development of novel therapeutics for the treatment of major disease states, has made the treatment of diabetes its top priority.

MannKind's lead product, inhalable insulin, is based on the company's Technosphere particle technology: an inhalable powder designed to provide efficient conveyance of pharmaceuticals to the respiratory tract for delivery into the systemic circulation. Technosphere particles have an approximate mean particle size of 2.5 microns and are formed by the intermolecular self-



Aerial view during construction: expansion outlined in green and connected to Building 1 outlined in blue.

Specialty reactor designed to form Technosphere particles.

Continued on page 20.

MannKind Corporation

Category Winner – Equipment Innovation and Process Innovation

Project: Technosphere® Insulin Manufacturing Facility
Location: Danbury, Connecticut, USA
Size: 251,876 sq. ft. (23,400 sq. m.)
Total Project Cost: $163,100,000
Duration of Construction: 20 months

Where does energy efficiency fit into the equation?

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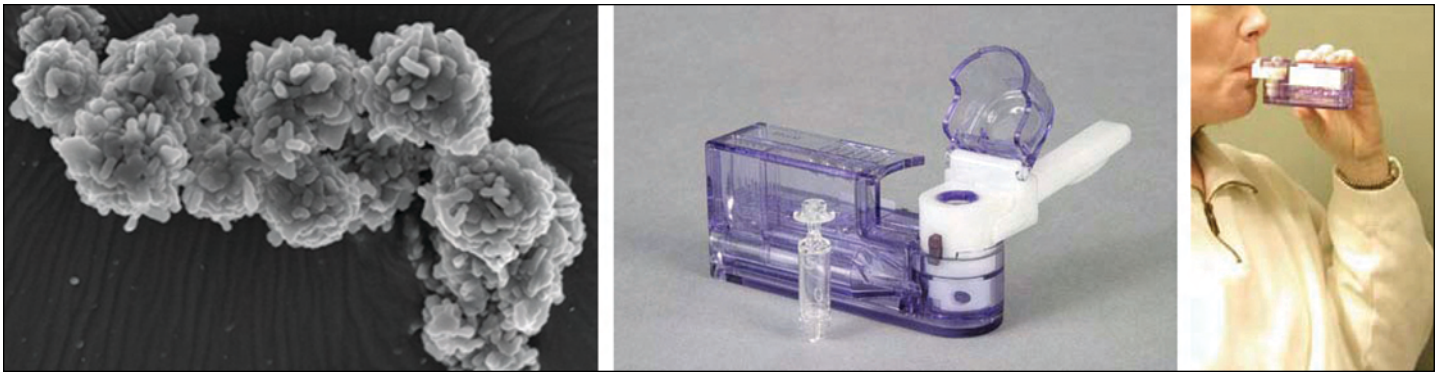


The Technosphere particle (average particle size 2.5 microns in diameter), cartridge and inhaler, and inhaler in use.

assembly of a small organic molecule. A wide variety of small organics, peptides, proteins, and other macromolecules can associate with the particles to create a variety of innovative oral inhalation products.

Technosphere Insulin Inhalation Powder (TI) is delivered by means of the reusable, high-resistance, breath-powered MedTone® inhaler, discreetly sized to fit into the palm of a patient's hand. The innovation represented by Technosphere Insulin's formulation and drug delivery system made it necessary for it to be manufactured on proprietary equipment in a proprietary process. Commercial scale-up of existing laboratory techniques was not cost-effective, and the TI cartridges, still under design, were incompatible with existing powder filling technology.

In early 2005, MannKind initiated conceptual design of an expandable manufacturing facility for TI. At the time, the company was producing TI for clinical trials in a small pilot plant, and the first Phase 3 clinical trials of TI were being planned.

In anticipation of the preparation and submittal of its first New Drug Application (NDA), MannKind designed and built a $163 million facility to manufacture TI. This included not just the building itself, but also the creation or novel adaptation of multiple pieces of process equipment.

Process Overview

MannKind's facility is divided into two main parts: 1) a bulk manufacturing facility where the Technosphere particle is made, combined with insulin to make TI, freeze dried, and packed into containers that can be stored prior to filling; and 2) a filling-packaging facility where the finished cartridges are produced from the bulk TI powder.

The process begins with raw materials (acetic acid and FDKP) to form the Technosphere particle in solution. Using a tangential flow filter, the particles are washed using diafiltration and the concentration of the particles is increased by removing liquid. Insulin is added to the suspension to form Technosphere Insulin suspension. In a process called cryopelletization, the suspension is flash frozen to make pellets that are dried in a bulk lyophilization process to remove the liquid components. Dry TI powder removed from the lyophilizers is packed into containers that are later affixed to the fillers during cartridge filling. Filled cartridges are individually packaged into foil envelopes, and then assembled into kits to provide to patients.

Cryopelletizer with the top section raised for inspection.

Cryopelletizer

After the Technosphere particle is formed, insulin is added to a process vessel that contains the Technosphere particle suspension pumped from a tangential flow filter operation. Insulin is adsorbed onto the Technosphere particles to form TI, still in an aqueous suspension.

Once the TI particles are formed, the suspension is flash-frozen and then lyophilized (freeze dried) in bulk to obtain the dry powder. Simple quiescent freezing would allow the product to agglomerate while freezing, which would result in inefficient drying and/or meltback and possible loss of pharmaceutical usefulness. Therefore, the project team needed to create a new method of flash-freezing.

This led to the selection of the cryopelletizer, which flash-freezes the TI suspension into small pellets within a defined size range and solves the agglomeration problem.

Though cryopelletization has been applied in processing of cellular material from bioreactors, its use appears to be novel in the formulation of a solid dosage form delivery as an aerosol. According to the vendors and engineers involved in the project, MannKind's large-scale application, applicable to most bulk lyophilization processes, is unique in the pharmaceutical industry.

In the laboratory, cryopelletization can be accomplished by dripping the product suspension into a pool of liquid nitrogen to form small frozen pellets. Although this method produces good product on a small scale, the technique is not commercially viable. Commercial-scale production required the application and modification

Award Categories – Equipment Innovation and Process Innovation

Equipment Innovation

Winners in this category exemplify the novel application of commercially available and custom developed process manufacturing and facility management tools, which yielded superior results, advanced processing understanding, and improved competitive position. Includes imaginative collaboration with vendors/suppliers/manufacturers.

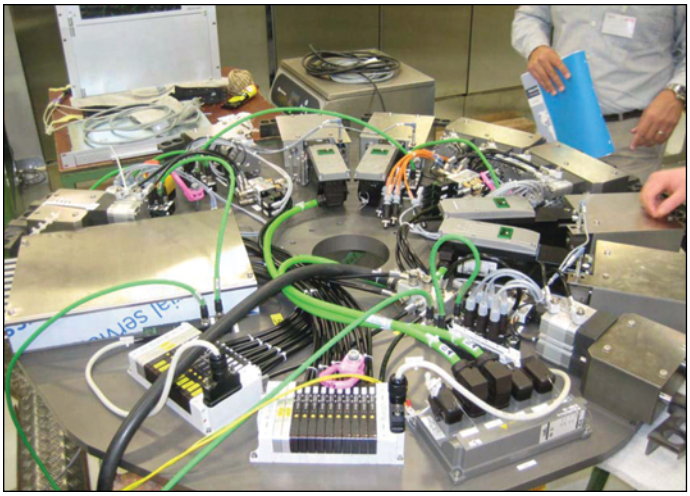
Process Innovation

Winners in this category exemplify the application of novel process manufacturing techniques on existing and new facilities, including fundamental scientific processing approaches and related applied science-based solutions to existing and new challenges.

Notes from the Judging Panel – What Impressed Them

For Process Innovation they were quite creative in what they accomplished. For Equipment Innovation, they designed a lot of the equipment from scratch.

Continued on page 22.



Powder filler.

Key Project Participants

Designer/Engineer: CRB (Plymouth Meeting, Pennsylvania, USA) *(See ad on page 21)*
Architect: KlingStubbins (Philadelphia, Pennsylvania, USA) *(See ad on page 21)*
Construction Manager: Torcon, Inc. (Red Bank, New Jersey, USA)
Additional Suppliers:
- Automated Control Concepts (Neptune, New Jersey, USA)
- Dynamic Systems, Inc. (Raleigh-Durham, North Carolina, USA)
- Cryogenic Equipment Systems (Bissegem, Belgium)
- Integrated Process Technologies (Devens, Massachusetts, USA)
- Serail (Le Coudray, France)
Siemens Building Technologies (Pine Brook, New Jersey, USA) *(See ad on page 19)*

of equipment previously used, to the best of the project team's knowledge, only in the food processing industry.

