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# Lean Maintenance – A Risk-Based Approach

by Gerard Clarke, Gerry Mulryan, and Padraig Liggan

**This article presents an industry case study of the application of lean maintenance methodologies carried out at the Pfizer Biotech, Grange Castle Campus, Dublin.**

## Introduction

Lean maintenance is defined as delivery of maintenance services to customers with as little waste as possible. This promotes achievement of a desirable maintenance outcome with fewest inputs possible.[1] Inputs include: labor, spare parts, tools, energy, capital, and management effort. The gains are improved plant reliability (availability) and improved repeatability of process (less variation).

The fundamental principles of lean are more frequently being applied to pharmaceutical asset maintenance. One of the most important aspects of lean maintenance is developing an understanding of the maintenance processes and applying a risk-based approach. This involves evaluating whether each element of maintenance practice used adds value to the product and benefits the customer. Lean maintenance drives efficiency and effectiveness and this ensures improved quality, equipment performance, and profitability.

Waste maintenance practices are associated with the following activities:

1. Unproductive work – efficiently doing work that does not increase equipment reliability.
2. Delays in motion – waiting for production equipment to be available to carry out preventive maintenance.
3. Unnecessary motion – unneeded travel, trips to parts stores, and looking for tools required to do a job.
4. Poor management of inventory – not having an adequate amount of the right parts at the right time.
5. Rework – having to repeat tasks due to poor workmanship.
6. Under-utilization of resources – maximizing resources available and harnessing the skill sets of the maintenance teams.
7. Ineffective data management – collecting data that is of no use or failure to collect data which is important.
8. Misapplication of machinery – incorrect operation or deliberate operational strategies leading to maintenance work being done when it needn't be.

It is important to note that lean maintenance is not simply an approach to do more with less resources.[2] It enables pharmaceutical companies to focus resources where they are needed to meet production and regulatory requirements.

## Why Choose Lean Maintenance?

Pharmaceutical companies recognize the need for change because of evolving regulatory requirements and competition in the marketplace. For example:

- The costs of product to market are rising and there are increased pressures from patent limitations and generic brands.
- Regulatory environment is continually evolving.
- The market is becoming increasingly competitive.
- Equipment is becoming increasingly specialized and automated. There are advantages to large scale production activities.

A lean maintenance approach mitigates against these factors and provides:

1. Consistent and coordinated approach across the plant.
2. Performance targets set through a combination of top-down aspirations and bottom-up site diagnostic assessments.
3. Accelerated timelines for implementation, because fast and efficient turnaround increases flexibility and profitability.

| Technique | Explanation |
|---|---|
| Value Mapping | A method of charting the transactions and processes required to satisfy a customer order with the aim of revealing opportunities for improvement in customer retention, productivity, lead time reduction, waste elimination, and reduced cash flow. |
| Criticality Analysis | An assessment of equipment and processes to identify the most critical areas, those with potential for human error and whose which impact the quality of service as a means of agreeing priorities and reducing risks. |
| Hidden Lost Cost Model | Defining the value of stabilizing/optimizing technology effectiveness and the cross functional agenda and techniques needed to deliver it. |
| Best Practice Development | A process for reviewing/refining existing working practices and standards to reduce accidents, breakdowns, contamination, and quality defect levels (ABCD). |
| Lean Maintenance Standards | Seven policy areas/standards which directly impact on reliability of equipment and the effectiveness of the maintenance department (preventive maintenance, servicing, technical information, planning, recording, budgetary control, spares management). |
| Focused Improvement | Tools to systematically address technology issues ad problem prevention techniques to secure breakthrough levels of equipment performance. |

Table A. Lean maintenance tools and techniques.

4. Increased quality and compliance through simpler systems/processes and focus on critical equipment and systems.
5. Better customer service by focusing on production needs.
7. Increased motivation of employees through true empowerment.
8. Linking individual contribution to overall business performance.
9. Faster response times to changing business and regulatory requirements.
10. Lower operation costs through rationalization of inventories along with less space and management requirements.

## Preparing for Lean Maintenance

A lean maintenance program begins with an assessment of the strengths and weaknesses of current maintenance practices (the current state). A major consideration is the demands placed on equipment by production needs and schedule. The reliability needs of the future state are identified and an action plan developed on how to achieve this. From there, improvement priorities are developed into a maintenance improvement project plan. This plan contains an analysis of equipment criticality to the process, optimization of maintenance, education of stakeholders, implementation of best practices and best fit of tasks to the appropriate functional area. Table A lists samples of the main lean tools used to support this activity.

The overall aim of the lean maintenance project at Grange Castle was to reduce non-value added maintenance activity and reduce cost 30% (stretch target). This was done by using lean maintenance principles and techniques. The key objectives identified after assessing the 'current state' were:

a. Optimizing the maintenance schedule by reducing preventive maintenance work by 30%.
b. Simplifying equipment maintenance documentation by reducing duplication in practices and complexity.
c. Implementing current best maintenance practices.

Table B summarizes what was identified as the current state at Grange Castle and the Lean Project Objectives. The objectives on the right were targeted during this phase of the project.

This article focuses on a number of these key areas targeted during the lean maintenance effort. The most effective way of engaging the workforce in the lean improvement agenda is to follow a growth strategy. In this project, one of the key drivers for lean was related to freeing up resources to support expansion projects in other areas of the plant. This added the flexibility to support a growing organization.

## Implementing the Lean Maintenance Process

### *Determination of Maintenance Strategy and Frequency for Process Equipment*

A formal engineering guideline document was written which enabled stakeholders, including the quality and engineering functions to review the current PM program with a view to agreeing the following:

- Identification and removal of non-value added maintenance tasks.
- A scientific and risk-based approach to revising and determining planned maintenance frequencies.
- Removal of duplication of tasks where these tasks were performed as part of procedural processes by Production Operations.

The approach was accepted across the site because it provided a

| Lean Maintenance Highpoints | |
|---|---|
| **Current Lean Maintenance Practices** | **Targeted Lean Maintenance Practices** |
| • Planning and Scheduling<br>• RCM<br>• Multi-Skilled Maintenance Technicians<br>• Work Order system<br>• CMMS System (SAP)<br>• Parts and Materials on a Just-in-Time Basis<br>• Maintenance Engineering and Reliability Engineering Group | • Proactive Maintenance<br>• Total Productive Maintenance (TPM)<br>• Empowered (self-directed) Action Teams<br>• SMED<br>• 6S – A method of workplace organization and visual controls<br>• Kaisen Improvement Events<br>• Autonomous Maintenance<br>• Distributed Lean Maintenance/ MRO Stores |

Table B. Lean maintenance methodologies and current practices.

| | Weighting | 5 | 4 | 3 | 2 | 1 | |
|---|---|---|---|---|---|---|---|
| **Factor** | **Criterion** | **Catastrophic/ High Impact** | **Critical/ Will Impact** | **Marginal/Could Impact/Med Cost** | **Low Impact/ Low Cost** | **No Impact/ No Cost** | **Weight** |
| Quality | Contamination/ Batch Loss/ Production Impact | Multi-batch loss or production stopped for several weeks | Single batch loss but production able to continue once problem resolved | Could impact a batch if failure occurs during certain process step | Will have an impact if a second system were to fail | Product will not be contaminated, loss or production stopped | X50 |
| Safety | Degree of injury to a person or impact to the environment | Cause death or lose IPA license; shutdown for several weeks | Serious injury to people or could impact IPA license | Injury to people or recoverable impact to environment | Second system would have to fail before people or the environment are at risk | Failure will cause no injury to people or impact the environment | X70 |
| Maintainability | Inspection/Repair/ Maintenance downtime to be determined by area requirements | Downtime high with no standby system in place | Downtime low but no standby system in place | Downtime high with standby system in place | System seldom down and standby system in place | System is never down and low cost to repair and no production impact | X30 |
| Impact to Schedule | How manufacturing schedule is | Loss of multiple batches | Loss of batch (3 days) | Medium impact to schedule (a day and possibly recoverable) | Low impact to schedule (hours and recoverable) | No schedule impact | X40 |
| Cost (at time of production) | Cost of the reinstallation/ recovery and lost production days | Cost > 10M | Cost > 2M | Cost 100K to 500K | Cost 10K to 100K | No recovery cost | X20 |
| Idle Time | Turnaround Time | Idle Time 0 to 1 day | Idle Time 1 to 2 Days | Idle Time 2 to 3 Days | Idle Time 3 to 4 Days | Idle Time > 4+ Days | X35 |

Table C. Criticality assessment matrix grid.

clear and transparent decision making process that was based on a scientific and risk-based approach to support business and compliance needs. The approach provides a framework and mechanism for continuous improvement.

The document also assisted the stakeholders in determining, understanding, and communicating the rationale behind amending maintenance task lists and frequencies and was based on well recognized maintenance engineering standards and guidelines. The approach followed the following rationale and sequence:

**Equipment Criticality** – qualitative weighted compilation of the effect of equipment failure on product quality, personnel safety, and equipment downtime, cost and facility idle time. It provides the means for quantifying how important an equipment or system function is relative to the production process. Table C shows the criticality assessment grid used, it includes all the key areas considered and weightings that were applied.

**Strategy Decision Logic Tree** – this process uses equipment criticality and a review of maintenance task lists to determine what the best maintenance strategy is for the equipment and its application in the process. This tool can be used to assess each maintenance task and decide its eventual outcome. Figure 1 below shows the flow diagram used.

Using the decision logic diagram (Figure 1) ensured that all process equipment was subjected to the same standard approach. It allowed the maintenance engineer/maintenance technician to select from one of the following maintenance strategies.

- TBM – time base preventive maintenance – replacement irrespective of condition
- CBM – condition based or predictive maintenance
- DOM – design out maintenance (re-design where possible)
- OTF – operate to failure

**Frequency Decision Process** – a process for determining time-based maintenance intervals based on historical data (mean times between failure) and probability of equipment failure. Figure 2 shows the flow diagram used.

### *Production Operator Autonomous Maintenance*

When a number of maintenance tasks were brought through the decision trees, it was noticed that many activities were already or would more logically be completed by production operators. It was agreed with the operations function to move tasks that routinely already had been carried out as part of standard operating procedures or could have been more easily executed by operations technicians. These tasks were classified as 'autonomous maintenance tasks' and were incorporated into operations daily routine as part of the business process or as part of standard operating procedures depending on the criticality of the task and equipment. Examples are cleaning and lubrication of equipment as well as visual checks for leaks. The term 'autonomous maintenance' is also widely referred to in industry as 'operator care.'

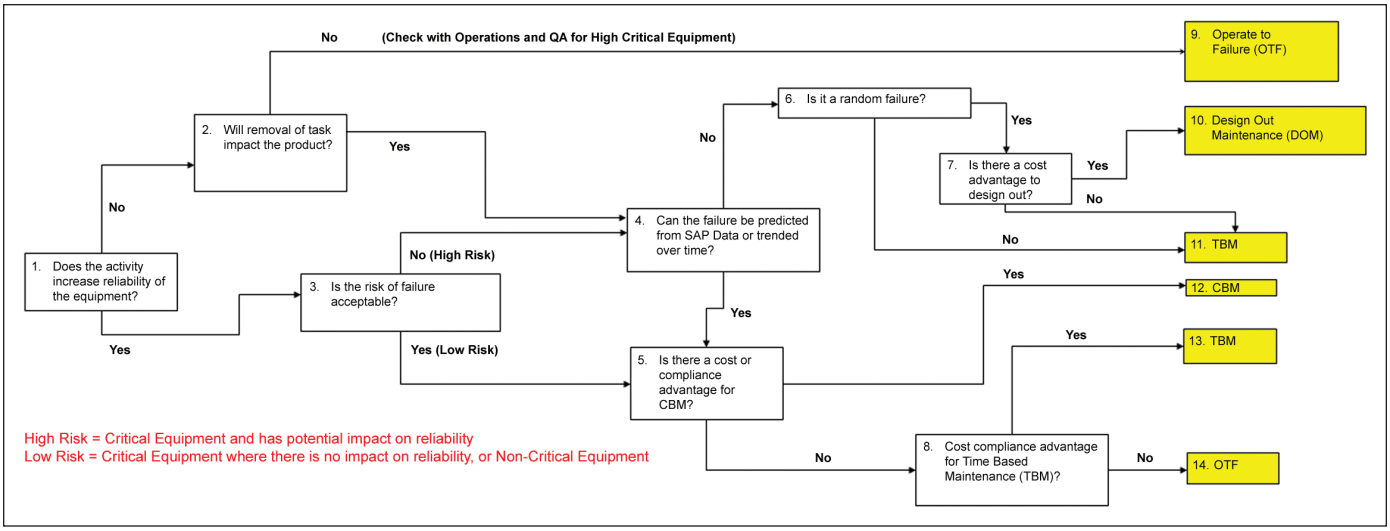


Figure 1. Strategic decision logic tree.

The operator accepts and shares responsibility (with maintenance engineering) for the performance and health of their equipment. The advantages are ownership and understanding of equipment and better use of existing resources.

As part of the business process, a check sheet was developed for each of the production areas called a "housekeeping list," which requested the operator to carry out basic checks prior to production. This list is similar to aircraft 'pre-flight checks' checks carried out by the pilot. Operators have a well-defined check list and a set of simple maintenance activities that can be performed during their shifts. Abnormalities are recorded and communicated to maintenance engineering. This ensures that appropriate resources and expertise are deployed where they are required to meet business needs and also allows prioritization of maintenance work.

As part of this process, basic checks such as look, touch, feel, and smell are explained to the operators by the equipment system matter expert. Operators are now more involved in root cause analysis programs to improve this understanding of failure modes and their elimination and improvements in the maintenance program.