Together with Cryogenic Equipment and Services (CES), MannKind designed a unique method to cryopelletize our product on a commercial scale. As with the laboratory technique, it utilizes liquid nitrogen to flash-freeze the product suspension, but rather than dropping or spraying the suspension into a pool of liquid nitrogen, it meters it into a liquid nitrogen stream. Internal components in the machine separate the frozen pellets from the nitrogen, recirculate the liquid nitrogen, and add

Why Our Project Should Win

The following is an excerpt from MannKind's submission, stating in their own words, the top reasons why their project should win the 2010 Facility of the Year Award:

- Our adaptations of cross-sector technologies for novel application in the pharmaceutical industry not only make the production of the innovative Technosphere® particle possible, they also make possible multiple new drug therapies in the future. Our cryopelletization technology can improve the production of hundreds of drugs worldwide that require bulk lyophilization in their manufacture; and our innovative, non-invasive drug delivery system can transport a potentially endless variety of macromolecules into systemic circulation via the lungs. Additionally, though our new facility was purpose-built for a drug with blockbuster potential to treat diabetes, it was also designed with tremendous flexibility and can be customized and expanded to suit new product needs and increased demand.
- Extensive use of standardization, automation, 3D design, field bus technology, S88 methodology, simulation software, labor-versus-automation cost analyses, and preinstallation testing permitted significant schedule accelerations and reductions in the overall project cost and the cost of post-installation issues, errors, and malfunctions. The resultant documentation and understanding gained from these techniques also greatly accelerated the commissioning and validation process and the development of SOPs.
- Our culture of empowerment and accountability, small-business flexibility, and unwavering focus resulted in a superior quality facility that was completed on time and 11% under budget despite numerous stumbling blocks and challenges (renovation of an in-use facility necessitating phased construction, environmental remediation, multiple equipment customizations, overseas sourcing, regional challenges, company infancy, lack of pipeline funding, lack of capital construction experience, process equipment design occurring in parallel with facility construction, etc.).
- Our innovative use of multiple scheduling and communication tools, many not commonly found in pharmaceutical construction and one completely custom-designed in house, sets a standard for future capital construction projects in our industry and others. Our integrated, nimble SCoRe management system, combined with Primavera scheduling, PIMS, SharePoint, block-sequential diagramming, process mapping, and other techniques, resulted in a highly energized and empowered workforce, a stellar safety record, and the discovery of many creative solutions that may otherwise have been overlooked in a lesser management/communication environment.
- Our unrelenting commitment to our region and our environment informed our choices from start to finish. From the removal of 15,700 cubic yards of contaminated dirt, to the selection of energy-efficient equipment, to the final touches of recycled and recyclable sustainable furniture, sustainability was at the forefront of our decision-making processes during facility construction and beyond.

Cartridge filling line.

make-up nitrogen to replace that which evaporates.

Once conceived, the process of design, construction, testing, and operation led to several improvements to the overall process. Application of lean manufacturing principles eliminated the need to store frozen pellets and handle them multiple times: the pellets were formed, loaded onto chilled trays, and delivered into the freeze dryer. This method saved large capital investment in storage and transportation equipment for frozen pellets.

MannKind's pioneering efforts in cryopelletization and bulk lyophilization allowed the introduction of a dosage form never before used for any active pharmaceutical substance. The same general process can be applied to future APIs. MannKind's cryopelletization technique offers significant reductions in process time and cost and significant improvements in the consistency of the resultant pellet size.

More Equipment Innovation

In addition to the new lyophilization technique, MannKind also made unique adaptations to the specialty mixer where the TI particle and the insulin are combined; designed a highly cost-effective method to move bulk powder from the lyophilizer to the filler; and designed a filling system that could work at high speed, while remaining safe for the operators and supremely precise in the metering of the bulk powder.

Conclusion

MannKind's Technosphere particle technology represents a radical leap forward in the pharmaceutical industry; together with their custom-designed, breath-powdered inhaler, it forms an entirely novel drug delivery method for a wide variety of therapies. Due to the innovative and highly specialized nature of the Technosphere Insulin (TI) particle, it was necessary for MannKind to conceive a new process technology for the production and packaging of the drug. Through innovative adaptations of cross-sector technologies for novel application in the pharmaceutical industry, not only did MannKind make the production of the TI particle possible, they also make possible multiple new drug therapies in the future. The cryopelletization technology can improve the quality and production of drugs that require bulk lyophilization in their manufacture.

Pfizer Biotechnology Ireland

A Green Approach to Biotech Facility Design

Introduction

Pfizer Biotechnology's Ireland's **Monoclonal Antibodies Small-Scale Facility (MAbs SSF)** in Shanbally, County Cork, Ireland, represents Pfizer's first biotechnology greenfield development.

From inception through implementation, this clinical trial product facility incorporated industry best practices for sustainability and Pfizer's green building guidelines into its design, including: extensive re-use of existing assets, waste minimization procedures, recycling utilization in both construction and operations, the inclusion of energy-efficient fixtures and equipment, and minimized air change rates to meet comfort conditions and classification standards.

The project, winner of the **2010 Facility of the Year Award for Sustainability**, was executed with an excellent safety record and delivered on target according to a very aggressive timeline of 29 months from start of preliminary design to completion of PQ, 35% better than the biotechnology industry benchmark average.

Aerial view of exterior.

Project Overview

Driven by a critical business need, Pfizer Biotechnology Ireland built the MAbs SSF to supply late state clinical trial material. The facility also serves as a strategic biotechnology manufacturing center of excellence and is planned to support the rapid development of new biotechnology products.

The initial product to be manufactured in the facility is Tanezumab, a humanized monoclonal antagonistic antibody with indications for osteoarthritis and chronic lower back pain in Phase III clinical trials.

The facility includes a warehouse with space adequate to meet the raw material and finished goods storage requirements of the manufacturing facility, and a combination of laboratories and administration offices within the same building to house the quality control laboratories and site staff. All facilities are incorporated within one structure. Other features of the facility include a technical services laboratory with a planned use to support technology transfers through, for example, lab prequalification) work for new products, process characterization, manufacturing support, and process validation.

The site was chosen for a variety of reasons, including its proximity to the adjacent Pfizer Ringaskiddy site which allowed the new facility to use spare capacity of the existing Waste Water Treatment Plant and fire main system rather than building a new treatment plant or bringing in new tanks and pumps for fire water retention.

The major elements of the project's approach to sustainability are detailed below.

Existing Asset Re-Usage

The choice of Shanbally as the site for the project and the fact that it was a previous manufacturing site with ready adjacency to the Pfizer Ringaskiddy API facility presented significant opportunity for asset re-use. The following highlight the green benefits and opportunities of this location:

- use of Pfizer Ringaskiddy (adjacent API site) Waste Water Treatment Plant spare capacity rather than the provision of a new treatment plant for process waste water and sanitary effluent treatment
- re-use of existing assets, e.g., existing tankage north of site for fire water retention
- use of gas, electrical, and city water supplies already on site

Pfizer Biotechnology Ireland

Category Winner – Sustainability

Project: Monoclonal Antibodies Small-Scale Facility (MAbs SSF)
Location: Shanbally, County Cork, Ireland
Size: 133,000 sq. ft. (12,356 sq. m.)
Total Project Cost: $189,613,542
Duration of Construction: 19 months

Notes from the Judging Panel – What Impressed Them

A top-tier sustainability project. Well done, well executed. Advanced automation, 3D, PAT, a lot of cutting-edge technology to make the facility happen. Their benchmarking data was exceptional.

Utilities area.

- use (through extension) of Pfizer Ringaskiddy Fire Main System rather than the provision of a new system with associated tanks/pumps, etc.
- 5,000 cubic meters of crushed rubble from an old adjacent facility were used in the building substructure
- 4,000 cubic meters of rock and stone which were excavated in the course of the works were crushed on site and used as backfill beneath the building and roads
- 2,000 cubic meters of topsoil were set aside and re-used for landscaping works
- 30,000 cubic meters of excavated material have been used on site for general fill and landscaping

Continued on page 26.

HVAC plantroom.

Award Category – Sustainability

Winners in this category exemplify the application of novel approaches, tools, and techniques intended to improve effective use of energy, minimize waste, reduce carbon footprint, incorporate green manufacturing techniques, reduce environmental impact, and result in more efficient processing, utilities support, and business advantage.

Utility, Electrical, and Architectural Design – Environmental Considerations

Utilizing best practice and Pfizer's Green Building guidelines, a large number of energy efficient features were applied in the design as well as items which were commonly applied across the majority of the utility system (e.g., utilization of variable frequency drives, metered parameters fed back to energy monitoring system, high efficiency motors). Specific measures undertaken include:

Boilers and Steam/Condensate System

- economizers on boilers
- heat recovery from blow down to pre-heat make-up water
- automatic oxygen trim, gas boilers, and low NOx burners
- All condensate systems are designed for return of condensate to central receiver/deaerator (excluding clean steam condensate).

Chilled and Cooling Water

- water cooled chillers (preferred over air cooled units) based on energy consumption
- Cooling water designed such that RO water waste stream, regeneration, and reject can be used as feed-water for make-up.
- automatic cell isolation/flow management and temperature control – automatic control of cooling towers designed based on climate conditions

Key Project Participants

Designer/Architect/Engineer: Fluor Enterprises, Inc. (Greenville, South Carolina, USA) *(See ad on page 25)*

Construction Manager: Jacobs Engineering, Ltd. (Cork, County Cork, Ireland)

Clean Water Systems

- For sanitization purposes, ozone is used on RIW rather than heat/steam.
- Final treatment on Purified Water systems is electro-deionized.
- Meters provided to monitor all water usage.
- Point of use coolers are utilized rather than loop coolers.

Compressed Air Systems

- Compressors are water cooled with all air intakes externally ducted.
- Air drying regeneration achieved by separate blower rather than air compressor.
- pipe sized to minimize pressure drops/pressure at source

HVAC

- use of Variable Air Volume (VAV) air distribution systems in office type areas
- use of outside air economizer cycle for office areas
- low velocity/friction rate duct design to reduce fan horsepower
- use of direct drive fans, high efficiency motors, and VFD's on supply and return air fans
- chilled water coils sized for low velocity across coil face in order to reduce fan HP
- cycle operation of air handling units serving office type areas during unoccupied periods, based on setback temperature

Plumbing

- use of low flow/water conserving plumbing fixtures

Electrical Systems and Energy Management Systems

- The sites electrical distribution system is metered for every area and major use point.

- All utility meters and instrumentation can be tied into an energy monitoring system in order to monitor and control the major utility systems for a site.
- A lighting management system has been installed in the facility across all floors. This ensures lighting is only operational in occupied areas. This has a projected cost saving of $83,234 per annum compared to a traditional switched system.
- use of energy efficient light fixtures and motors

Architectural

- All offices and desks are adjacent to exterior glazed walls.
- extensive use of glazing/glass walls in the facility to maximize the amount of natural light in the processing suite and make the building a more pleasant working environment
- An ecoseal grey insulated roof membrane has been used to reduce heat island effect.
- Building orientation optimized for solar gain.

Pre-Ops Energy Savings Study

An energy saving study was built into the early C&Q stage of the project, involving the sustaining operations personnel. Detail of set points and operating ranges were examined for all plant utilities and HVAC systems. Some key recommendations were incorporated back into the design. These included room temperature reduction throughout the facility. Air change rates for classified areas were challenged and minimization was successfully implemented (Grade D). The cooling tower water temperature was set to track the ambient wet bulb to allow for greatest efficiencies.

Process Chemistry

The processes, based on the Pfizer platform, have been developed such that solvent utilization is very limited in the processes. Beyond small quantities of ethanol in which chromatography resins are stored (between uses), the entire process is aqueous based.

Cell culture harvest train.

Concludes on page 28.

Waste Management

The facility also operates a total waste management system. There is intensive recycling of all appropriate components under this system, i.e., fluorescent tubes, batteries, waste electrical and electronic equipment, cardboard, paper, cans, and glass.

Emissions

There are no major emission points from the facility, as defined by the Irish Environmental Protection Agency. There are only two minor emission point (boilers), both of which are significantly less than the 5 MW threshold.

Conclusion

Driven by a critical business need, Pfizer Biotechnology Ireland's project mission was to deliver a new cGMP multi-product mammalian cell culture manufacturing facility for monoclonal antibodies under an aggressive timeline and budget. Not only did the project team accomplish this mission, it also incorporated industry best practices for sustainability and Pfizer's green building guidelines into the facility's design, making the MAbs SSF a model sustainable biotech facility worthy of recognition.

Why Our Project Should Win

The following is an excerpt from Pfizer Biotechnology Ireland's submission, stating in their own words, the top reasons why their project should win the 2010 Facility of the Year Award:

People/Team

- The overall team approach to the delivery of the project reflected a strong belief in the experience, strength, and capability of the core project team.
- At various points along the way, the team has been supplemented with highly capable design and construction partners.
- In the later stages of the project, there was full integration of the start-up resources and the sustaining operations team.
- It is a measure of the overall success of the job that each phase can be independently gauged as a success, in isolation from the other phases.
- This team have delivered an extremely high level of performance to achieve the results highlighted above.

Excellence in Project Execution

- It was recognized that extraordinary performance would be necessary to achieve the aggressive targets set to meet a critical business need for Pfizer.
- The project has excelled in delivery and exceeded Pfizer internal and industry benchmarks for all the major categories of safety, quality, schedule, and costs.
- New and innovative approaches to project challenges have been successfully implemented.
- A complex biotech facility has been designed, constructed, commissioned, and qualified to a point where batch production can proceed in less than 2.5 years. This represents a 35% improvement against the average time for this scope.
- The overall cost is almost 20% less than the project budget (excluding contingency). It also represents a 35% improvement against the average cost ($/sq.ft), based on the industry benchmarks established for similar projects.
- A truly global project.

Operational Excellence

- Bearing in mind that this is Pfizer's first green field biologics facility, it is a significant achievement to complete a successful start-up in a timely manner. It is an even more noteworthy achievement when one considers the range of innovative operational approaches and structures that the plant has chosen to implement from inception.
- The project and sustaining operations team embraced Right First Time (Six Sigma) and Lean concepts and tools.
- A diverse operations team were brought together from various companies and geographic locations. They have operated in a non-traditional 'flat' organization which is focused on team performance.
- The Team successfully achieved all of this, despite a very challenging timeline, establishing a culture of operational excellence, flexibility, quality, and delivery.

Safety and Quality

- In terms of safety, based on overall construction person-hours of almost one million, the safety record achieved as zero lost time incident rate.
- The facility quality is of an excellent standard in terms of architectural finish, equipment, documentation, and systems. Re-work levels for mechanical and electrical were less than 1%.
- This plant represents the next step in the improvement of cleanroom design and construction for projects within Pfizer in Ireland.

Balance of Flexibility, Technology, and Sustainability in a Cost Conscious Manner

- The project has been constructed using a mix of technologies, both fixed and flexible.
- As well as being designed and constructed with sustainability and 'green' technology in mind, it has incorporated automation solutions in keeping with a modern biotechnology facility.
- Through this mix, the plant has maintained the capability to provide a competitive cost of goods, comparing favorably with biopharmaceutical contract manufacturing organizations.

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Pfizer Ireland Pharmaceuticals

Facility Integration at its Finest

Introduction

Pfizer Ireland Pharmaceuticals' **Aseptic Expansion** project in Dublin, Ireland – winner of the **2010 Facility of the Year Award for Facility Integration** – is notable for the way in which it successfully integrates a new production module with existing manufacturing operations and the surrounding residential neighborhood.

To respond to community and environmental issues associated with building a manufacturing facility so close to neighboring residential properties, the project team used a series of site analyses to optimize the current and future use of a very tight suburban site. The proposed design was specifically tailored to respond to its context and minimize the impact on the neighboring residences. Many other measures, along with extensive consultation with local residents groups, resulted in an aesthetically pleasing facility that meets Pfizer Ireland Pharmaceuticals' business need for additional freeze drying capacity, while demonstrating excellence in facility integration.

A Need to Increase Capacity

Located on a 17-acre site in Pottery Road Dun Laoghaire, the Pfizer Dublin Manufacturing facility has been in operation since 1970. Currently, Dublin is a global sourcing unit for both Vfend and Zithromax and is approved in the EU/US for both products. Pharmaceutical production has increased from an original volume of 750,000 vials to five million vials in 2008, increasing to 11 million vials in 2014.

In 2004, an overview of the freeze drying network within Pfizer concluded that there was a need for additional freeze drying capacity within Pfizer Global Manufacturing. A significant expansion of the Pfizer Dublin site was approved to provide additional capacity.

The project involved the construction of one new production module (PM2) containing four freeze dryers and the following support facilities: laboratories, warehousing, central utilities building, dispensary, and personnel and administrative support areas. The facility was designed to manufacture products for global markets and is registered to be a global sourcing unit, working to FDA, EU, and JP standards.

Aerial view.