### *Single Minute Exchange of Die (SMED)*

Single Minute Exchange of Die (SMED) is widely used in lean production. SMED was originally used in industry to streamline and reduce the time taken to change a die. Since then, it has been applied more generally to changing of tools, materials, and machines between repetitive jobs. The goal of

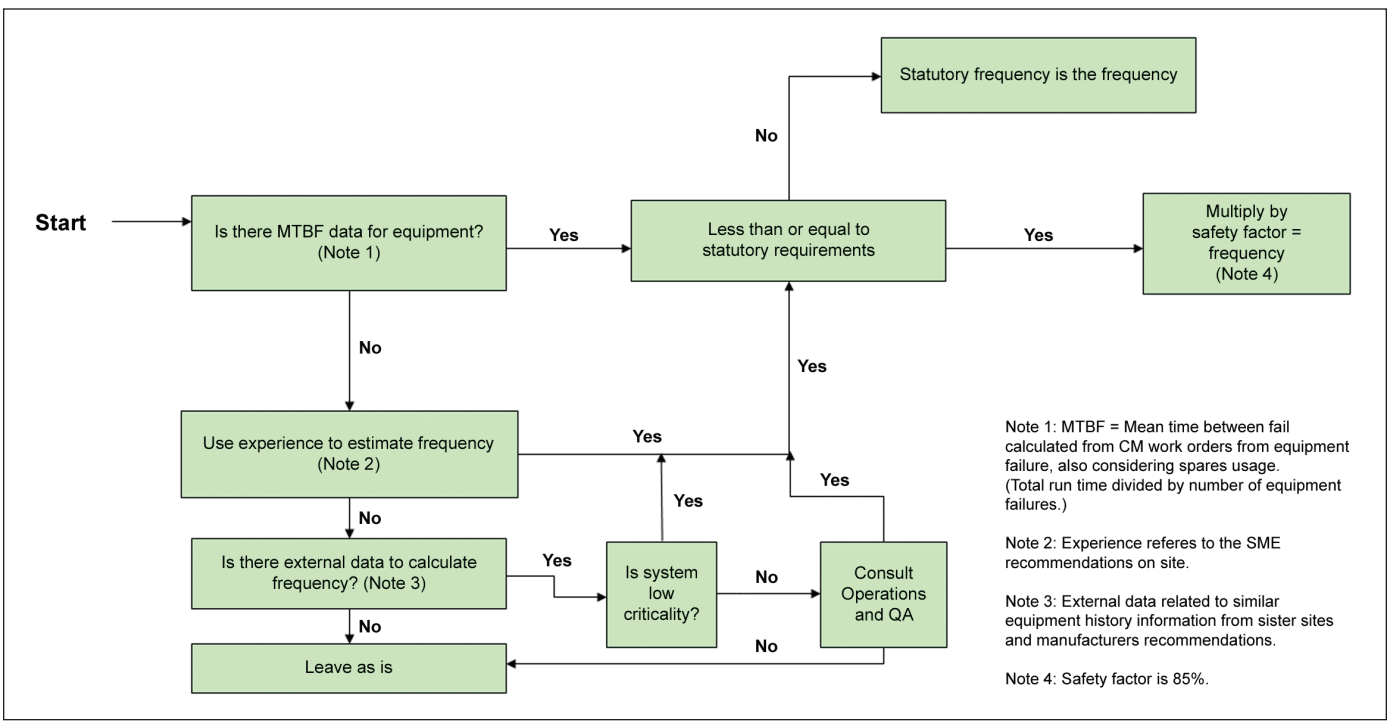


Figure 2. Frequency decision tree.

Figure 3.Process diaphragm valves.

SMED is to safely achieve the shortest possible change-over time. This is achieved by thoroughly examining all aspects of the task and removing wasteful activity.

During the lean maintenance project at Pfizer Biotech, Grange Castle, the SMED process was used effectively to minimize downtimes for scheduled Elastomer Change Outs (ECO) on bioreactors. In a biotechnology facility, diaphragm valves (Figure 3) are widely used, the sizes vary from ½ inch up to 4 inch diaphragm valves with the diaphragm material used being either Ethylene Polymer Diene Monomer (EPDM) or Polytetrafluroethylene (PTFE). The diaphragm valves targeted for the SMED process are located on bioreactors; they are subject to high process use and regular steaming cycles which require the internal diaphragms to be changed out on an annual basis.

The change management program known as Elastomer Change Out (ECO) involves a complete disassembly of the valves and diaphragms. This involves the following:

- isolation of system (for safety reasons)
- disassembly of the valve housing and building valve with new diaphragm

The SMED process was used to divide the steps involved in elastomer change out maintenance into three types, as follows:

- Waste – steps which did not add any value
- Internal – steps which could only be done within the maintenance task
- External – steps that could be performed prior to the maintenance task

Video was used to record a number of elastomer change-out activities. This helped categorize the steps required to complete the task. ECO's performed on different shifts were recorded by different people. This showed a huge variation in the steps taken and in the time needed to complete each step. By analyzing the steps into waste, internal, and external the maintenance technicians evaluated their own performance and identified inefficiencies. The outcome of the SMED process was a reduction in bioreactor downtime by 25% through greater preparation and simplification of the tasks.

## Results of the Lean Maintenance Program

Figure 4 summarizes the initial results of the lean maintenance program. The project yielded a 22% reduction in maintenance man-hours required. The following original goals and objectives were achieved:

1. Non-value activity was removed from the preventative maintenance program.
2. A risk-based structured process was created to remove non-value added maintenance activities and to allow for consideration for the addition of future maintenance tasks.
3. Technician resources were released to support other projects or focus resources where they were most needed.
4. Autonomous maintenance was introduced.
5. Using the main lean principle Single Minute Exchange of Die (SMED) the time to complete elastomer change outs in production areas was significantly reduced.
5. Lean maintenance projects are now ongoing as part of a continuous improvement program.

The reduction in planned maintenance activity has reduced the amount of corrective maintenance required significantly since its implementation 12 months ago. There has been no negative impact on equipment performance, availability, and reliability.

## Summary and Conclusions

Before lean maintenance was introduced, the company suffered from "iatrogenic failures," i.e., failures caused by over maintaining or not focusing on critical activities. Symptoms of this included:

1. **Over production:** the maintenance technicians completed tasks more times than needed.

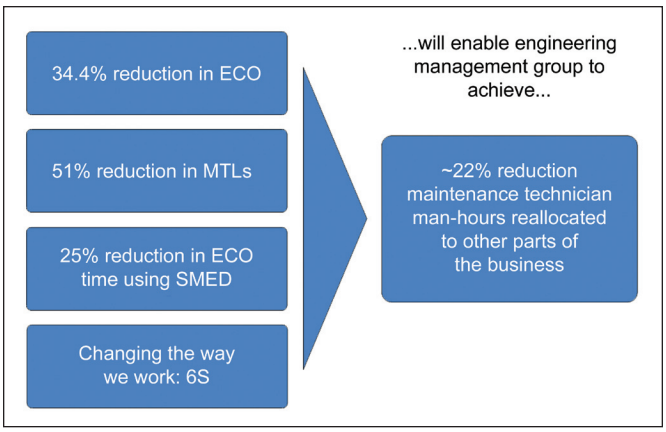


Figure 4. Overall results from the lean maintenance transformation.

2. **Inventory:** the store room had to unnecessarily stock more spare parts. For example elastomers, gaskets.
3. **Motion:** the maintenance technicians misused their time by moving back and forth looking for tools.
4. **Waiting:** excessive production downtime required for maintenance.
5. **Transportation:** additional preparation for conducting the maintenance was done which was not needed.
6. **Over processing:** extra maintenance work orders were created that needed to be audited and verified by maintenance technicians, supervisors, and final approvers.
7. **Not right the first time:** provided the opportunity for "not getting it right" more times than was needed.
8. **Under-utilization of people:** technician doing non value added work.

These areas were targeted as part of this project and significant progress has been made in eliminating or significantly reducing the associated impact. The process of improvement is continuous and has resulted in a positive cultural change around maintenance and its objectives.

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**This article presents a novel approach to designing pharmaceutical powder processing equipment.**

# A Powder Handling Methodology in Pharmaceutical Manufacturing

by John D. Sherwood and Dr. Eddie McGee

## Introduction

Powder handling during pharmaceutical manufacturing has always been a challenge for process engineers. Get it right and the process runs smoothly, get it wrong and production capacity can be significantly reduced, and in the worst case, disrupted completely. Powder flow problems can lead to inconsistencies between pharmaceutical batches. Powder segregation during processing and storage may result in poor flow, a buildup of hopper residue, and problems with stock handling and filling and packing operations.

Flow problems are usually avoided by testing the powder to identify its flow characteristics. However, with the increasing cost of drug development and need to reduce time-to-market, competition for samples for powder testing prior to manufacturing is fierce with clinical trials often taking a higher priority. As a result, what powder testing can be conducted has to be as meaningful as possible.

This article presents a new technical and collaborative approach to the design of pharmaceutical powder processing equipment that resolves flow problems with existing equipment, based on maximizing the interpretative approach to powder testing data.

## Pharmaceutical Powders

At some stage during its manufacture, every pharmaceutical compound is in the powder state. Typically, there are three types of powder encountered in pharmaceuticals production: 1. crudes – involving 'wet' chemistry during manufacture of the crude Active Pharmaceutical Ingredient (API), 2. pures – the purification and size reduction (milling) of the dry crude powder to produce the pure API for further processing, and 3. the bulked-up powder produced when the API is converted into the finished product, for example, tableting.

In general, processing dry powder is more difficult than liquid systems, due to the unpredictability of powder flow. A predictable powder flow is important to ensure product quality. Depending upon whether the compound is unmilled, milled, or granules, the variability of powder size has a significant impact on its processability. Furthermore, variation in powder flow can be observed even between batches of the same compound, due to changes in temperature, humidity, powder particle size, and storage. Other factors affecting powder flow can be the process equipment design. For example, the toxicity of the powder may require high levels of containment and special handling equipment. In some cases, the size of the equipment can affect powder flow – generally, the smaller the equipment the greater the powder's propensity to 'bridge' across a hopper/vessel valve exit preventing flow.

## Understanding Powder Flow

The pharmaceutical industry is not alone in experiencing flow problems. In the chemical and food industries, flow problems occur all too frequently, leading to capacity shortfall, production interruptions, and quality and safety issues. Research by Merrow and the Rand Corporation[1] has shown that solids handling problems arise not from the chemistry of processes, but from the tendency of bulk solids to cause blockages, stick, and flow erratically. Powder flow property testing is essential to avoiding these flow problems and critical to achieving the correct design of hopper slope, shape and outlet size, and consistent flow.

The powder handling equipment supplier is aiming for the optimum powder flow condition of mass flow, where all the powder moves during discharge. In a mass flow hopper, the first material in is the first material out – all material moves toward the outlet during discharge. This

Figure 1. Stable rathole in hopper.

brings a number of benefits. It reduces powder segregation and facilitates efficient flow toward the vessel outlet. Achieving mass or near mass flow is dependent upon designing the storage and plant hopper in harmony with the powder flow behavior. For example, a high friction material requires a hopper with a flow channel sufficiently large to destabilize any 'rathole' that may form, and a wall angle steep enough to self-clear if they are to function well.

Ratholes occur when the central region of the hopper immediately above the outlet empties well, but there is a stagnant zone close to the hopper wall, forming a stable rathole - *Figure 1*. This zone is where the bulk of the hopper storage capacity is tied up and so only a small proportion of the hopper's contents are readily retrievable – material in the central flow channel discharges before material in the peripheral regions can flow out. In addition, the hopper's capacity for new material is significantly reduced.

For example, titanium dioxide powder has very high friction and is prone to ratholing, even against polished stainless steel. It is rarely practical to make a conical hopper wall sufficiently steep to generate mass flow to avoid bridging or ratholing. A better alternative to the cone is one where the material only has to converge in one plane (to flow through a cone material has to reduce simultaneously in both x and y planes), for example, a steep walled "V" shaped hopper with a long outlet slot.

Avoiding hopper flow problems relies on ensuring the hopper geometry and interface between the hopper and feeder design are correct. The flow pattern in the hopper can be affected by:

- stresses acting on the structure and within the bulk material
- the order in which the contents are discharged: mass flow – the first material in is the first material out; or non mass flow where the central flow channel discharges before material in the peripheral regions can flow out leaving material trapped in a dead zone in the hopper.
- the size of the opening that is needed to ensure that the discharge can be reliably achieved and complete.

The advantages of mass flow are that it avoids segregation of the powder, gives 'live' storage with no 'dead' zones, and makes flow through smaller outlets possible.

## Characterization of Pharmaceutical Powders

The process engineer has a number of models they can call on to assist in understanding powder flow behavior. For instance, the Jenike 'flow no flow' gravity flow theory says flow will take place provided the solid's yield strength, developed as a result of the actions of consolidating pressures during storage, is insufficient to support an obstruction to flow.[2]

Creating the conditions for Jenike mass flow is possible through a knowledge of the powder's flow characteristics and the ability to interpret these results when designing hoppers, screw feeders, and conveyors within the plant's space and processing constraints.

Tests such as those which time how long it takes for powder to flow from a funnel or measure the energy used to stir a paddle in a powder bed are sometimes used because they are relatively easy to carry out, but unfortunately these are difficult to relate to actual plant conditions. Moreover, descriptions, such as 'free flowing' or 'poor flowing' are subjective and only reflect a specific condition in particular circumstances. A powder can appear to be 'free flowing' when it is loosely poured, but may settle to a very firm and stable condition when de-aerated or subject to compacting stresses. A dry, crystalline product will usually flow through a relatively small orifice, but have extreme reluctance to deform if damp or 'caked' due to the presence of tiny crystal bridges binding particles together.

## Predicting Powder Flow

Predicting the behavior of pharmaceutical powders has led some to look for a single number to use as a guide to flow. A variety of techniques are available that use the single number approach to quantify 'flowability,' for example, angle of repose, Hausner ratio, Carr Flowability Index, and the more scientific Jenike Flow Function. However, these approaches are fraught with problems.

For example, there is no obvious reason why a powder that has high friction also should have a strong cohesive tendency or vice versa. So while powder flow may worsen when both these features are present, they are not necessarily correlated. Indeed, it is the complexity of multiple attributes of a bulk solid and their interaction with the many facets of equipment design, such as hopper and reactor vessels, screw feeders and conveyors, that defines the actual bulk flow behavior in practice.

The most important physical characteristics of a bulk solid with regard to flow are:

- Wall friction, how the product slides on a contact surface, because powders often have to slide down the face of a mixer blade, chute, or hopper wall.
- Shear or failure strength, the resistance of the bulk solid to deformation, because it is a measure of the powder's resistance to flow.

Both properties are influenced by the 'condition' or 'compaction' of the bulk so bulk density is important as well, as quantifying the bulk 'state' and the driving force for gravity flow.