A Desire to Be Considerate Neighbors

In early 2005, the foundations for the new aseptic facility in Dublin were started. The Dun Laoghaire site, which was originally built on reclaimed land, has a significant incline rising 12 meters from front to rear of the site. The new manufacturing facility was built at the back of the site and part of the design brief was to integrate the new plant with the existing buildings, while minimizing the impact on the surrounding residential neighborhood.

This required excavation of a significant hole in the site to reduce the profile of the building. Approximately 85,000 m3 of soil was excavated and reformed into large earth mounds (berms) around the site. When the building was constructed, significant time and effort was put into integrating it with the surroundings through the thoughtful landscaping of these berms.

Other significant contributions to the integration of the facility with the local community included: consistent color scheme in grey to neutralize impact on the landscape; curved roofs and plan elements for variety and liveliness and also to enhance the visual impact; and glazed areas and attractive design features on the buildings to raise the aesthetic content of the site.

A site master planning exercise completed during the conceptual phase of the project provided for significant future expansion space at the Dublin facility through the demolition of an existing Cadbury Adams gum based plant. In the short term, this space has been converted into a colleague garden.

Pfizer Ireland Pharmaceuticals

Category Winner – Facility Integration

Project: Aseptic Expansion
Location: Dublin, Ireland
Size: 177,066 sq. ft. (16,450 sq. m.)
Total Project Cost: $254,674,792
Duration of Construction: 29 months

Notes from the Judging Panel – What Impressed Them

They took so much time and effort into putting it together and consideration of neighbors. Very well-thought out.

Courtyard view of link corridor to PM2.

The site master plan also made provision for future expansion through the construction of a central utilities building with capacity and equipment space to support future modules.

Another key component of the project was the integration of the new facility (PM2) with the existing facility (PM1). A new warehouse was constructed as part of the project with adequate space to meet the raw material and finished goods storage requirements of both production modules, thus freeing up the original warehouse space for conversion into an administration area. This administration area is now located at the heart of the site and is central to both production modules.

Continued on page 32.

View of PSF integrated with PM1 from colleague garden.

Design Process for Success

Pfizer approached each decision for this facility using a structured and rigorous assessment process. Thus site selection, site due diligence, and site master planning tackled the macro issues and likewise the internal facility scoping and planning tested the optimization of the operations and logistics. A good example of the complexity and thoroughness of this process is the site master plan described below.

Site Master Plan

Every successful project takes into consideration the receiving site and the scale and demands of the project. In Pfizer's case, the site was difficult as highlighted by the following facts:

- narrow site with lots of neighbors
- visually and environmentally vulnerable (especially the landfill area)
- adequacy of space for existing and project demands and future growth
- steeply sloping site for both fill area (piling) and good ground
- good services availability
- Currently very tightly planned. Additionally, a desire to improve parking/plant boundary definition and security, municipal authority plans for frontage road realignment, desire to improve fire/ambulance services access, and an own door access required by electrical utility company for the new HT station.

A series of site analysis and options diagrams sought to optimize the use of these valuable suburban lands, as well as to respond to neighbor and environmental issues.

The use of the site was further complicated by the existence of a third party legacy gum manufacturing plant occupying the center of the site; although its capacity was scheduled for eventual transfer to another site, it would remain operational for the duration of the construction works.

The analysis of these and many other options clarified how best Pfizer should develop the site. Two sets of criteria, "the

Award Category – Facility Integration

Winners in this category exemplify the application of good design practices and superior conceptual planning which led to excellent integration of facility and process, yielding efficient, clean, pleasant environments promoting business advantages for staff and enterprise, encouraging excellent processing outcomes. Synergistic merging of process and building to create environment of form and functional excellence.

The Classics	The Criticals
Cost	Neighbor response and environmental (including road safety etc.)
Schedule/phasing	Facility integration/production/logistic synergies
Disruption	Management span and control
Expandability	Predictable growth patterns

Classics" and "the Criticals" were used in this assessment as shown.

This structured process of reviewing five and 20 year site planning options together simplified the decision making. Each option was reviewed to consider the implications both on manufacturing and the neighboring context. The final site was selected with consideration to manufacturing adjacency and synergy with the existing Pfizer facility and the rising topography to screen the new buildings.

Designed to Minimize Impact

The site design was developed to minimize its impact on its neighbors with the following characteristics:

- The overall manufacturing program is divided in five distinct buildings, each with smaller massing and impacts, but linked to a coherent site manufacturing pattern.
- Each building in turn is given a distinct shape to further break down the visual scale and optimize its manufacturing function.
- The new buildings and structures are consistently colored grey to prevent them forming a monolithic mass with the existing brown structures and to neutralize its color in the landscape.

Primary neighbor elevation: the top photo shows the existing views, the middle photo shows the effect of the berms, and the bottom photo shows the final effect of the landscaped berm. Up to 14 of these composite images were developed and discussed with the neighbors for their feedback and agreement.

Concludes on page 34.

Key Project Participants

Designer/Architect/Engineer: Jacobs Engineering (Dublin, Ireland)
Construction Manager: Jacobs Engineering (Dublin, Ireland)
Major Equipment Suppliers:
- IMA Edwards (Dongen, The Netherlands)
- Robert Bosch GmbH (Crailsheim, Germany)
- ATEC Pharmatechnik GmbH (Sörup, Germany)
- STERIS FINN-AQUA (Tuusula, Finland)

- The buildings have large glazed areas and attractive design features to raise the aesthetic content of these industrial buildings. Curved roof and plan elements add variety and liveliness, enhancing the visual impact.
- The main buildings are cut into the existing site to lower visual impact. The car park can become multi-storey in the future.
- The earth released by this deep basement cutting is used to generate a large scale attractive bermed structure to fully enclose the site, and in particular, to build a local attractive planted hillock beside the nearest residences so that their views are predominantly of landscape structures rather than buildings.
- The bermed and landscaped enclosure of the site also would significantly reduce and remove any residual noise or night lights from the site.
- A new safer car and truck entrance was integrated into the site plan, including improved fire truck access.

Micro laboratory.

Conclusion

Pfizer Ireland Pharmaceuticals' Aseptic Expansion represented a unique proposition for modern pharmaceutical companies: How to act sustainably to support new products on a long standing established site in a residential suburban area. Through a rigorous and inclusive design process, Pfizer successfully integrated a new production module into its existing manufacturing site in terms of manufacturing capacity, effectiveness and flexibility, social and neighbor integration, and economics and city planning.

Why Our Project Should Win

The following is an excerpt from Pfizer Ireland Pharmaceuticals' submission, stating in their own words, the top reasons why their project should win the 2010 Facility of the Year Award:

- The successful integration of a new production module, warehouse, central utilities building, and personnel support facility with existing operations (an aseptic manufacturing suite, a bioprocess suite, and QC laboratories) with no impact to manufacturing output during construction and qualification, while delivering improvements in quality, cost of goods, and colleague engagement.
- The sympathetic integration of the new facility within the surrounding residential area. An extensive process of consultation with local residents groups resulted in an aesthetically pleasing facility, carefully blended into the suburban landscape. The project team organized weekly follow up meetings with the local residents to continue the dialogue during the full execution of the project.
- State of the art equipment was used throughout the facility, including two highly automated compounding suites, vial washing/depyrogination tunnel, pressure/time filling equipment, automatic loading/unloading of pass through freeze driers, capping in grade B background, highly innovative inline inspection equipment, fully automated stopper processing.

  An innovative solution to the industry wide issue of sticking stoppers was the combination of a specific surface structure of the freeze dryer metal shelf and coating with a Teflon-containing layer.
- The maximization of sterility assurance through the novel integration of the Atec Stopper Processor and a Restricted Access Barrier System (RABs) filling machine.
- The project involved the construction of a new production module and warehouse on reclaimed land on an existing Pfizer site. In addition to making use of vulnerable land, the considerable resources dedicated to conceptual planning resulted in a waste management strategy that has delivered an increase in the sites recycling from 15% to 85%.

In order to minimize the energy consumption, a lot of attention went to the optimization of the air changes in the clean rooms. The project team worked out an optimum proposal that balances the reduction the air changes and the assurance of the air quality in the cleanroom.