Consequently wall friction, shear strength, and bulk density are three properties of bulk solids that need to be measured to ensure mass flow in a hopper and avoid arching at the outlet. Wall friction can be measured using a linear strain device and a force gauge; strength by using a vertical shear cell tester.

## Improved Powder Flow Predictability

Perhaps a better approach to predicting flow behavior is to take the measured characteristics of wall friction ($\phi_w$) shear strength ($\tau_s$), bulk density ($\rho_b$), and add three further factors: hopper or reactor wall angle ($\beta_c$), outlet size ($D_{crit}$), and Hausner ratio (*H.R.*) Equipment parameters like wall slope and outlet size affect the resulting flow so it is important to integrate the equipment features into the analysis. The Hausner ratio is the ratio of tapped to loose bulk density. The greater the ratio the more sensitive the powder is to vibration and hence flowability worsens.

Using these factors, we can produce a 'spider' diagram comprising a series of three concentric circles divided by axes for each of the characteristics. These axes intersect with the smallest diameter circle where that particular characteristic describes 'easy flow' with subsequent bigger diameter circles defining 'modest' and 'poor flow.' Two idealized situations can then be presented in Figure 2 for an 'easy flow' material and a 'poor flow' one with the in-filled part of the 'web' detailing the particular characterization attributes.

The spider powder flow predictability model recognizes the different facets that affect flow, it represents each of the aspects separately rather than the aggregate process used by Carr. The spider diagram is good at showing visually that, for example, a low friction material which has a high shear strength may well be indicative of a worse flow outcome than an average friction material and average shear strength product – the Carr index would simply aggregate these two features to the same result.

The spider diagrams can be more than qualitative if the data from the tests on a large number of materials is used to define the 'easy,' 'modest,' and 'poor' flow circles.

Note that the bulk density axis is the reverse of the others because decreasing bulk density usually means poorer flow. For example, most milling operations lower bulk density and worsen flowability of powders when they are stored. Although in some cases the uniform particle size may lead, in fact, to a well defined packing with high bulk density.

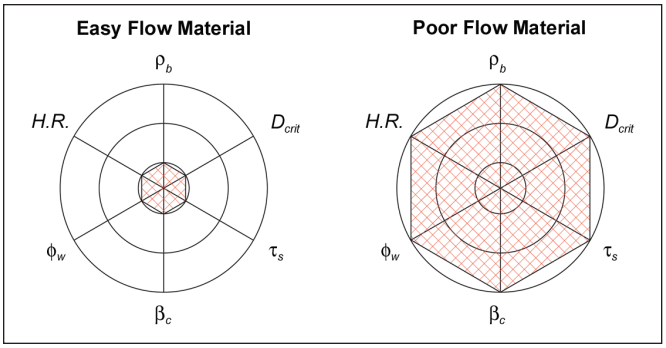


Figure 2. Idealized situations for an 'easy flow' material and a 'poor flow' material.

## Easy and Poor Flow Powders Examples

An 'easy flow' powder is a free flowing grade of lactose with wall friction angle of 17 degrees against stainless steel, shear strength 197 N/m$^2$ (4.11 lb/ft$^2$ ), Hausner ratio of 1.1, rathole outlet diameter 9 cm (3.54 inch), and requiring a 64 degree wall angle for mass flow in a conical hopper. With a bulk density 867 kg/m$^3$ (54.13 lb/ft$^3$), this particular example has a small spike on the density axis of the spider diagram indicating a slight deviation from the ideal flow material.

A 'poor flow' material is fine milled icing sugar with wall friction of 30.5 degrees against stainless steel, bulk density of 540 kg/m$^3$ (33.71 lb/ft$^3$), shear strength 2144 N/m$^2$ (44.78 lb/ft$^2$), Hausner ratio of 1.49, rathole diameter 149 cm (58.66 inch), and requiring a wall angle for mass flow in a conical hopper of 80 degrees to the horizontal.

## Applying the Spider Powder Flow Predictability Model

Figure 3 shows the resultant spider flow diagram for an intermediate powder; all aspects for flow are good except the shear strength and outlet size. To overcome potential flow

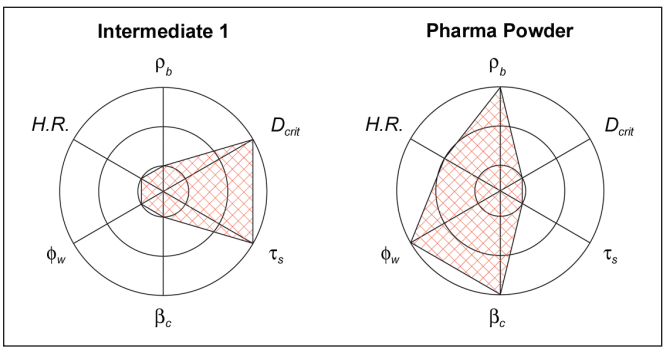


Figure 3. The resultant spider flow diagram for an intermediate powder.

| Circle | Wall friction (deg) | Bulk Density kg/m$^3$ (lb/ft$^3$) | Shear Strength N/m$^2$ (lb/ft$^2$) | Hausner Ratio | Outlet Size cm (inch) | Mass Flow Wall Angle |
|---|---|---|---|---|---|---|
| Easy flow | < 20 | 1200 (74.9) | 300 (6.27) | 1.1 | 15 (6) | 65 |
| Average | 25 | 800 (50) | 1000 (20.89) | 1.25 | 50 (19.7) | 73 |
| Poor flow | > 30 | 400 (25) | 2000 (41.77) | 1.5 | 100 (39.4) | 80 |

Table A. Parameters suggested by the tests reported in McGee Thesis.[3]

Figure 4. Invertible IBC for intermediate.

problems for batch handling of this material, invertible IBC bins (Figure 4) were used with a larger outlet that upsets the consolidation of the material to ensure reliable flow to process. Alternatively, in a fixed hopper, an inverted cone type of insert could be used to reduce the shear strength by shielding the material in the crucial zone next to the outlet and creating a larger flow area in the annular gap between the wall and the insert.

The spider diagram for the API powder in Figure 3 indicates high wall fiction but low shear strength. Had this material been stored and transferred without thought to its flow characteristics difficulties, with chute work featuring insufficiently steep slope and sharp corners, flow problems would have occurred. The spider diagram in this case directs attention toward examining the effects of surface finish and using generous radiused corners as practical solutions to provide trouble free powder flow.

In summary, the spider diagram approach to integrating the three measured parameters: wall friction, shear strength, bulk density, and three calculated parameters: hopper wall angle, outlet size (shear strength/bulk density ratio), and Hausner Ratio, offers a more rounded and informative picture of flow characteristics.

The technique was developed for general flowability with bounds based on the data from the large number of tests conducted on a wide variety of powders, including many handled in the pharmaceutical industry. A development of the technique can be used for individual materials (e.g., different grades, batches, suppliers, seasonal variations, etc.) to set acceptable boundaries which could be modified by plant performance or indicate processing strategies for optimum performance. Refinement of this approach to include other factors, such as internal friction, lateral stress ratio along with increased definition in scale can only improve the engineer's ability to match plant performance/design to bulk solids characteristics for reliable handling.

## Case Study

A plant integration project has provided the opportunity to assess the 'spider' powder flow predictability model in practice.

A 'Pures' production plant contained screw feeder, rotary valves, and micronizer. Analysis of samples of the pure powder using the spider powder flow predictability model indicated that the feed screw rate of up to 50 kg/hr (110.2 lb/hr) to the micronizer could not be satisfied by gravity flow alone. The spider diagram for the premilled pharmaceutical powder is presented in Figure 5 – this indicates a powder with high bulk density and wall friction, and therefore, poor flow, potentially leading to bridging or formation of a rathole. An agitator would be required to promote flow into a narrow flow channel containing the small diameter feed screw needed to meet the low process feed rate. A twin bladed agitator with intermittent control was used to satisfactorily encourage flow into the feed screw.

Above the screw feeder, a supplementary hopper was added with substantial batch holding capacity. Again the design used the spider diagram powder characterization presented in Figure 5 as the design basis for the hopper. The result was a hopper with very steep walls and plane flow geometry. However, the height of the hopper design did not fit well with the plant's physical constraints. A revised approach was then

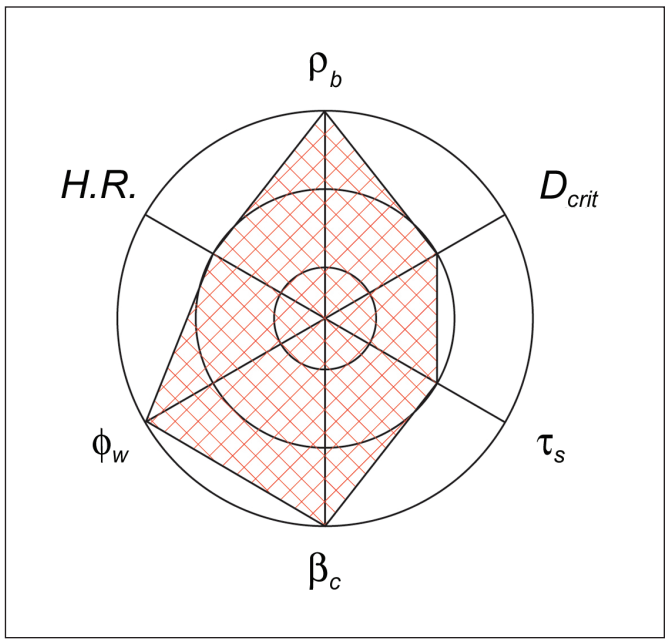


Figure 5. Pre-milled pharmaceutical powder spider diagram.

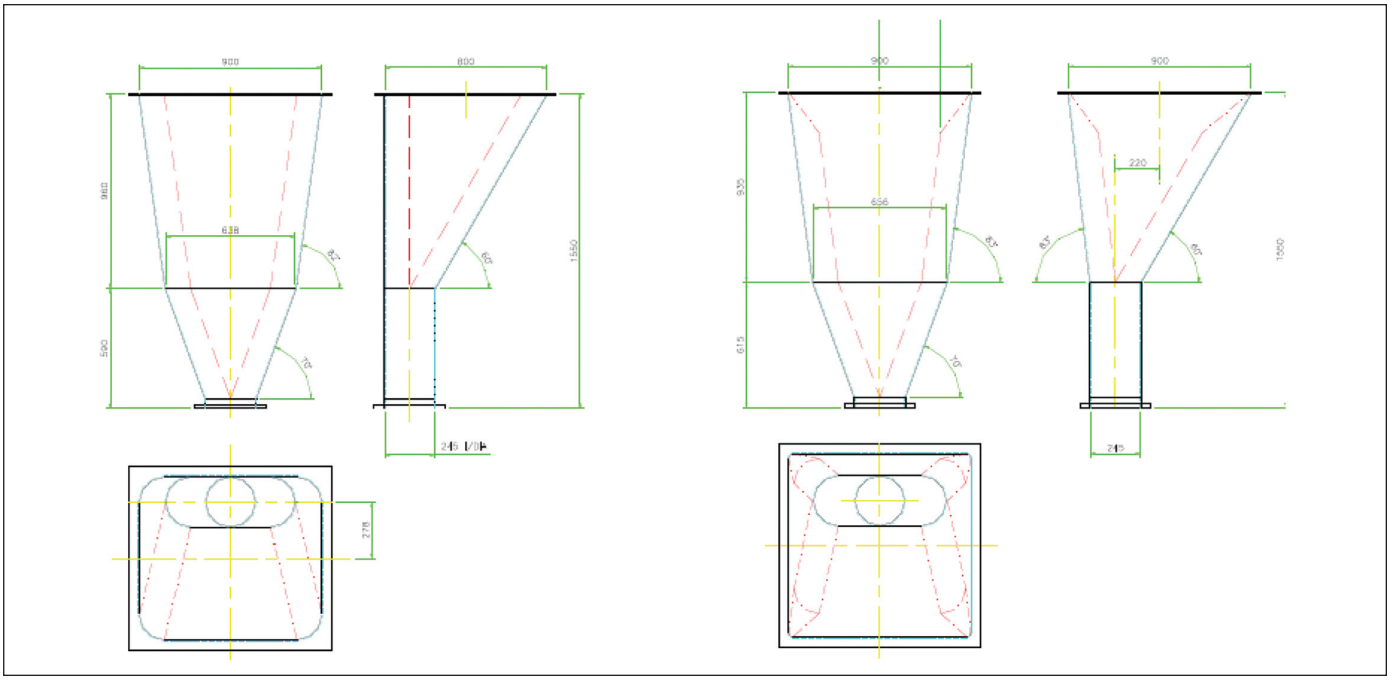

Figure 6. The 'ideal' hopper design (left) and the final hopper design (right).

produced which met the plant's constraints; this revised approach maintained the same geometry for the crucial lower section of the hopper, but modestly altered the upper section with only marginally less steep walls than was originally intended. Site performance feedback on the performance of the hopper has confirmed its ability to deliver reliable flow into the process.

## Conclusion

Given the competition for pharmaceutical powder samples with which to conduct powder tests, the process engineer needs to maximize the powder flow information they can extract from testing. Adopting a powder characterization technique based on appropriate tests, including particle size and particle shape, Hausner Ratio, friction angles, and shear strength, which can be translated into spider diagrams, give important practical insights into powder flow that can be used when designing process equipment.

It is important to exploit available powder characteristics information and develop a multiple attribute appreciation of powder flow. Spider diagrams are a useful tool for helping to appreciate all the aspects. The key factors for process engineers to consider when preparing plant for powder storage, handling, and processing include:

- Remember the importance of wall friction and strength in storing powders in hoppers.
- Use gravity flow whenever possible – it's free and can be relied upon.
- Exploit the flow benefits of good flow geometry, e.g., single plane convergence.

Remember the feeder/hopper interface to mixers, screw feeders, and conveyors can be a potential source of flow problems as powder moves from one environment to another. Matching the components of the powder handling system has to be done with care if the system is to work well.

Importantly draw on your own experience and that of your equipment supplier and systems integrator. This 'team' based approach needs to be used to satisfy the end user expectations properly, the equipment suppliers design criteria, and the critically important matching of all parts of equipment for reliable performance.