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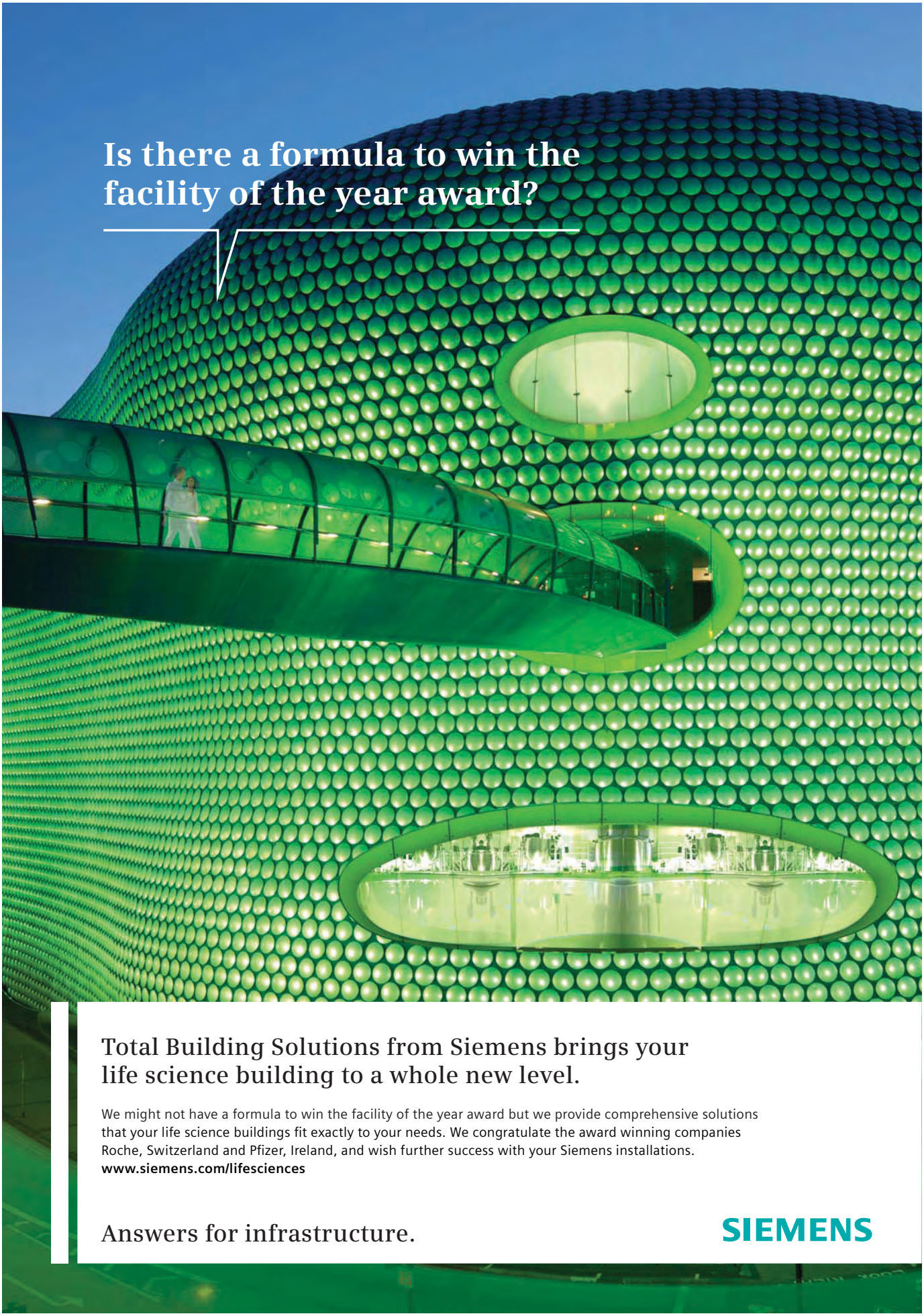
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ISPE Milan Congress Report: Cooperation, Collaboration and Harmonization

by Dr. Kate E. McCormick

"An unparalled opportunity to face the regulators in a risk-free environment."

With these words, Gordon Muirhead (GSK) and Alan Mac Neice, Chair of ISPE, introduced the seven senior regulators from EU agencies, US FDA, and WHO during the Regulatory Affairs keynote session at the Milan Congress in March. Short presentations on critical topics were followed by a question and answer session. The key, recurring message was the desire by all parties for co-operation, collaboration, and harmonization.

EU Update from the QWP Perspective

Diana van Riet-Nales from RIVM (Netherlands) is Deputy Chair of the EU Quality Working Party (QWP). She provided an update on current activities, including revision of guidelines on near infrared spectroscopy, radiopharmaceuticals, real-time release testing, and the impact of new technologies and approaches. Topics for which new guidelines are under development include the use of paediatric medicines and impurities in antibiotics.

Regulatory Update on EU GMP

Jacques Morénas from AFSSAPS (France) announced that the so-called "Pharma Package" will be presented to the European Parliament in the near future and hopefully will be finalized by the end of 2010. He reminded delegates to check on the internet the status of GMP/GDP documents from the Inspectors' Working Group; provided an update of Mutual Recognition Agreements (MRAs) and Agreements of Conformity Assessment and Acceptance (ACAAs); and introduced the new logo and acronym for the European Medicines Agency (EMA) – formerly known as the EMEA.

The presentation also covered the EUDRA GMP database which will contain information of licenses, new medicines, non-compliance, and inspection planning. The latter in particular will reduce duplication of inspections – a benefit both to the agencies and to industry. An update was provided on revisions of various chapters and annexes of the EU GMP guide plus the GDP guidelines. In particular, revisions of Annexes 2 and 14 are due out soon.

Significant progress has been made in training inspectors within the EU "Joint Audit Program." Since the same training is being used for assessment of agencies applying to join PIC/S, this is another step toward global harmonization of inspections. Other collaborative activities include secondment for a Japanese inspector to the EMA and a product testing working group within the Heads of Medicines Agencies forum.

Seated, from left: Alan Mac Neice, Gordon Muirhead, and Dr. Steve Wolfgang. Standing from left: Jacques Morénas, Tor Gråberg, Dr. Moheb Nasr, Richard Friedman, Dr. Lembit Rägo, and Diana van Riet-Nales.

PIC/S Regulatory Update

Tor Gråberg from MPA (Sweden) is the current Chair of PIC/S. He described PIC/S as an informal co-operative arrangement between national competent authorities, aimed at "leading the international development, implementation, and maintenance of harmonized GMP standards and quality systems of inspectorates in the field of medicinal products." The 2010 annual seminar in Malaysia will address inspection of traditional medicines while in 2011 in South Africa the focus will be good inspection practices.

There are currently 37 agencies that are members of PIC/S, with seven more being assessed for membership and a further eight having expressed interest in joining. The fact that US FDA is one of the seven under assessment is seen by all as a great step toward harmonization. Delegates were reminded they can play a role in increasing harmonization of inspection practices by encouraging drug regulatory authorities to apply for membership of PIC/S if they have not already done so.

The presentation ended with a note of caution. Supply chain is a topic currently on everyone's agenda and Gråberg emphasized that industry should ensure the message does not get diluted by duplication of efforts. He confirmed that PIC/S would include GDP in their approach to securing the supply chain.

Regulatory Issues in Countries Not Associated with ICH

Dr. Lembit Rägo from WHO (Switzerland) provided an overview of key issues within countries outside of Europe, USA, and Japan. These include a shift toward biological products which has resulted in release of a WHO guideline on biosimilars.

Continued on page 3.

"We Hear You"

ISPE Launches Career Solutions

In response to a changing industry, ISPE is rolling out a series of resources for Members in job transition or insecure in their current employment. One of these resources is "Career Solutions," a new section on the ISPE Web site that is a starting place for career development and advancement. Exclusive only to ISPE Members, Career Solutions features tools for a more comprehensive approach to further enhance job search and career development needs.

Career Solutions features free resume / CV postings for job seekers and free job postings for employers, dozens of resources and links designed to help maximize your job search, job lists from around the world, and information on ISPE's Hardship Program that enables you to keep your ISPE membership even when you are out of work.

Job Lists

Job Lists is an extensive list of pharmaceutical science and manufacturing jobs through ISPE's job listings board as well as external sites from other organizations from around the globe. Additionally, you may post your resume or CV, create a personal job alert, and a job seeker account. Begin your search by going to http://www.ispe.org/joblists.

Career Resources

Career Resources contains a wealth of free videos, webinars, articles, and links to help maximize your job search. If you are looking for a career change or would like to better manage your current career, you will find helpful articles under this section. One of the most valuable tools in Career Resources is found under Resume and Cover Letter Writing. When you need to make the most of your first impression with a potential employer, these insightful articles will help you secure that next interview.

Additional informative topics include Finances, Interview and Salary Negotiation, and Job Search. For more information, go to http://www.ispe.org/careerresources.

Career Events

Career Events is where we list select networking opportunities. Even if you are not attending an event as a delegate, Members are encouraged to attend and network at any ISPE International Conferences. Industry contacts are the keys to finding that next great job. For more information on Career Events, visit http://www.ispe.org/careerevents.

Career Discussion Group

Career Discussions is a public Community of Practice Members-only forum for those facing career changes or transitions. Communicating with other Members who are going through, or who have gone through, similar experiences may offer you valuable insight on overcoming career challenges. To get involved, visit http://www.ispe.org/careerdiscussion.

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ISPE understands that there may be times when you are going through a job transition. When you are affected by this type of life change, you may qualify for ISPE's Membership Hardship Program to keep your membership active. This program also allows Members free access to networking events at international conferences, such as the Washington, D.C. Conference, Brussels Conference and the Annual Meeting. For additional information, Please contact Member Services Department at ask@ISPE.org.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

ISPE Milan Congress Report...

Continued from page 1.

It was emphasized that regulation is meaningless without good control of markets, which is often a problem in the less-regulated countries. Blood products are poorly regulated if at all. WHO hosts the Blood Products Regulators' Group in which members from well-regulated countries are using their influence to get others to improve performance.

Many new guidelines are being developed in collaboration with the WHO Prequalification Program. For example, given the large number of Clinical Research Organizations (CROs) being set up in emerging countries like India, a new guideline has been published on the preparation of a CRO Master File. There are also moves to bring major regulators from outside ICH (China, Russia, etc.) into the harmonized environment. Smaller agencies, like those in the sub-Saharan Africa nations are also being assessed in a move toward regulatory harmonization. Rägo applauded the cooperative projects between WHO and other regulatory authorities and pressed for still greater collaboration between agencies for the benefit of the patient.

Regulatory Update from ONDQA

Dr. Moheb Nasr from the FDA's Office of New Drugs Quality Assurance (ONDQA) began by recommending the ICH Implementation Working Group training workshop on ICH Q8, 9, and 10 in Tallinn in June and in both Washington and Tokyo in October. He told delegates the program "will be outstanding." (Later in the session, Morénas reminded delegates that these sessions are open to industry as well as regulators).

There followed an update on the increasing use of QbD in NDAs. During the pilot program, 11 QbD-containing applications were approved. There have since been 30 to 40 further applications received. This has introduced many challenging concepts to the CMC review process. In some cases, assessors are participating in inspections and plans are being developed to enhance collaborative efforts on the review of such applications with European regulatory authorities. Nasr emphasized that the FDA is taking QbD very seriously and is working hard to facilitate its implementation within industry.

Hot Topics from Office of Compliance

Richard Friedman from the FDA's Office of Compliance provided an update on strengthening enforcement against serious cGMP non-compliance. He told delegates that Warning Letters are now being issued in as little as five days.

He then spoke of the Quality System which he described as both one of the six elements of a QMS, and also its nucleus. He also highlighted Materials systems as an area of concern. He stressed management responsibility, extending outside the local facility. At a time when offshoring counts for increasing proportions of manufacture, procurement considerations may deflect attention from quality. Adherence to supplier contracts is an integral component of any quality program.

Accompanying Friedman was Dr. Steve Wolfgang, who participated in the panel Q&A session.

Question and Answer Session

How will regulatory agencies support increasing requirements for inspection, including overseas?

[Morénas] It will be managed by co-operation schemes (MRAs, ACAAs, PIC/S). Sharing inspection reports facilitates risk-based planning of inspection programs. EU/US/TGA/EDQM are collaborating on inspection planning for API manufacturers. EMA and FDA are planning joint inspections for centralized applications. Collaboration between EU and US is also being established for GCP and pharmacovigilance. **Where appropriate, industry should request joint inspections, and do it as early as possible in the planning process.**

How to differentiate acceptable from non-acceptable risk? Will companies from developing industries automatically be high risk?

[Friedman] All new applications will be inspected since an unknown risk is intolerable; after that, they will slot into the system at the appropriate point. At some point, manufacturers need to start disqualifying high-risk suppliers. QRM should not be used to qualify companies with lower quality.

[Nasr] Any high risk needs to have an associated control strategy.

Elaboration on update of guidelines on genotoxic impurities and residual metal catalysts? Will they be added to the ICH Q3 list of topics for harmonization?

[Riet-Nales] The guidelines are not changing; there is an inconsistency in interpretation which needs further clarification. This will allow consistency both for industry and regulators.

[Morénas] Two new Expert Working Groups will be set up within ICH to harmonize guidelines for genotoxic impurities and residual metal catalysts. Work will commence at the next meeting in June.

More information on inspection of traditional medicines?

[Gråberg] A traditional medicine can be derived from plant, mineral, or animal source.

[Riet-Nales] Homeopathic products are harder to regulate.

[Rägo] There are a number of problems, especially safety issues, in some parts of the world. There are also emotional, cultural issues (e.g., in China) where traditional medicines

Continued on page 5.

ISPE International Board Member Appointed VP with GMS

Dr. Guy Wingate, Site Quality Director, Barnard Castle, has been appointed Vice President and Compliance Officer for Global Manufacturing and Supply (GMS). In this role, he will provide strategic oversight, direction, and guidance for the compliance and risk management program within GMS, based at GSK House. Wingate will report to David Pulman, President, GMS, and Simon Bicknell, SVP, Company Secretary and Corporate Compliance Officer. He succeeds Keith Lamb, who moved to R&D last year.

Wingate has led the Quality team at Barnard Castle since 2006, with particular focus on strengthening the Quality Strategic Intent for the site. He also served as a member of the Barnard Castle Site Leadership Team. Wingate joined GSK in 1999, and has been responsible for the QMS, QA technology strategy, product quality information management and knowledge management within the above-site Quality team in GMS.

"Please join David and me in welcoming Guy to his new role," said Bicknell. "His experience in GMS in roles focused on quality and risk governance make him well qualified to join the Compliance team." PE

Philippines Affiliate Welcomes Best

The Philippines Affiliate welcomed Bob Best, President/CEO of ISPE, when he visited Manila, Philippines on 15 March. This was Best's first visit to the country since the Affiliate was established in 2008.

During the half-day meeting, Best first met with the Affiliate's Board of Directors to understand and discuss the Board's plans for the affiliate and the pharmaceutical community in the Philippines. Nancy Tacandong, RPh, MPA, Acting Director, Philippines Food and Drug Administration (FDA) was also present during the meeting. Best presented an overview of ISPE, its membership benefits, and how ISPE may contribute its Body of Knowledge to growing the professional skills of the local community – manufacturers, suppliers, and regulators. PE

The Philippines Affiliate Executive Committee with Bob Best, President and CEO, ISPE. Seated, from left: Shemaine Castillo, Treasurer; Rhoda Manaloto, Training Committee, Chief, Regulation Division II, FDA; Bob Best, President and CEO, ISPE; Nancy Tacandong, R Ph, MPA, Acting Director, FDA; Pura G. Averilla, President. Standing from left: Gilbert A. Vargas, Membership and Communications Committee; Eufe Tantia, Ethics Committee; Joyce Cirunay, Regulatory Committee, Chief, Product Services Division, FDA; Rosario B. Barangan, Vice-President; Frances Evelyn P. Robles, Committee on Community of Practice; Remedios A. Rivera, Auditor; George Salvilla, Training Committee.

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have a strong reputation. It is difficult to regulate these products, but progress is being made.

Should regulators do more to encourage industry professionals to participate in Continuous Professional Development (CPD)?

[Morénas] In France, CPD is a legal requirement for physicians and pharmacists. It should certainly be promoted. Attendance at events such as the ISPE Congress underlines company interest in training their professionals. Regulators should also undergo CPD. There should be joint (industry/regulator) training to allow each to learn from the other.

[Friedman] It is very important that companies encourage their people to undergo CPD.

[Riet-Nales] It is important that such training is repeated regularly both for new and established employees.

Will the materials from the ICH IWG workshops be in the public domain, where and when?

[Morénas] The materials will be available via the ICH website after the final event in October. Any modifications made during the three workshops will be incorporated into the final version.

QWP states of QbD: don't claim it, do it. The EC and PIC/S draft SMF document states: note any process using QbD. How should these two approaches be reconciled?

[Morénas] The SMF relates to the manufacturing site, not specific Marketing Authorizations. At EU and PIC/S level, there is a need to mention QbD since otherwise the inspectors may not be aware of it.

[Riet-Nales] The QWP statement is based on the fact that process knowledge is necessary in order to make good products.

[Wolfgang] It should be obvious to inspectors if a company is using a QbD approach as opposed to finished product testing.

Can there be a better approach to pack insert changes and harmonization within Europe?

[Riet-Nales] This topic comes under the remit of Notice to Applicants, not assessors or inspectors.