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**This article proposes an approach for qualification target selection and demonstrates how this can be applied to API manufacturing facilities.**

# Target Selection and Qualification – The Case of API Manufacturing Facilities

by Masatoshi Takemata, Mitsuyuki Nakajima, Toyohiko Takeda, Tomio Tsurugi, Kimihiro Imamura, Yoshifumi Hara, Norio Yanagisawa, and Naoki Matsumoto

## Introduction

Industry associations and regulatory bodies indicate that qualification should be restricted to facilities and equipment that have an impact on product quality. However, the literature[1] does not provide guidelines for identifying facilities or equipment required to be qualified. For the establishment of facilities and equipment for API manufacture, statutory regulations require qualification of those facilities and equipment to be the manufacturer's (i.e., user's) responsibility. In Japan, there are a number of different interpretations of the regulatory requirements based on individual perceptions and understandings. Thus, the targets covered by the requirements and the qualification methods vary in accordance with the users' interpretations, yielding redundant qualification of facilities and equipment. Therefore, an adequate systematic approach for selecting qualification targets and determining qualification methods is necessary.

ICH published Q7: *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* (ICH Q7) in November 2000.[1] Although it gives a definition of qualification, it does not explicitly define what must be qualified or how qualification should be performed.

ISPE published the *Baseline® Pharmaceutical Engineering Guide, Volume 5: Commissioning and Qualification (C&Q)*, a practical guide for qualification, in March 2001.[2] The Baseline Guide implies that qualification is required in addition to commissioning in accordance with Good Engineering Practice (GEP).

C&Q also asserts that a system impact assessment for facilities and equipment should be performed to classify the systems on the basis of their impacts on the quality of the product. The systems are classified into three groups: the direct impact systems, those that are critical to the quality of the product; the indirect impact systems, those that only indirectly affect it; and the no impact systems, those that have no impact on it. The components of the direct impact systems are then assessed for criticality and classified as critical components, which have a direct impact on the quality of the product, and noncritical components, which do not have such an impact. Qualification practices in addition to GEP should be applied exclusively to the critical components. Compliance with GEP only is sufficient for the noncritical components, the indirect impact systems, and the no impact systems.

The GMP Committee of the Japan Society of Pharmaceutical Machinery and Engineering (JSPME) has been studying a practical approach for selecting qualification targets and determining qualification methods since 2001. The committee published two case studies, one of a pan coating system in 2003,[3] and the other of blister filling/packaging systems and pillow packaging systems in 2007.[4] In addition, based on these studies, the committee also published a case study of an API manufacturing facility in 2008 as part of its joint research with the GMP Committee of the Japan Bulk Pharmaceutical Manufacturers Association (JBPMA).[5]

Extracting some portion from the case study of the API manufacturing facility, this article proposes a new approach for target selection and execution in qualification practices and also indicates how this approach can be applied to the reactor systems used for the production of intermediates and APIs. The concepts and definitions of qualification activities (DQ, IQ, OQ, and PQ) in this article are based on ICH Q7.

*"In ordinary manufacturing processes, some of the important dynamic and static functions have a direct impact on the quality of the products, while the others have an indirect impact."*

## Fundamental Concepts of Target Selection and Execution

ICH Q7 states that before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. The authors propose the following fundamental concepts of qualification of the critical equipment and ancillary systems (hereinafter referred to as facilities and equipment) as to what should be qualified and how the actual qualification activities should be performed.

1. Facilities and equipment for API manufacture have various dynamic functions (work and action) which are performed by the static functions (structure, form, and material) of the facilities and equipment. Manufacturing API products using certain facilities and equipment entails utilizing such dynamic and static functions under prescribed conditions and within ranges of control to produce intended products. In ordinary manufacturing processes, some of the important dynamic and static functions have a direct impact on the quality of the products, while the others have an indirect impact.

   Here, product quality is linked to the ICH Q6A definition "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as identity, strength, and purity" as described in ICH Q9.[6]

2. Quality risk assessment for those dynamic and static functions, based on the principle of ICH Q9[6], should be performed to classify the functions on the basis of their risks to the quality of the product. The functions are classified into two groups: the direct functions, those that have a risk of a direct impact on the quality of the product; and the indirect functions, those that have a risk of an indirect impact, or no risk of an impact on it.

   Qualification practices in addition to GEP should be applied exclusively to the direct functions. Compliance with GEP only is sufficient for the indirect functions.

3. The suitability and appropriateness of the facilities and equipment, regardless of their impacts on product quality, are verified, documented, and approved with GEP from the standpoint of quality risk at each stage of the engineering activities from design through commissioning.

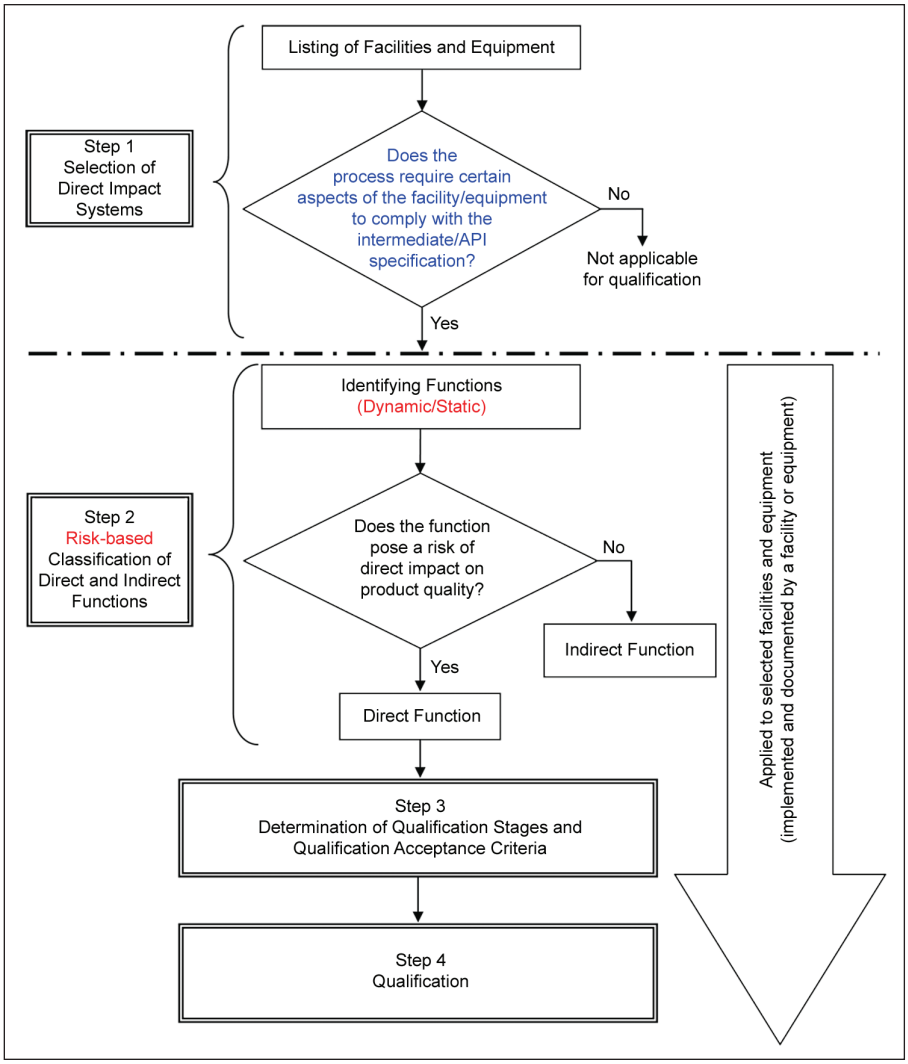


Figure 1. Work flowchart for qualification.

| Facilities and Equipment Unit | | Selection criterion satisfied? | | Reason | Remarks |
|---|---|---|---|---|---|
| Name | Area | Yes (direct impact system) | No | | |
| Reactor A System | Area shown in Figure 3 | X | | Reaction of key intermediates | |

Table A. Selection of direct impact systems.

***"Users do not necessarily need to duplicate the verification activities of the items that are already verified with the exception of the high level risk items mentioned later."***

Therefore, it is sufficient for users in some qualification activities to confirm that these items are properly verified in the engineering activities. Users do not necessarily need to duplicate the verification activities of the items that are already verified with the exception of the high level risk items mentioned later. However, engineering change control should be applied to ensure that any changes made post verification are adequately addressed in respect to the impact of previously performed and completed verification activities. Qualification can be performed after all the engineering activities are completed, or it can be performed at an appropriate stage of the engineering activities: Design Qualification (DQ) at the design stage, Installation Qualification (IQ) and Operational Qualification (OQ) at the construction and commissioning stages.

| | Class | Definition |
|---|---|---|
| Severity | 5 | Direct impact on product quality; reworking or destruction is required. |
| | 4 | Direct impact on product quality; reprocessing is required. |
| | 3 | No direct impact on product quality; recoverable in subsequent processes under standard manufacturing conditions even when deviations occur. |
| | 2 | No direct impact on product quality when manufacturing occurs under standard conditions. |
| | 1 | No impact on product quality |

Table B. Severity classification (impact on product quality).

| | | Probability | | |
|---|---|---|---|---|
| | | Low | Medium | High |
| Severity | 5 | B | A | A |
| | 4 | B | B | A |
| | 3 | D | C | C |
| | 2 | E | D | C |
| | 1 | E | E | D |

Table C. Level of risk.

| Level of Risk | Scope of Qualification | Extent of Qualification |
|---|---|---|
| A | Applicable for qualification (Direct function) | Direct verification by user<br>QA approval for documents |
| B | | Supplier-prepared document review by user is permitted.<br>QA approval for documents |
| C | Not applicable for qualification, verification under engineering practices (Indirect function) | Verification and documentation at engineering stage in accordance with risk level. Approval by head of related section. |
| D | | |
| E | | |

Table D. Scope and extent of qualification.

| Direct Functions | Qualification Stages | | | |
|---|---|---|---|---|
| | DQ | IQ | OQ | PQ |
| Static Direct Functions | → | → | | |
| Dynamic Direct Functions | → | → | → | |
| Among Dynamic Direct Functions, Direct Functions Related to Process Control | → | → | → | → |

Table E. Direct functions and qualification stages.

4. The direct functions are further classified as static direct functions (e.g., form, material, and surface finish) and dynamic direct functions (e.g. revolutions, temperature, and pressure). Dynamic direct functions can be further classified as either being subject to process control in the Standard Operating Procedure (SOP) or not.

5. If deemed critical, measurement and control devices and computerized control devices are targets of calibration and computerized system validation, and are not discussed in this article.

## A New Method for Qualification Practice

Based on the concepts discussed in the previous section, the following explains the required activities and documentation in each stage of qualification using the flowchart in Figure 1.

### *Step 1: Selection of Direct Impact Systems*

Among all the facilities and equipment, the facilities and equipment which have a direct impact on the quality (direct impact systems) are selected based on the selection criterion described below.

Selection criterion: Does the specified manufacturing process require

certain aspects of this facility/equipment to comply with the intermediate/API specification?

Examples of such manufacturing processes include the agitating processes of multiple ingredients, the phase conversion processes, the isolation processes (concentration or filtration), the temperature and pH sensitive processes, the processes that yield essential molecular components of the products, the intermediate processes in which principal chemical conversions take place, and the final purification processes. The selection is performed using a checklist as exemplified in Table A.

### *Step 2: Risk-Based Classification of Direct and Indirect Functions*

For the direct impact systems selected in Step 1, dynamic and static functions having the potential to affect product quality are identified and classified through quality risk assessment in accordance with ICH Q9.[6,7]

Specifically, the risk-based classification of direct and indirect functions is performed in conformity with the contents of Tables B, C, D, and F. The quality risk assessment consists of risk identification, risk analysis, and risk evaluation as shown in Table F.

At the stage of risk identification, the dynamic functions and static functions are identified and challenged by the question, "What might go wrong?"

At the stage of risk analysis, the consequences are identified and their severity is classified in accordance with Table B. Also, the degree of probability that the unwanted event will occur is determined.

At the stage of risk evaluation, a level of risk is determined in accordance with the criteria shown in Table C. Then, the direct functions and indirect functions are classified using the following classification criterion.

| Subsystem | Components | Quality Risk Assessment | | | | | | | | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Risk Identification | | Risk Analysis | | | Risk Evaluation | | | |
| | | Functions (Dynamic/Static) | What might go wrong? | What are the consequences? | Severity | Probability | Level of Risk | Direct Functions (Qualification Applied) | Indirect Functions (only GEP applied) | |
| Reactor System | Reactor Vessel A | Material (contacted process fluid) | Selected material not resistant to process fluid | Has impact on the purity of intermediate and product. Reworking or destruction is required when metal corroded material is mixed in process fluid. | 5 | L | B | X | | |
| | | Capacity | Capacity incorrectly defined | Has impact on productivity, but has no impact on quality of intermediate or of product. | 1 | L | E | | X | |
| | Agitator | Material (contacted process fluid) | Selected material not resistant to process fluid | Has impact on purity of intermediate and product. Reworking or destruction is required when metal corroded material is mixed in process fluid. | 5 | L | B | X | | |
| | | Agitability | Insufficient study of scale-up | Has impact on impurity profile because of insufficient solid-liquid dispersion for proper reaction. Reprocessing is required when agitation is inadequate. | 4 | M | B | X | | |
| | | Revolution Speed | | Individual functions have no direct impact on quality of intermediate and product as various combinations of these functions can achieve proper agitability. | 2 | M | D | | X | |
| | | Blade Shape | | | 2 | M | D | | X | |
| | | Blade Position | | | 2 | M | D | | X | |
| | | Motor Output | | | 2 | M | D | | X | |
| Temperature Control System | Heat Source Unit, Controller | Reactive liquid temperature (condensation) | Incorrect temperature control range specified | Cause reaction time delay or abnormal reaction. Has impact on impurity profile when abnormal reaction occurs due to improper temperature control. Reworking or destruction is required when temperature is inadequate. | 5 | M | A | X | | |
| Solvent Supply System | Piping | Material (contacted process fluid) | Selected material not resistant to process fluid | Has impact on purity of intermediate and product. Reworking or destruction is required when metal corroded material is mixed in process fluid. | 5 | L | B | X | | |
| | | Key: Probability L = Low, M = Medium, H = High | | | | | | | | |

Table F. Excerpt from example of risk-based classification of direct and indirect functions (Reactor A system).

***"Qualification activities (i.e., DQ, IQ, OQ, and PQ) determined in Step 3 are performed and documented in this step. The qualification activities are implemented and reported in accordance with the pre-approved protocol."***

Classification criterion: dynamic and static functions that can pose a risk of direct impact on the quality of the product (Severity Class 4 and 5 shown in Table B) are direct functions, while others (Severity Class 1, 2, and 3 shown in Table B) are indirect functions.

The scope and extent of qualification is determined by the level of risk as outlined in Table D.

### *Step 3: Determination of Qualification Stages and Qualification Acceptance Criteria*

In this step, required qualification stages are determined for each direct function obtained in Step 2 in accordance with the criteria shown in Table E.

The acceptance criteria for each direct function in determined qualification stages are also established at this step.

Table G is an excerpt from an example of the determination of qualification stages and qualification acceptance criteria. This table is useful for capturing the entire picture of qualification to facilitate its smooth execution as the table comprehensively shows direct functions (items and contents) as well as required qualification activities and acceptance criteria.

### *Step 4: Qualification*

Qualification activities (i.e., DQ, IQ, OQ, and PQ) determined in Step 3 are performed and documented in this step. The qualification activities are implemented and reported in accordance with the pre-approved protocol. Examples of data sheet formats (part of reports) are shown in Tables H to K.

## Outline of API Manufacturing Facilities

This section introduces the outline of API manufacturing facilities and equipment to be studied in applying the new method proposed in Section 2.

### *The Manufacturing Process of API Intermediate*

Compounds A and B, potassium carbonate, and dimethylformamide are agitated at 25°C for 24 hours. Then sodium borohydride, suspended in dimethylformamide, is dropped into the admixture in the presence of N2 gas, keeping the temperature of the reaction solution below 35°C. The admixture is agitated at 25°C for another 24 hours to obtain an intermediate (intermediate C). Figure 2 is a block flow diagram of the manufacturing process.

### *Components and Functions of the Reactor A System*

The major equipment and instruments

| Subsystem | Components | Direct Functions | | Qualification Stage and Qualification Acceptance Criteria | | | | | Remarks |
|---|---|---|---|---|---|---|---|---|---|
| | | Level of Risk | Items | Contents | DQ | IQ | OQ | PQ | |
| Reactor System | Reactor Vessel A | B | Material (contacted process fluid) | Resistance to corrosion in acid and alkali | Glass lining | Glass lining | - | - | |
| | | | | Chemical resistant gaskets | Fluororesin gasket | Fluororesin gasket | - | - | |
| | Agitator | B | Material (contacted process fluid) | Resistance to corrosion in acid and alkali | Glass lining | Glass lining | - | - | |
| | | | | Chemical resistant gaskets | Fluororesin gasket | Fluororesin gasket | - | - | |
| | | B | Agitatability | Solid-liquid dispersion (reagent in DMF) | Designed agitator (motor, sealed axis, blades, controller) operating conditions: (i) Revolution speed (XX ~ YY rpm) (ii) liquid level (min. xx ~ max. yy mm) | Installed agitator (motor, sealed axis, blades, controller) operating conditions: (i) Revolution speed (XX ~ YY rpm) (ii) liquid level (min. xx ~ max. yy mm) | Agitator operating conditions: (i) Revolution speed (XX ~ YY rpm) (ii) liquid level (min. xx ~ max. yy mm) | Potassium carbonate to be dispersed under agitation after charging 6 0L DMF and 11.8 kg potassium carbonate into the Reactor Vessel A | |
| Below Omitted | | | | | | | | | |

Table G. Excerpt from example of determination of qualification stages and qualification acceptance criteria (Reactor A system).

| Subsystem | Components | Direct Functions | | | DQ Acceptance Criteria | Verified Doc. Name/ No. (Note) | Result | Date | Sign | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Level of Risk | Items | Contents | | | | | | |
| Reactor System | Reactor Vessel A | B | Material (contacted process fluid) | Resistance to corrosion in acid and alkali | Glass lining | | OK/NG | | | |
| | | | | Chemical resistant gaskets | Fluororesin gasket | | OK/NG | | | |
| | Agitator | B | Material (contacted process fluid) | Resistance to corrosion in acid and alkali | Glass lining | | OK/NG | | | |
| | | | | Chemical resistant gaskets | Fluororesin gasket | | OK/NG | | | |
| | | B | Agitatability | Solid-liquid dispersion (reagent in DMF) | Designed agitator (motor, sealed axis, blades, controller) operating conditions: (i) Revolution speed (XX ~ YY rpm) (ii) liquid level (min. xx ~ max. yy mm) | | OK/NG | | | |
| Below Omitted | | | | | | | | | | |
| Note: Refer to attachment for verified documents. | | | | | | | | | | |

Table H. Excerpt from example of a DQ report (Reactor A system).

of the Reactor A system are illustrated in Figure 3. This system is composed of the following six subsystems:

1. Reactor system: performs the chemical reaction of compounds; composed of a Reactor Vessel A, an agitator, and an agitator controller.

2. Temperature control system: controls the temperature of the Reactor Vessel A; composed of a thermometer, a heat source unit, a pump, piping, and a controller.

3. Solvent supply system: supplies solvent to the Reactor Vessel A and the Dropping Vessel A; composed of piping.

4. Dropping system: drops sodium borohydride suspended in dimethylformamide into the Reactor Vessel A; composed of a Dropping Vessel A, a pump and piping.

5. N2 gas supply system: supplies N2 gas to the Reactor Vessel A and the Dropping Vessel A; composed of a flow meter, piping, and a filter, etc.

6. DCS: controls the manufacturing process; subject to computerized system validation.

| Subsystem | Components | Direct Functions | | | IQ Acceptance Criteria | Test Method | Verified Doc. Name/No. (Note 2) | Result | Date | Sign | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Level of Risk | Items | Contents | | | | | | | |
| Reactor System | Reactor Vessel A | B | Material (contacted process fluid) | Resistance to corrosion in acid and alkali | Glass lining | Visual | | OK/NG | | | |
| | | | | Chemical resistant gaskets | Fluororesin gasket | Visual | | OK/NG | | | |
| | Agitator | B | Material (contacted process fluid) | Resistance to corrosion in acid and alkali | Glass lining | Visual | | OK/NG | | | |
| | | | | Chemical resistant gaskets | Fluororesin gasket | Visual | | OK/NG | | | |
| | | A | Agitatability | Solid-liquid dispersion (reagent in DMF) | Installed agitator (motor, sealed axis, blades, controller) operating conditions: (i) Revolution speed (XX ~ YY rpm) (ii) liquid level (min. xx ~ max. yy mm) | Verify with designed documents checked/ verified in DQ (Note 1) | | OK/NG | | | |
| Below Omitted | | | | | | | | | | | |

Note 1: If drawings and specifications are revised after DQ completion, re-DQ must be done for the drawings and specifications prior to IQ start. Change control is required in the case of any change.
Note 2: Refer to attachment for verified documents.

Table I. Excerpt from example of an IQ report (Reactor A system).

| Subsystem | Components | Direct Functions | | | OQ Acceptance Criteria | Test Method | Verified Doc. Name/No. (Note 2) | Result | Date | Sign | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Level of Risk | Items | Contents | | | | | | | |
| Reactor System | Agitator | B | Agitatability | Solid-liquid dispersion (reagent in DMF) | Agitator operating conditions: (i) Revolution speed (XX ~ YY rpm) (ii) liquid level (min. xx ~ max. yy mm) | Water operation | | OK/NG | | | |
| Temperature Control System | Heat Source Unit, Controller | A | Reactive liquid temperature (condensation) | Mixture of Compounds A and B, potassium carbonate and DMF to be kept at 25 ±5°C for 24 hours | Temperature control system operating conditions: (i) temperature (XX ~ YY °C) (ii) liquid level (min. xx ~ max. yy mm) | Water operation (Note 1) | | OK/NG | | | |
| | | A | Reactive liquid temperature (reduction) | Reactive liquid to be kept at 25 ±5°C for 24 hours after charging DMF suspension liquid of sodium borohydride | | | | | | | |
| Below Omitted | | | | | | | | | | | |

Note 1: The temperature range that cannot be verified by water operation is verified in PQ.
Note 2: Refer to attachment for verified documents.

Table J. Excerpt from example of an OQ report (Reactor A system).

## A Case Study of the New Qualification Method

This section describes a case study of the new qualification method applied to the Reactor A system. The description follows the steps shown in Figure 1 except for Step 1 where direct impact systems are selected, referring to Table A.

### *Step 2: Risk-Based Classification of Direct and Indirect Functions*

Table F shows how the components in each subsystem shown in Figure 2 and the direct and indirect functions are classified through the quality risk assessment described in Section 2-2.

### *Step 3: Determination of Qualification Stages and Qualification Acceptance Criteria*

Table G is a list of qualification stages and qualification acceptance criteria for the direct functions selected in Step 2.

### *Step 4: Qualification*

Since the requirements of good documentation practice (version control, etc.) for qualification protocols and reports are widely known throughout the pharmaceutical industry, this article focuses on the content and structure of the documents. The following text describes the content and should be read in parallel with Tables A, B, C, and D, where the Tables provide the structure.

#### *DQ*

The DQ protocol describes 1) subsystems, 2) components, 3) direct functions (level of risk, items, and contents), and 4) the DQ acceptance criteria. The DQ report includes the description of the documents checked or verified, the results, etc., as well as 1) to 4) of the DQ protocol. Table H is an excerpt from an example of a DQ report. (It also includes the requirements of the DQ protocol.)

#### *IQ*

The IQ protocol describes 1) to 3) of the DQ protocol, the IQ acceptance criteria, and the test method. The IQ

report includes the description of the documents checked or verified, the results, etc., in addition to all the items in the IQ protocol. Table I is an excerpt from an example of an IQ report. (It also includes the requirements of the IQ protocol.)

### *OQ*

Targets in the OQ are only the dynamic direct functions. The OQ protocol describes the relevant items among 1) to 3) of the DQ protocol. It also should describe the OQ acceptance criteria and the test methods. The OQ report should include the description of the documents checked or verified, the results, etc., in addition to all the items in the OQ protocol. Table J is an excerpt from an example of an OQ report. (It also includes the requirements of the OQ protocol.)

### *PQ*

Targets in the PQ, which is always performed at the user's site, are restricted to the dynamic direct functions that are subject to process control. The PQ protocol should describe the relevant items among 1) to 3) of the DQ protocol. It also should describe the PQ acceptance criteria and the test method. The PQ report should include the description of the documents checked or verified, the results, etc., in addition to all the items in the PQ protocol. Table K is an excerpt from an example of a PQ report. (It also includes the requirements of the PQ protocol.)

## Conclusion

The authors propose a new approach for the target selection and execution of qualification practices by quality risk assessment based on the principles of ICH Q9.[6] This new approach is explained for the Reactor A system used in the production of an intermediate, for example. An outline is provided as follows.

Facilities and equipment for API manufacture have various dynamic functions (work and action) which are performed by the static functions (structure, form, and material) of the facilities and equipment. It is necessary to execute such dynamic and static functions under prescribed conditions and within ranges of control to produce the intended products. However, only some of the dynamic and static functions in the critical processes have a direct impact on the quality of the product, while other dynamic and static functions have indirect impact, and others exist in non critical processes.

Quality risk assessment for those dynamic and static functions, based on the principle of ICH Q9,[6] should be performed to classify the functions on the basis of their risks to the quality of the product. Functions are classified into two groups: direct functions, those that have a risk of a direct impact on the quality of the product; and indirect functions, those that have a risk of an indirect impact on or no risk of impact on it.

Qualification practices in addition to GEP should be applied exclusively to the direct functions. Compliance with GEP only is sufficient for the indirect functions.

Qualification execution consists of the following steps:

| Subsystem | Components | Direct Functions | | | PQ Acceptance Criteria | Test Method | Verified Doc. Name/No. (Note) | Result | Date | Sign | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Level of Risk | Items | Contents | | | | | | | |
| Reactor System | Agitator | B | Agitatability | Solid-liquid dispersion (reagent in DMF) | Potassium carbonate to be dispersed under agitation after charging 60 L DMF and 11.8 kg potassium carbonate into the Reactor Vessel A | Visual | | OK/NG | | | |
| Temperature Control System | Heat Source Unit, Controller | A | Reactive liquid temperature (condensation) | Mixture of Compounds A and B, potassium carbonate and DMF to be kept at 25±5°C for 24 hours | Temperature to be controlled at 25±5°C for hours after charging the specified amounts of compounds A and B, potassium carbonate and DFM according to the procedure | Record by temperature recorder | | OK/NG | | | |
| | | A | Reactive liquid temperature (reduction) | Reactive liquid to be kept at 25 ±5°C for 24 hours after charging DMF suspension liquid of sodium borohydride | Maximum temperature to be below 35°C during dropping and kept at 25±5°C for 24 hours after dropping under the conditions of specified amount of charge volume of sodium borohydride/DMF | Use thermometer and stopwatch | | OK/NG | | | |
| Below Omitted | | | | | | | | | | | |
| Note: Refer to attachment for verified documents. | | | | | | | | | | | |

Table K. Excerpt from example of a PQ report (Reactor A system).

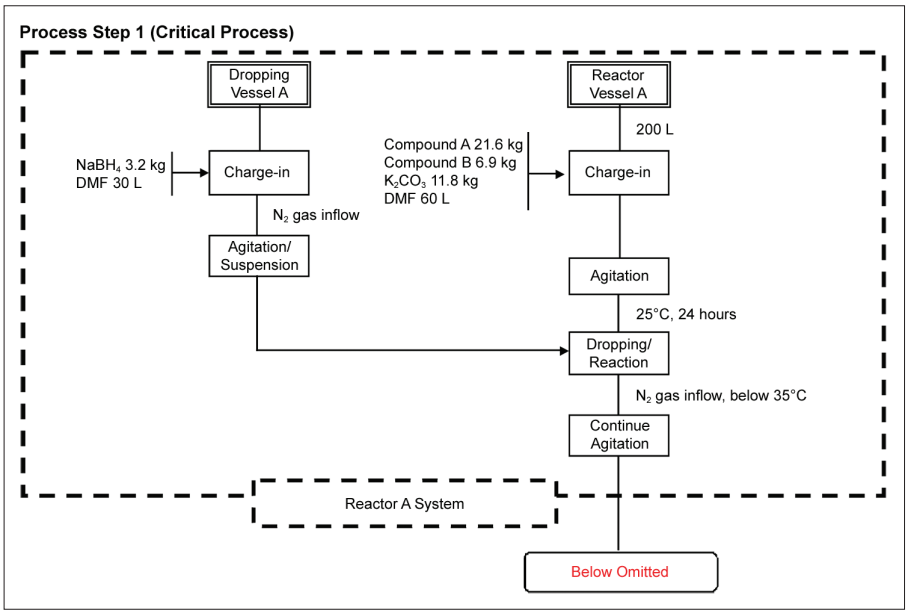


Figure 2. Manufacturing block flow diagram for intermediate products.