Should process validation be considered as an ICH topic for harmonization? If not, shouldn't the FDA be identified as an interested party during revision of the EMA guideline?

[Morénas] There is certainly a need for a more harmonized approach to GMP/GDP although it is more a case of looking for equivalence, rather than harmonizing guidelines. ICH only covers three regions. We already have a global guidance document in WHO GMP. A key factor is harmonization of approach between the EU and US FDA. However, achieving a single GMP guideline is unlikely.

[Friedman] The FDA general principles of validation are contained in a high level document and there is no disagreement between FDA and major regulatory authorities such as EU member states or TGA. Differences only appear with more detailed topics and more work is required on this by the regulators.

Is the EUDRA database open to public access?

[Gråberg] Some parts will be open to all; others will have restricted access.

Is there any interest from China, India, and Taiwan to join PIC/S?

[Gråberg] There has been no PIC/S application from India or China to date. Taiwan's application ran out of time and the process needs to be recommenced.

[Morénas] PIC/S is an apolitical organization. Discussions take place successfully between DRAs from politically-sensitive countries such as China and Taiwan.

What are the timelines for the current revision of chapters and annexes of EU GMP? Will all draft revisions be issued for industry comment?

[Morénas] There are two key stages to the process: white paper/concept and revision of the actual document. At both these stages, draft documents are issued for industry consultation over a period of three to six months. No GMP document is issued without this consultation. For example, Annex 6 is at draft concept stage; the first draft of the revised Annex 7 is expected in May; Annex 14 is in final draft.

How can the ACAA between Turkey and the EU be facilitated?

[Morénas] This is a political, not a technical issue. There is no difficulty at the level of DRA.

Many of the documents requested in the GMP Part 3 guideline on Site Master Files (SMFs) are already accessible via the EUDRA database. Why the duplication?

[Gråberg] The philosophy behind Part 3 is not new. It was

Concludes on page 6.

India Affiliate's Young Pharmaceutical Professionals' Educational Program a Success

The ISPE India Affiliate held a free workshop on 27 February, entitled Pharmaceutical Young Professional on Documentation, as part of their Young Pharmaceutical Professionals' Educational Program (YPEP).

The one-day workshop attracted 120 participants from the pharmaceutical industry in India. It provided them with an excellent opportunity for participants to learn about all aspects of documentation. Ajit Singh, Chairman, India Affiliate, opened the session by welcoming all the speakers and participants. He was followed by Gopal Nair, Vice-Chairman, India Affiliate, who gave a brief background on quality management systems and documentation.

The following speakers took the stage to speak about various topics on documentation: Satish Rajkondawar, freelance Technical Consultant; Kapil Bhargava, former Assistant Drug Controller, Central Drugs Standard Control Organisation, West Zone, India; Ananth Prabhu, Pharmaceutical Consultant; Prasad Kanitkar, Director, Plant Operations, Pfizer Limited; and Sangeeta Sardesai, Manager, Quality and Compliance, Sanofi-Aventis; J.Sipahimalani, Director, CMA Laboratories, Vijay Kshirsagar, Executive Vice-President, Unichem Laboratories and R. Raghunandanan, Pharmaceutical Consultant, Director, ISPE India. The workshop ended with a question and answer session. The presentations are available on the ISPE Good Control Laboratory Practices Community of Practice (GCLP COP) site.

A good turnout of 120 attendees at the ISPE India Affiliate's free workshop: Pharmaceutical Young Professional on Documentation, part of the Affiliate's YPEP program.

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originally proposed to lodge ICH Q9 in Part 3, before it transitioned to Annex 20. Part 3 is intended for advisory (for information) documents, not mandatory requirements. It is easier to leave all aspects of the PIC/S document in place, even if this implies duplication, rather than rewrite.

Since risk assessments are subjective activities, carried out differently by different companies, how do the regulators evaluate the outcomes of the process?

[Friedman] The regulator checks to see if the approach taken is reasonable. If the conclusion is that there is a problem, comment would be made. However, it would be the specific issue that would be cited, not the risk assessment process.

[Nasr] There is no established policy and each individual case is subject to review. The key point is not the number of pages, but the rationale and justification of decisions.

Comment on purpose and proposed use of the PIC/S document PS/INF 1/2010 on QRM?

[Morénas] This is a philosophical suggestion, not an overall recipe for QRM. It will not be a mandated approach. It provides science and good sense and can be used as the basis for training workshops. ISPE has entered discussions with representatives of PIC/S on the development of a Quality Risk Management training tool for the benefit of both industry and regulatory agencies.

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Europe

Denmark

The Danish Medicines Agency's Questions and Answers on Variations after 1 January 2010[1]

The Danish Medicines Agency published 13 questions and answers regarding variation after 1 January 2010.

European Union

Work Program 2010 of the European Medicines Agency (19 March 2010)2

The following areas of focus are identified for this year's work program: conducting the Agency's core activities to the highest quality standards, amid the increasing volume and complexity of activities; successfully implementing tasks vested by new legislation; strengthening the European medicines network; continuing to improve the safety-monitoring of medicines; cooperating with international partners and contributing to international activities; fostering communication, provision of information and increasing transparency; and contributing to an environment that stimulates innovation and improved availability of medicines.

Finland

New Decree on Fimea's Activities Subject to a Charge 1 February 2010 to 31 December 2011[3]

The Monetary Committee of the Finnish Government has approved a new decree on the activities of Fimea that are subject to a charge. The payment decree includes price changes, new prices and new activities subject to a charge. The payment decree also differentiates between payments for pharmaceuticals intended for humans and those intended for animals.

Germany

BfArM Moves to Nearly Paperless Submissions[4]

Starting 31 March 2010, the Federal Institute for Drugs and Medical Devices will accept nearly paperless electronic-only submissions for new applications for authorization or registration of medicinal product as well as for post authorization procedures (e.g. variations, renewals, PSURs) of those medicinal products which have already been submitted under these new rules after 31 March 2010.

Iceland

The English name of Lyfjastofnun has been changed to Icelandic Medicines Agency[5]

The English name of Lyfjastofnun, which previously was the Icelandic Medicines Control Agency (IMCA) has been changed to Icelandic Medicines Agency (IMA). Consequently the URL of the Agency´s website and e-mail addresses of the Agency and all staff will change, i.e. www.ima.is, ima@ima.is and forename.surname@ima.is. Bookmarks and address books should be amended accordingly. It should be noted that earlier URL and email addresses will be valid until the end of 2010.

Sweden

Sweden's MPA to Lead European Collaboration on Drug Effectiveness[6]

During 2010, Medical Products Agency will be in head of a collaborative effort to improve the dissemination of knowledge about medicinal effects in clinical everyday life in Europe. The MPA will support networks within the EU as a successful working in the field of "drug effectiveness".

The MPA has now taken on the task to form an Oversight Committee that will select a limited number of pilot projects in Europe, which are producing data of value for the assessment of drug effectiveness.

The focus will be on the improvement of generation, collecting and sharing of data that can be useful for the care of patients as well as for research, regulatory and industry purposes. The knowledge gained from the pilot projects will be disseminated from the Oversight Committee by the internet and meetings.

New Routines in Sweden for Handling Recalls of Medicinal Products[7]

On 15 March 2010, new routines for handling recalls will be introduced in Sweden for all products regulated by the legislation (Medicinal Products Act (SFS 1992:859) of the medicinal products: conventional medicinal products, herbal medicinal products, traditional herbal medicinal products, natural remedies, certain medicinal products for external use, homeopathic medicinal products and standardized extemporaneous preparations (stock manufacturing).

A procedure for dealing with complaints and recalls called "Röda Pärmen" was introduced in 1980 and was developed within The Swedish Association of the Pharmaceutical Industry (LIF) in co-operation with the Medical Products Agency, and Apoteket AB (the former National Corporation of Swedish Pharmacies). A working team, ARI-group, was established. In 2003 this procedure was uppgraded from a paper version to a web version, "The Red Web". Until now the procedure is based on different recall forms depending on the extent or distribution of the concerned product or batch and the degree of seriousness of the recall.

Today the regulation of the Swedish market for medicinal products is changed and the monopoly of the National Corporation of Swedish Pharmacies is changed to new clusters of pharmacies and private pharmacies. In addition some OTC-products will be available from the retail trade. Thus it seemed logical to leave the old procedure and to develop a new simple procedure, the same for the whole market.

Now it will be only one recall form for all recalls from both retail trade and pharmacies and the health care. The recall form will reach the destination by a cascade effect. The recall will be sent from the pharmaceutical company (the Manufacturing Authorization Holder (MAH) and/or its local representative) to the wholesalers/distributors and further to the pharmacies or retail traders and finally to the health care and in serious and urgent cases to the patients/customers depending on the distribution of the product to recall. The distribution of the recall will preferably be by e-mail. Every part in this chain is responsible to distribute the information to the next part.