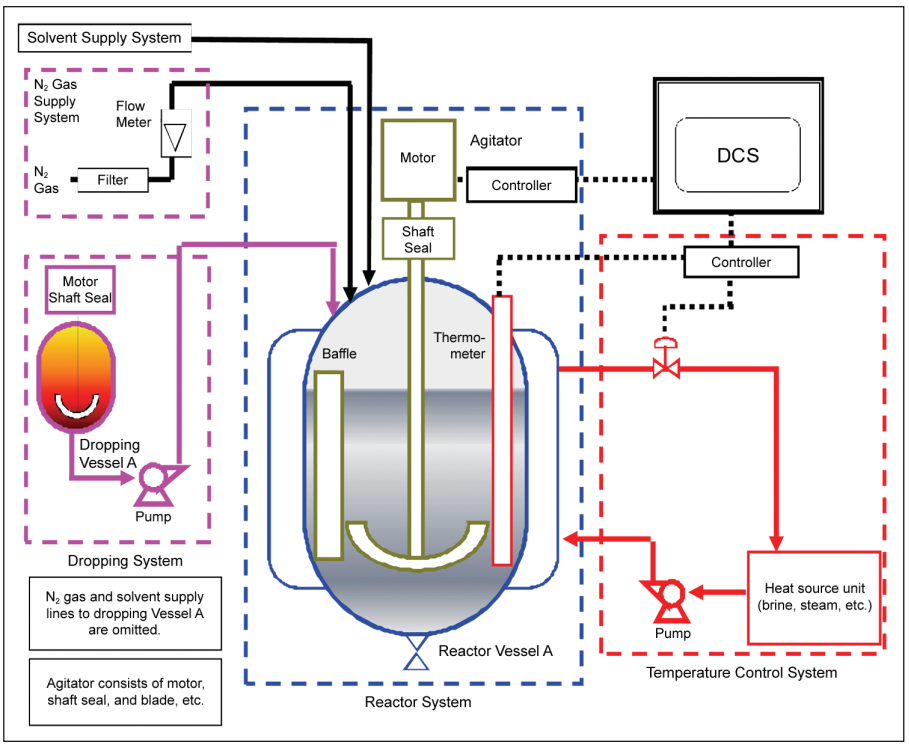


Figure 3. Equipment and instruments of Reactor A system.

1. Select direct impact systems used in critical manufacturing processes.

2. Identify functions (Dynamic/Static) of the direct impact systems and then classify them as either direct or indirect functions in accordance with the level of quality risk determined by risk assessment.

3. Determine qualification stages and qualification acceptance criteria. Static direct functions are to be the targets of DQ and IQ. Dynamic direct functions not subject to process control are to be the targets of DQ through OQ. Dynamic direct functions subject to process control are to be the targets of DQ through PQ.

4. Prepare protocol, implement and prepare a report at each stage of qualification.

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**This is a summary of a White Paper on "Supply Chain Security: A Comprehensive and Practical Approach." developed by members of the ISPE International Leadership Forum.**

## Executive Summary

# Supply Chain Security: A Comprehensive and Practical Approach

The pharmaceutical supply chain is a complex process which spans many geographical regions and involves numerous parties, such as raw material suppliers, contract manufacturers, logistics, and transportation providers.

Pharmaceutical quality systems alone cannot guarantee supply chain security.

This white paper "Supply Chain Security: A Comprehensive and Practical Approach" presents how an integrated approach can facilitate supply chain security by suggesting ways of augmenting the pharmaceutical quality system to prevent and detect adulteration, counterfeiting, illegal diversion, and theft. It looks at supply chain security holistically, including the application of environmental scanning methods and risk management principles at each step in the supply chain.

Strategies and principles outlined in this document include:

- augmenting specific quality systems
- being alert to signals in the environment
- applying risk management principles
- developing specific programs

The document is divided into sections which consider:

### 1. Risk and Supply Chain Security

Risks to the supply chain can include:

- adulteration (including economically motivated adulteration)
- counterfeit medicines
- illegally diverted medicines
- cargo theft

This section refers to the process described in ICH Q9, Quality Risk Management, as a basis for the development of a risk-based approach to supply chain security. It explains the need to understand the types of risks throughout a supply chain and how a pharmaceutical quality system can be augmented with respect to controls and approaches for each type of risk.

### 2. Common Processes to Enhance Supply Chain Security

This section discusses several processes common to help control the risks to the supply chain including, signal detection and response, supplier quality management, and management of logistics and transportation services providers. Three examples of how adulteration of an excipient can have broad effects on the quality of finished products across several countries and impacting several firms are presented. It also contains a discussion of linking outcomes, the signal detection process, and environmental scanning, which can be used to better understand supplier and supply chain data, and can help in the early identification of problems.

### 3. Supplier Quality Management

There are three key elements of supplier quality management, which are each detailed:

1. Supplier assessment and selection
2. Written agreements for quality activities
3. Supplier monitoring and review

Recommendations include a multidisciplinary approach, the use of quality risk management principles in assessing and selecting a potential supplier, along with the relevance of material being supplied, geographic location, and the regulatory environment.

The appropriate contents of written agreements are discussed, who should be bound by written agreements, and how they can be used

to help ensure compliance. Discussion of the periodic review of written agreements, helping to determine supplier performance, is included.

The document recommends that supplier performance is monitored and reviewed on a regular basis to promote continuous improvement and check the effectiveness of the supplier controls. How audits, changes within agreements, and supplier activities should be managed is discussed

Items to include in supplier audits for product security are listed along with enhanced oversight activities which may form part of risk reduction/risk mitigation strategies.

## 4. Logistics and Transportation Service Providers

The discussion of management of logistics and transportation service providers focuses more on elements of security features such as securing physical distribution channels, as the processes for the assessment, selection, monitoring and review are similar; those for supplier quality management.

Controls which are needed to assure logistics service providers do not become an avenue for either illegal diversion of product outside of the legitimate supply chain, or introduction of counterfeit or diverted product into the legitimate supply chain are discussed.

## 5. Transport and Control of Materials

Checks required for materials controls, monitoring and detection processes, including personnel aspects, for warehousing and distribution controls are discussed. Recommendations include a seven-point inspection process and aspects of storage for containers. Types, personnel aspects and procedures for seals and shipping & receiving processes are discussed.

## 6. Specific Programs

Specific programs related to the risks to the supply chain (counterfeit medicines, illegally diverted medicines, and cargo theft) and enabling of authentication are discussed. Interactions with customer sand distributors, awareness and prevention of cargo theft, and 'deter, detect, and disrupt' aspects are considered.

The complete White Paper will be made available on the ISPE Web site for download in PDF format on 15 September 2010. To obtain a copy, visit www.ISPE.org, select Publications, Other Publications.

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# Challenges to Establishing External API Manufacturing in China

by Matteo Giovinazzi

**This case study presents the establishment of a new multipurpose API plant by a major Chinese API manufacturer, supported by a major international pharmaceutical company.**

## Introduction

There are several business models that western companies consider when doing business in Asia. They include the following:

- joint ventures with local companies (common, for example, in China)
- the marketplace approach (a traditional relationship supplier/customer)
- fully-owned subsidiaries (more and more frequent)
- take-over of local companies (especially in India, where major pharmaceutical companies have, for instance, purchased generic manufacturers in recent years)

The list is not comprehensive and there are many other approaches. Successful examples of each of these models could be easily pointed out, meaning that there is no optimal solution, and that the shift between advantages and disadvantages depends strongly upon local environment, business perspective, etc. The ultimate goal is to combine the different features to maximize cost-effectiveness, while minimizing the related business risks.

This article will present a slightly different business model, closer to a partnership, in between the acquisition and the marketplace approach.

## External Manufacturing – A Case Study

In recent years, the volume of the business outsourced in the pharmaceutical industry has grown dramatically. Although the exact worldwide figures are still a matter of discussion,[1] this growth has led major pharmaceutical companies to develop new skills and new organizational models to deal with this increasingly crucial aspect of the business - *Figure 1.*

In our case, External Manufacturing (EM) business accounted for 25% of cash flow in 2008. It is expected that by 2012, 40% of our cash-flow will be generated by our EM network - *Figure 2.* The term EM network is used here to indicate the group of companies (suppliers, partners, etc.) which are qualified to manufacture and supply (fully or in part) products to be later commercialized by big pharma. The EM network now spans the globe, currently comprising approximately 150 EMs, 70% which are in developing markets like India, China, and North Africa, etc.

There are several reasons to outsource manufacturing, including: cost competitiveness, shorter reaction time to planning modifications, available production capabilities outside, which avoid internal capital investment, etc.

One reason is becoming more and more strategic: delocate production to an EM in an area with great market potential, as a stepping stone for the future. In this way, the presence in the area is ensured as well as the insight of the local environment. In the coming years, it will be easier to make acquisitions or create entities should the market become profitable. In our case, six emerging markets have been identified – Brazil, Russia, India, China (BRIC) plus Mexico and Turkey – as being critical to growth ambitions between now and 2015; sales are expected to be boosted three times by 2015.

In general, technical expertise and regulatory understanding are critical factors that can determine success or failure of the outsourcing process. Intercultural knowledge is an important factor as well, as many initiatives happen outside the western hemisphere. In this case, when it came to consolidating the outsourcing of some productions (late intermediates, final APIs) to Asia, and to concentrate an otherwise scattered outsourcing portfolio, the idea was to find a reliable, high-developed supplier capable

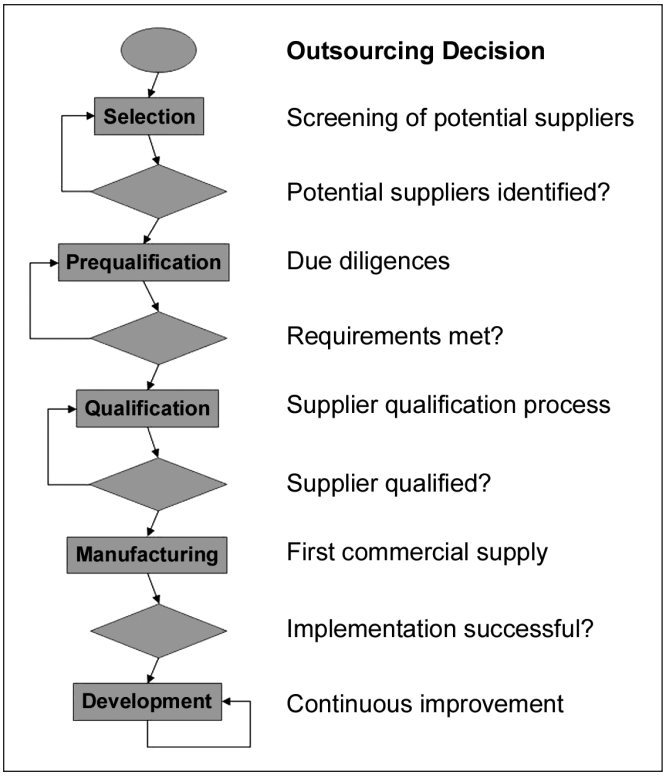


Figure 1. The API outsourcing process from the decision to outsource until ongoing supply.

of producing most of the quantities and overseeing the production steps required.

Since the survey showed that, at that time, it was difficult to find a company with the required organizational strength and technical capability to satisfy the strict parameters required, the decision was made to start a developing program for the company that showed the most promise of reaching such a level.

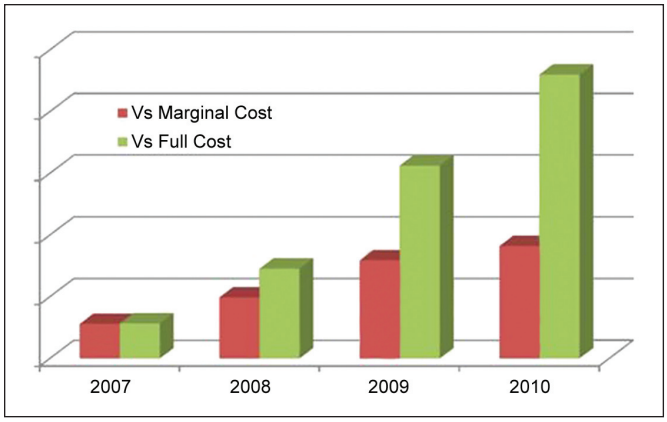


Figure 2. Volume of business outsourced.

First of all, the production capability needed to be improved and upgraded; therefore, the site would have been expanded. This expansion has involved:

- new grass-root production building (chemical systems, product isolation, solid processing, and final packaging)
- new tank farm
- new solvent recovery system
- expansion of utility area
- new emission containment plant

The production building shown in Figure 3 consists of several production lines; some of them to manufacture late stage intermediates and crude APIs; others (in a separate area) expressly designed to manage APIs. The production lines consist of a classical sequence of equipment, namely vertical reactors, horizontal centrifuges and dryers, all provided with their ancillary units. Inertization and blanketing facilities are provided to all the hazardous equipment to minimize the risk of explosions.

Figure 3. The new production plant and its utility building.

Also included is the powder handling equipment like blender, mill, dosing, and packaging systems. The handling of the powder is managed via IBCs to minimize exposure and contamination. Multiple HVAC circuits ensure compliance with air quality requirements. The API production area is designed for class ISO 8. The production support activities (sampling and dispensing, staging of materials, technical areas, etc.) are performed in dedicated area of the building. Process emissions are treated before going to the atmosphere; emergency vents are collected in a catch tank. Spent solvents and mother liquors are collected and processed; solvents are recovered and reused, low Chemical Oxygen Demand (COD) layers are sent to the Waste Water Treatment Plant (WWTP), high COD layers are sent to external disposal. New utilities like compressors and chillers have been installed to sustain the growing consumption; the site is situated in an industrial area; thus, the steam supply is ensured by public distribution.

The building has been designed to satisfy the following requirements:

### *1. Minimize Cross-Contamination*

A multipurpose plant is impacted from cross-contamination issues that cannot be solved only by implementing the right operational procedures. Proper design has been implemented in order to minimize this risk. As an example, it could be mentioned:

- physical segregation of the different production bays
- closed product loading/unloading operations
- dedicated individual HVAC circuits

### *2. Maximize Containment*

The products managed in the plant fall in the lower range of the Operational Exposure Levels typical for the industry. Containment has been ensured through fixed connections and gravity flows, as much as practically possible, and proper containment techniques during handlings. During start-up, the effectiveness of the containment approach was tested; a proper sampling campaign under operation has been implemented, according to international guidance.[2] The outcome of these measurements have been taken into account to define the most convenient personal protective equipment to cover the residual exposure of the operators. This pragmatic approach satisfies industrial hygiene requirements, is the best technology currently available and is consolidated locally.

### *3. Maximize Flexibility*

The business case for the expansion of the site included future implementation of additional processes, not even known at the time of the design. Therefore, the concept of multi-functional, independent production bays has been introduced with an extensive use of manifold connections.

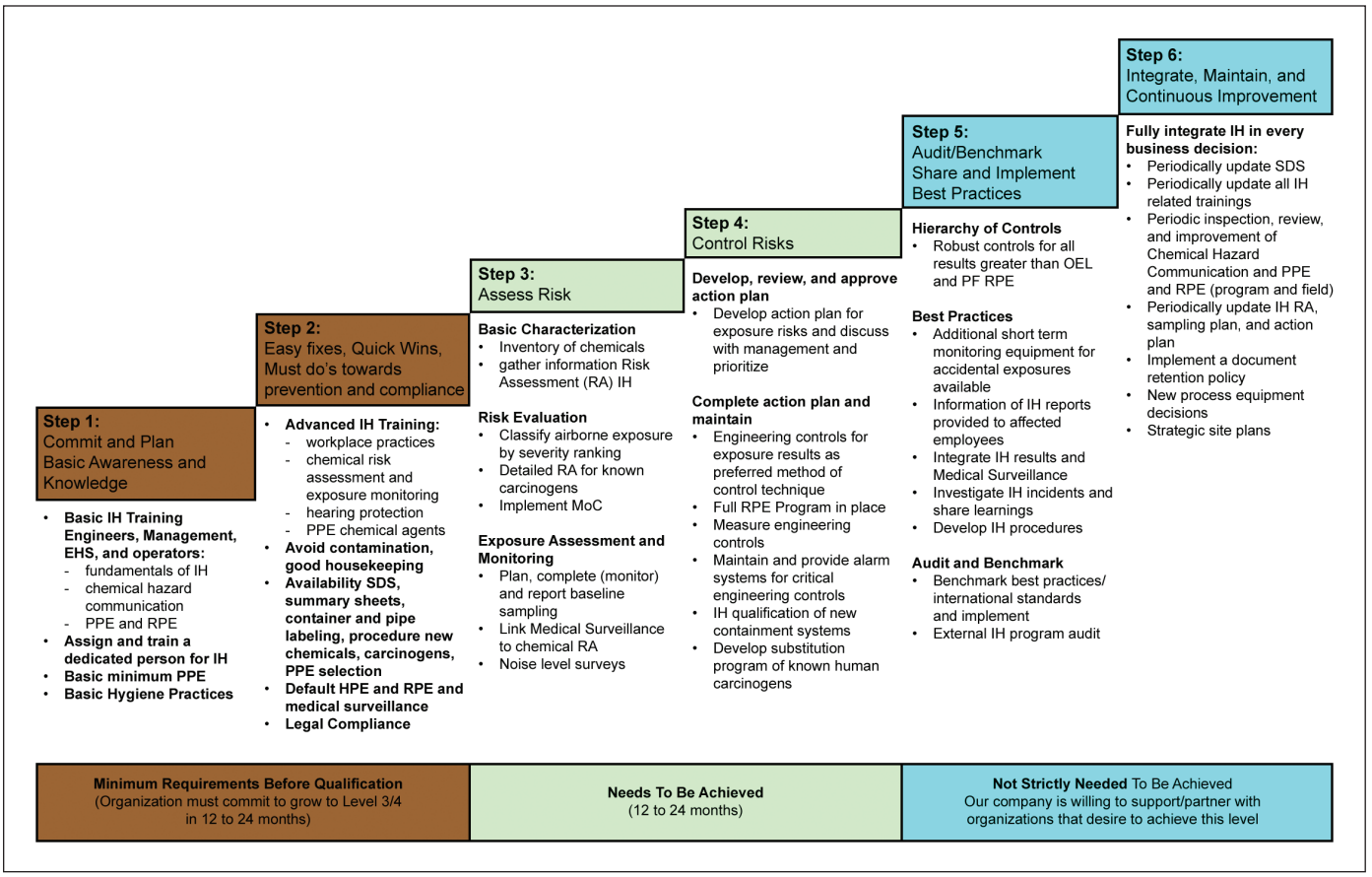


Figure 4. The EHS ladder concept applied to Industrial Hygiene.

### *4. Optimize the Life Span of the Investment*

It is not uncommon for Chinese companies to consider for their investment a lifetime cycle sensibly shorter than western standards. The selection of the infrastructures and of the process equipment (in terms of quality, material of construction, mechanical resistance, etc.) comes as a consequence. By enlarging the target life time of the investment, the selection was forced toward high-quality, high-standard elements. The realization of a brand-new, state-of-the-art production building (along with its supporting facilities) would be a short-sighted investment without a sustained, systemic growth of the entire organization. Extensive support has been given to the Chinese partner on different organizational "streams" (quality systems, lab/QC/microbiology, EHS systems) in order to bring the level of the organization up to a level to easily fulfill the requirements coming from worldwide health authorities (such as the FDA).

The support was not limited purely to training, but has been conveyed into a jointly defined improvement action plan, and a constant monitoring of the progress. Independent reviews and preparatory mock inspections have been performed to ensure objective assessment of the progress.

## The EH&S Maturity Ladder

To highlight the importance of the quality (GMP) and of the EH&S issues, dedicated separate documents (i.e., Quality Agreement and EH&S Agreement) were established within the parties, as formal attachments to the contract; in particular, child labor policy and business integrity were explicitly referred to. In particular, intensive effort has been put to raise the EHS awareness. The concept of **"EH&S maturity ladder"** has been applied to enable the external manufacturer to raise the first steps of the "ladder."

The EHS ladder concept consists in a structured approach to rank the External Manufacturers in level of expertise, against predefined criteria - *Figure 4*. The approach is called "ladder" because it lifts the outside company from a status of basic awareness and legal compliance to a sustainable condition, until real partnership with shared best practices.

The main benefits for the **External Manufacturers** are:

1. Clear expectations in terms of EH&S, resulting in clearly defined EH&S priorities and risk-based action plans.
2. Access and support to EH&S tools (procedures, training, guidelines, work-instructions, etc.) and EH&S experience from the international pharmaceutical company.
3. Pass EH&S assessments: robust EH&S systems open the door to the western market.

The main benefits for the EM's **environment and community** are:

1. The assurance that mature EM partners protect the environment, while improving working conditions and the health of employees and surrounding communities.
2. Economic growth.

The main benefits for the **international pharmaceutical** company are:

1. Reduction of business and reputational risks when working with EMs.
2. Standardization of the respective EMs' EH&S approach, focusing on key EH&S risk areas and allowing for the easy assessment and overview of the current EM program status.

The main benefits for the **worldwide market** are:

1. From a macroeconomic perspective, it is very cost effective to increase the EH&S knowledge and experience of smaller and medium sized enterprises through a collaborative approach with large enterprises.
2. Increasing the EH&S knowledge, experience and performance of developing economies and companies creates a level playing field, while increasing fair competition.
3. Fostering the transfer of knowledge and experience to less-developed partners and economies highlights how effective simple solutions can be and how certain alternative approaches can be used to achieve the same or a similar outcome.

## Harmonization of Technical Topics

An immediate and obvious task of the new plant project has been to find the best compromise among different requirements:

### *1. Chinese FDA vs. EMEA/US FDA Requirements*

Although great progress on homogenization of requirements has been made, there is still a conservative approach from local authorities toward the introduction of new concepts, especially by regional officers. Typical examples are the gowning and degowning strategy or the request for the extensive use of several small airlocks. Originally, Chinese health authorities were forced to apply strict rules in the design of locker rooms in pharmaceutical plants. In the past, the use of migrant seasonal workers was frequent in drug manufacturing processes, even in API or finishing steps. The training of this personnel was sometimes inadequate or completely absent; forcing them into physical separation stages was a way to minimize the effects of this. The Chinese pharmaceutical industry has evolved since then, making obsolete most of these requirements, but still local authorities tend to pursue a conservative approach.

### *2. Major Pharma Standards vs. Minimum (Optimum) Requirement*

Major international pharmaceutical companies are frequently beyond compliance when it comes to highly critical issues (cross-contamination, microbial growth, etc.). The pre-alarm levels and the values that trigger actions are well below the accepted limits. This is reflected as well in design standards. A leaner, risk-based approach is more common in the outsourcing environment. Moreover, a country like China has

*"The collaboration (including the progress of the contractual relationship) is structurally defined in detail, and linked to the positive outcome of predefined milestones. The clear assignment of roles and responsibilities between the two partners makes the process transparent and accountability is ensured."*

a lot of design codes (both national and regional), which are sometimes subject to interpretation from both designers and local officers.

Finally, the design must be performed and certified by an officially authorized engineering company (the Design Institute), which is granted some specific licenses to do so. Therefore, the implementation of the local requirements into a "western" design need compromises in terms of design and discussion with local authorities. The use of an authorized Design Institute is compulsory, meaning that the technological concepts behind the investment must be conveyed in a way which is locally intelligible.

### *3. Western Technology vs. Locally Available*

Although it was theoretically possible to select and import technology from abroad, it was decided to select equipment which were commonly produced, used, and serviced locally. Our analysis showed that the disadvantages to implement western latest development equipment would have offset the advantages. A typical example would be a technology like centrifuge-drying, extensively used within our company for processes where the product is highly active. Unlikely other types of equipment, this one is still not completely absorbed by the Chinese industry; therefore, the choice went to a more classic approach (centrifuge and dryers as separate equipment). The same apply to some exotic and expensive materials (like tantalum, for instance).

### *4. State of the Art Technology vs. Actual Capabilities*

Partially because of the less intensive impact of labor cost on the total cost of production, Chinese plants still use a generally low degree of automation. Hardware suppliers and software developers aren't as widespread as in the west. To introduce a fully automated process management system to a company who is not familiar with one, would have certainly been ineffective, and could have generated problems instead of solving them (additional production idle times or even safety concerns). On the other hand, concepts like piping manifolds and flexible connections in place of classic fixed lines are relatively new, but not completely unknown; its implementation has been proven possible. Recovery of solvents is a common practice as well, and local knowledge can easily be found.

## Harmonization of Intercultural Issues

Although it is not within the scope of this article topic, harmonization of intercultural issues should be considered. Asian cultures are a typical example of high context communication environment.[3] Taking this into consideration and putting it in the right perspective should help avoid flaws in the project. The chosen business model represents a win-win situation; however, miscommunication could lead to misunderstandings, delays, and frustration.

The standard high context communication framework applies (body language, indirect communication, etc); business relationship begins with a personal relationship. The Chinese culture emphasizes collaboration (as opposed to individualism).[4] The decision making process is affected by miscommunication whether it be technical or organizational. Miscommunication because of language barriers must be taken into consideration:

- English is a foreign language for everybody involved.
- Not all the Chinese people can speak and understand English.
- The use of a translator (especially in technical fields) could not solve all the problems and could possibly amplify them, especially if not carefully selected and monitored.

Additionally, some technical words don't have Chinese translation, while others, once translated, have completely different meanings. For example, the word which is used from the Chinese project group to indicate the standard elliptical-bottom reactor would sound in English something like watermelon reactor! The more practical solution is to extend the use of the other ways of communication, especially visual (drawings on large boards, projectors, big printout of document, and marked-up comments, etc.), while minimizing the oral communication.

## Comparison with the Other Business Models

In this model, the general accountability and the leadership is assigned to the Chinese partner, while the knowledge and the expertise to the western partner. This means that the invested capital is coming directly by the Chinese company (through capital ventures or standard bank financing), which therefore assumes on itself the entrepreneurial risk. However, depreciation of the plant is paid back by the big pharmaceutical company as part of the product cost, which is approached as cost plus fee in an open book framework. Minimum committed volumes (by the international company to the local manufacturer) and minimum guaranteed production slots (by the local manufacturer to the international company) are among the measures put in place for mutual risk minimization.

The collaboration (including the progress of the contractual relationship) is structurally defined in detail, and linked to the positive outcome of predefined milestones. The clear assignment of roles and responsibilities between the two partners makes the process transparent and accountability

is ensured. The main advantages against the acquisition (or the joint-venture) approach is of course the virtual absence of capital investment. The headcount expenses are reduced to a minimum as well (basically the ones directly related to production). The following are advantages of this approach against the market place approach:

For the major pharmaceutical company:

- More insight of the partner internal procedures. It's easier to perform gap analyses and identify corrective action plans.
- Consolidated business relationship, which makes future outsourcing more cost-effective and less time-consuming.
- Local reliable source at acceptable costs.
- Local knowledge of regulations, permitting, business environment (material suppliers, contractors, etc.).

For the local manufacturer:

- Access to international standards, guidelines, and best practices.
- Consolidated business relationship, which elevates them to be the frontrunners for future acquisitions of outsourced products.
- Build state-of-the-art new plant with positive impacts on overall business.
- Implement quality and EHS standards enough to satisfy the requirements of other international customers.
- More trust-building than with the customer/supplier approach. This is a typical win-win situation and an advantage for both companies.

The following are some disadvantages:

- The final result will be achieved through influence more than giving direction. Communication management becomes highly critical.
- Although the strategic goals could be fairly aligned between the two companies, the tactical ones (i.e., middle terms achievement) could be different or even partially divergent (the two business models are basically different!). Therefore, one of the tasks of the project is to continuously assess the present situation against the target and to keep on the right track the efforts of the two organizations.