Till now a color system has been used but in this new procedure only

classification of the state of seriousness according to the Rapid Alert System will be used. This Rapid Alert System is the same for the entire EU and will be found at the web site of EMA. www.ema.europa.eu/Inspections/GMPCompproc, Procedure for Handling Rapid Alerts and Recalls Arising from Quality Defects.

The classification is in three stages where Class I is the most serious one and Class III is the less serious one. When a recall is to be initiated by the pharmaceutical company the following has to be done:

- Trace the distribution of the concerned batches/products to the wholesaler/distributor who received the product at the first level.
- Stop further distribution from this wholesaler/distributor.
- Immediately call the Medical Products Agency, Drug Inspectorate and make a proposal for a recall form.

From 15 March 2010, no more recalls will be handled according to the old system but from this date only the new system will be used.

United Kingdom

New Area of the MHRA Web Site for the Pharmaceutical Industry Launched[8]

MHRA launched a new section of their Web site specifically for the pharmaceutical industry. The section, which has been developed following feedback from users, provides targeted links to information throughout the site, as well as content relevant to industry. The section includes links to the latest news for industry, information about fees, legislation and guidance, and specific contact details for industry.

Asia/Pacific

Australia

TGA Releases Guidance Documents[9]

The TGA's Office of Manufacturing Quality has released two guidance documents to assist complementary medicines manufacturers to comply with the requirements of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products 2009.

These guidance documents were developed through the Complementary Medicines Technical Working Group which brings together regulators and industry representation to develop additional guidance materials. They are: *The Technical Guidance on the Interpretation of Manufacturing Standards for Process Validation for Listed Complementary Medicines*, which aims to provide guidance on processes and operations to effectively produce medicinal products according to specifications and quality attributes; and *The Technical Guidance on the Interpretation of Manufacturing Standards for Supplier Qualification*, which aims to provide the process of assessing the reliability and qualification of the supplier to consistently provide material of acceptable quality.

The guidance documents are available at http://www.tga.gov.au/manuf/twg.htm#cmguides.

TGA Publishes Therapeutic Goods (Multi-Site Manufacturing Licenses) Guidelines of 2010[10]

These guidelines cover circumstances in which a license may cover two or more manufacturing sites.

China

SFDA Standardizes the Naming of Cosmetics[11]

In order to meet the needs of administrative licensing for cosmetics, intensify supervision on the naming of cosmetics, ensure scientific and standardized naming of cosmetics, and protect the rights and interests of consumers, the State Food and Drug Administration (SFDA) formulated and issued Requirements on Naming of Cosmetics and Guide to the Naming of Cosmetics in accordance with Regulations Concerning the Hygiene Supervision Over Cosmetics and the rules for the implementation of the Regulations.

To better implement Requirements on Naming of Cosmetics and Guide to the Naming of Cosmetics, SFDA released Notice on Issues Concerning Implementation of Requirements on Naming of Cosmetics and Guide to the Naming of Cosmetics.

Compilation of 2010 Chinese Pharmacopoeia held in Beijing[12]

On 1 February 2010, The Third General Assembly of the Ninth Chinese Pharmacopoeia Commission and the Summing-up Conference on Compilation of Chinese Pharmacopoeia (2010 Edition) was held in Beijing. Shao Mingli, Deputy Minister of Health, Commissioner of SFDA, and Chairman of the ninth Chinese Pharmacopoeia Commission Efforts, announced future efforts to establish and improve legal system for drug standards; continuously enhance the overall level of national drug standards; continue to optimize drug standard management mechanism; actively plan for the compilation of the 2015 edition of Chinese Pharmacopoeia; accelerate building a high-quality and comprehensive professional team.

2010 Chinese Pharmacopoeia, the 9th edition of the Pharmacopoeia of the People's Republic of China, contains a total of 4567 monographs, including 1386 new admissions; in Volume I, it contains 2165 monographs of Chinese materia medica and prepared slices of Chinese crude drugs, vegetable oil/fats and extractives, traditional Chinese patent medicines and simple preparations, with 1019 new admissions, and 634 revisions; Volume II includes 2271 monographs of chemical drugs, antibiotics, biochemical preparations, radiopharmaceuticals and excipients, with 330 new admissions and 1500 revisions; Volume III contains 131 monographs of biological products, with 37 new admissions and 94 revisions; and there are 47 new admissions and 154 revisions in the Appendix.

SFDA Strengthens Supervision to Oxygen Supplies for Medicine[13]

State Food and Drug Administration issued a notice requiring the local food and drug regulatory departments to firmly strengthen the supervision to the use of medical oxygen generators with molecular sieves, strictly control the approval of medical oxygen generator with molecular sieve and crack down the illegal behavior of using industrial oxygen (or compressed gas) as medical oxygen.

Global Regulatory News

North/South America

USA

FDA Expands Commitment to Patients with Rare Diseases[14]

Expanding on its commitment to facilitate the development and approval of safe and effective drugs for Americans with rare diseases, FDA announced the newly-created position of Associate Director for Rare Diseases in the Agency's Center for Drug Evaluation and Research's Office of New Drugs. Dr. Anne Pariser, has been selected as the new Acting Associate Director for Rare Diseases and the Agency will move quickly to fill the position on a permanent basis. Dr. Pariser will report to the Director of the Office of New Drugs.

The Associate Director for Rare Diseases will serve as CDER's focal point to the rare disease drug development community and assist stakeholders and developers of drug and biologic products in navigating the complex regulatory requirements for bringing safe and effective treatments to patients in need.

The Associate Director for Rare Diseases will also coordinate an initiative to develop CDER policies and procedures for the review and approval of treatments for rare diseases and to ensure appropriate training of CDER staff. An important focus of this new initiative will be to ensure collaboration among scientists and clinicians throughout CDER, to promote the adoption of new scientific and regulatory innovations that will help facilitate timely development and approval of new treatments for patients with rare diseases.

The OND Associate Director for Rare Diseases will focus on the development and regulatory review of drugs for rare diseases and will complement the work of FDA's Office of Orphan Products Development (OOPD). OOPD will continue to exercise its authority under the Orphan Drug Act to recognize products that demonstrate promise for treating rare diseases with the designation of "orphan" status and offer financial incentives to manufacturers to develop and gain approval for these products. OOPD also administers the Orphan Product Grants Program. The OND Associate Director for Rare Diseases will work closely with staff in OOPD in applying the regulatory requirements for approval of drugs for rare diseases.

USP

USP and India Strengthen Partnership[15]

As part of its mission to help ensure the quality, safety, and benefit of medicines and foods worldwide, the U.S. Pharmacopeial Convention (USP) held a groundbreaking ceremony for a planned expansion of its USP-India Private Limited facility in Hyderabad. USP-India Private Ltd., located in Hyderabad's ICICI Knowledge Park, was USP's first laboratory and office facility outside the United States. Existing strong relationships between USP and Indian government, academic and industry representatives have been enhanced by USP's direct presence since the facility opened in 2005. USP-India Private Ltd. now employs 40 people, all Indian nationals, and provides in-country service to its many stakeholders in India and elsewhere in South Asia.

International

FDA and EMA Agree to Accept a Single Orphan Drug Designation Annual Report[16]

FDA and the EMA announce that they have agreed to accept the submission of a single annual report from sponsors of orphan products (drugs and biologics) designated for both the US and the EU. Both regulatory agencies require the submission of an annual report for orphan designated products. These reports provide information on the status of the development of orphan medical products, including a review and status of ongoing clinical studies, a description of the investigation plan for the coming year, any anticipated or current problems in the process, difficulties in testing, and any potential changes that may impact the product's designation as an orphan product. This one annual report submission to both regulatory agencies is voluntary, and will only be applicable to sponsors who have obtained an orphan designation status for their product both in the EU and US. Starting on 28 February 2010, sponsors may send the single Orphan Drug Designation Annual Report to each Agency.

PIC/S

Memorandum of Understanding between PIC/S and Russia / Roszdravnadzor[17]

A Memorandum of Understanding (MoU) was signed in Moscow on 12 February 2010 between the PIC/S Chairman and the Head of the Federal Service on Surveillance in Healthcare and Social Development in the Russian Federation (Roszdravnadzor). The MoU aims at facilitating Roszdravnadzor's application for PIC/S membership (and accession to PIC/S). The MoU will only come into effect after its formal approval by the PIC/S Committee at its next meeting in Geneva on 19 to 20 May.

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