On the other hand, the selection of such a partner is highly critical; the first phase of the relationship (the "screening" and the "qualification") is shaping already the future relationship. Inputs will come from several sources (marketing, purchasing, license and acquisitions, manufacturing, EHS, quality, etc.) and the different feedbacks have to be aligned to elaborate a consistent judgment. Mistakes or underestimation of possible issues in this phase could lead to a costly and painful relationship with mutual unhappiness and distrust. Once the partner is selected, in fact, it will be more difficult to change companies (as in the marketplace scheme) or to make direct organizational changes to fix problems (as in the acquisition or subsidiaries scheme).

## Reverse Learning

As always in business as well in life, there is no enterprise from which one cannot be enriched. Projects like this make no exception at all, and if possible, overcome brighter expectations. As an organization, not to capture the lessons learned and spread it thoroughly would be an unjustified waste of opportunities. A proper formalized "reverse learning process" has been established, within our organization, to capture the several positive feedbacks that come from outside, be it different technological possibilities, leaner solutions to common regulatory problems, or simply a help to put in perspective in-house procedures and beliefs.

This reverse learning initiative covered a broad range of issues, from the technical ones to the organizational ones. In summary:

- Lifecycle of the plant. Does it still make sense to design a plant that has a lifetime of 25 to 30 years? Is technology changing so fast that we still believe that in 10 years time, a plant designed today will be up to the standards? Where is the optimal compromise and which ones are the decisional factors?
- Planning production. Chinese companies prefer to approach planning in terms of complete synthesis (raw materials to intermediate to API) rather than different intermediate campaigns, later converted to API. Which model is more in line with today's fast changing customer needs and growing inventory costs?
- Automation and computer system validation. Once automation is pushed to extreme, its validation becomes very heavy and difficult to achieve, while later modifications become more difficult to handle. Which is the right balance between automation and skilled, reliable, and trained operators?
- Batch and continuous production. Is the continuous production a suitable alternative to the batch manufacturing concept? Largely used in other businesses, is it still struggling to find his way in the pharmaceutical world. Is there a technological or a cultural limitation?

It is important to mention that to import from "outside" (another company, another country, another business model, etc.) concepts and standard practices to the "inside," could undergo the same kind of issues and resistance that were listed in this article, just in the opposite way. However, an organization that allows this process to happen with an open mindset is surely shaping its business vision for the future.

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# Process Simulation Using VBA Code with Variable Input Data

**This article explains how to use Visual Basic for Applications (VBA) code with variable input data to create a process simulation.**

by Stephen M. Hall, PE

The adage, "garbage in, garbage out," describes a common problem with process models. Whether elegant or simple, plant simulations rely on the assumptions that are provided. They require a set of inputs before they can give outputs. While the modeling activity itself may be interesting and challenging, the computer reports flawed results if the underlying data is poorly characterized.

This article shows how to use Microsoft Excel and Visual Basic for Applications (VBA) to create a process simulation. An example problem is defined and solved with step-by-step instructions. Follow the thought process as a simple simulation is built. The example should be familiar: sizing a purified water storage tank. However, the tank is a prop, used to illustrate the model building process. The input data and assumptions become crucially important. The variability of the input data is especially critical. Due to many factors, such as production scheduling and random events, the input data change each time the model is run. The model's output changes in response to the variable inputs.

The ability to incorporate randomness defines the difference between a model and a simulation. Successful simulations are often built with the following steps:

1. Formulate the problem. Set objectives, plan the effort, and conceptualize a simulation model.
2. Collect data. Determine the key assumptions and inputs; collect real-world data if possible, qualify the data.
3. Analyze the data and model the inputs to the simulation. Determine how the input data will interact with the simulation and perform sensitivity analyses. For data that have a relatively big impact on the simulation, model the inputs using an appropriate statistical correlation.
4. Build the simulation. Start simple and then build to the necessary complexity.
5. Verify the simulation model. Ensure the computer code generates results that are consistent with the problem objectives and validate the model against the real world.
6. Run design cases. Decide which sets of input data to use, what output to collect, and how to report the results; document both the computer code and the input/results.

To decide the appropriate size for a purified water storage and distribution vessel, the water generation and usage rates must be known. To optimize the tank size, the time-of-day usage profile and knowledge about sanitization practices are important. The model uses these input data and constructs a graph that depicts the water level in the tank over the course of a day. The graph changes whenever an assumption is changed.

When inputs are treated as fixed values, the resultant model is deterministic. Results are calculated from the input data. The calculations can be checked for their sensitivity to changes to the assumptions; this improves process understanding and might signal areas that could benefit from further optimization.

The breakthrough in process understanding comes when it's recognized that certain inputs to the model vary in accordance with probability distributions. For the water tank example, the user points are unlikely to draw water on the exact same schedule day after day. The number of times per day that water is used may vary as well as the time of day and duration of a particular usage. Statistical variation of input variables, when incorporated into a process model, result in a stochastic simulation. Results from such models are typically presented as frequency histograms or opinionated consensus.

## Water Consumption Histogram – An Example Problem

Problem statement: a purified water system, consisting of generator and storage tank, provides water for formulation and cleaning in a manufacturing plant. Size the generator and tank.

Discussion and solution: the primary goal is to determine the optimal size for the water storage tank. Assuming the generation unit can operate at constant volume around the clock, the problem reduces to an analysis of water usage.

Start the analysis by making a list of usage points in the water system. The water usage points are estimated in terms of the flow rate, and in some cases, the duration of flow. For this example, to characterize water demand on an hourly basis, the time of day that each usage point may demand water is generalized by specifying the operating shift(s) when the point may be active. Then, an estimate is made of the number of times per day that each point draws water.

Notice that the system definition is fuzzy. The duration of flow is known "in some cases." And "an estimate is made" of the number of usages per day. If given precise values, it would be easy work to size the generator and storage tank. Contrarily, the usage is variable and can have wide ranges.

Consider these typical water uses:

- Clean-in-Place (CIP) systems and parts (washers) are programmed and use a precise quantity of water for each recipe. However, there may be several different recipes, the recipes may be changed as cleaning verification data is collected, and the frequency of use varies with production demand.
- Formulation tanks that are filled with water to make an aqueous batch use a precise quantity of water. However, the number of batches per day may vary from zero to many depending on production demand. And the quantity of water used for each batch is often very large compared with other water uses.
- Incidental uses with manual control, such as rinsing parts in a sink or hosing out an open tank, cannot be precisely predicted. However, it should be possible to understand the duration of uses over a range (e.g., one to five minutes).

For this example, it was decided that the usage durations may vary around an average value and that they will have a normal distribution with characteristic bell-shaped curve. The engineer estimated the average number of usages per day, but in addition to a use point that he thinks will usually be near the estimate, other points will vary uniformly over a range. In a uniform distribution that ranges from one use per day to 10 uses per day, there is an equal (10%) probability that the number of uses on any particular day will be one, two, three, …, or 10.

Excel was used to model the water system. The model creates an hourly water consumption profile for one day, but since every day is different due to the variations discussed above, the model must be run many times to give a feel for how the tank level might vary over time. The results from running the model for four simulated days are shown in Figure 1. The tank level is on the ordinate and time is on the abscissa. On the fourth day, the tank runs dry. Each day is characterized by the tank level increasing in the first hours; this is due to our input assumptions that place highest water demand on the day shift (the charts begin at midnight which is the night shift). After running the model for many simulated days, statistics are collected and analyzed. Then, using engineering judgment, the Decision variables are adjusted to test a different scenario. The process is repeated until consensus is reached for the tank size and water generation rate. Along the way, different combinations for the input parameters are tried which provides data for a sensitivity analysis.

Now the process of developing the spreadsheet is explained. The main lessons are to design the spreadsheet for easy use, pay attention to formatting and documentation, and to utilize Visual Basic for Applications (VBA) to solve problems for which Excel lacks intrinsic functions.

All of the usage information was assembled into a table in Excel as seen in Figure 2. Because consistent volume units are used throughout the model, the Draw Rate units are not labeled (e.g., l/min, gpm, $m^3$/min). The mean Duration of each use was estimated, along with a Standard Deviation (SD), to define a bell-shaped normal distribution. If SD is zero, there is no distribution; every use has the same duration. The range of Usage Starts and also a Distribution characteristic are listed.

Next, a list of plant design decisions to analyze was created. These are the water generation rate and tank size which are the primary objective for the model, plus the maximum total usage rate (which affects sizing of the circulation pump and piping) and starting level in the tank. How full is the tank at the beginning of the day? The importance of this parameter is explored later.

There is one more thing for this example before doing any modeling. Assume that water circulates at ambient temperature with heat exchangers at the beginning and end of the loop so the tank remains hot. To maintain the

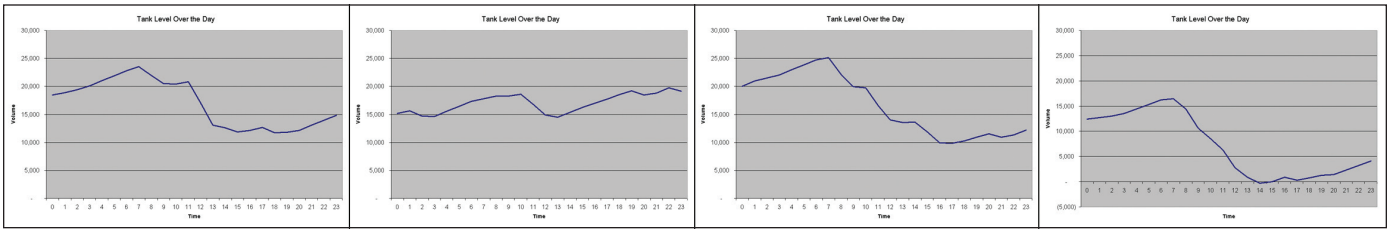


Figure 1. The simulation creates histograms showing tank level through one day.

| Use Point | Description | Draw Rate (l/m) | Schedule | Duration (min) | Std Deviation (SD) | Distribution | Usage Starts (minimum per day) | Usage Starts (maximum per day) | Distribution |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Formulation Tank | 25 | Day & Evening | 80 | 0 | NA | 1 | 3 | Uniform |
| 2 | Formulation Tank | 35 | Day | 135 | 0 | NA | 0 | 4 | Uniform |
| 3 | Washer | 10 | Anytime | 15 | 5 | Normal | 2 | 20 | Uniform |
| 4 | Washer | 10 | Anytime | 15 | 7 | Normal | 10 | 30 | Normal |
| 5 | Washer | 15 | Anytime | 5 | 1 | Normal | 0 | 30 | Normal |

Figure 2. Initial input data collection.

loop, the heat exchangers are turned off for a period of time every night and the loop gets hot. The model should address whether the duration of the sanitization cycle affects the tank sizing. In other words, provide the model with a way to block out a time when no water is available to the use points. Figure 3 shows how all of the input data looks in Excel.

The goal is to decide on a tank size and water generation rate. If the input parameters were fixed, the calculations are easy: add up the daily uses and divide by 24 to get the generation rate per hour; chart the hourly usage variation and pick a tank size that will operate between 20% and 80% full. But the parameters are assumed to be variable. Therefore, to solve the riddle, the steps listed below are followed, applied to a random day. Then the steps are repeated many times to simulate the plant operation over a period of time. As the simulation proceeds, statistics are collected, and finally, engineering judgment is applied to decide on a tank size and generation rate.

1. Calculate how many times each usage point is used in the day.
2. For each instance, calculate the duration of the usage.
3. Assign each instance to a particular hour of the day.
4. Calculate the material balance for the tank for each hour of the day and chart the results.

The intermediate calculations for Steps 1-3 are performed on separate worksheets. This way, the input parameters and final charted results can be neatly formatted together on the primary worksheet.

Visual Basic for Applications (VBA) is a great tool for solving this type of problem. VBA sits beneath the Excel spreadsheet. It is ideally suited for iterative and repetitive problems that are difficult or confusing to perform within the Excel environment. The entire spreadsheet may be downloaded for free from http://www.pipesizingsoftware.com/PW/CaseStudy.xls.

An alternative to VBA is to use an Excel Add-In program that contains tools for performing Monte Carlo simulations, optimizations, and other statistical analyses. Several of these are listed at the end of the article. The advantage to using an Add-In is that the work is done completely within Excel with Add-In environment. Disadvantages include a new learning curve, inability to share models with those who lack the Add-In, and limitations will still exist that may require VBA anyway.

| | A | B | C | D | E | F | G | H | I | J | K |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **PURIFIED WATER GENERATION AND STORAGE TANK ANALYSIS** | | | | | | | | | | |
| 2 | | | | | | | | | | | |
| 3 | **Parameters** | | | | | | | | | | |
| 4 | | | | | | | | | | | |
| 5 | | | Daily Sanitization? | TRUE | Time | 4.00 | | Duration | 3 | hours | |
| 6 | | | | | | | | | | | |
| 7 | | Use Point | Description | Draw Rate (l/m) | Schedule | Duration (min) | Std Deviation (SD) | Distribution | Usage Starts (minimum per day) | Usage Starts (maximum per day) | Distribution |
| 8 | | 1 | Formulation Tank | 25 | Day & Evening | 80 | 0 | NA | 1 | 3 | Uniform |
| 9 | | 2 | Formulation Tank | 35 | Day | 135 | 0 | NA | 0 | 4 | Uniform |
| 10 | | 3 | Washer | 10 | Anytime | 15 | 5 | Normal | 2 | 20 | Uniform |
| 11 | | 4 | Washer | 10 | Anytime | 15 | 7 | Normal | 10 | 30 | Normal |
| 12 | | 5 | Washer | 15 | Anytime | 5 | 1 | Normal | 0 | 30 | Normal |
| 13 | | | | | | | | | | | |
| 14 | | | | | | | | | | | |
| 15 | **Decisions** | | | | | | | | | | |
| 16 | | | | | | | | | | | |
| 17 | | Maximum simultaneous draw | | 60 | liters per minute | | | | | | |
| 18 | | Tank size | | 30,000 | liters | | | | | | |
| 19 | | Generation Rate | | 15 | liters per minute | | | | | | |
| 20 | | Starting level | | 13,250 | liters | | | | | | |
| 21 | | | | | | | | | | | |

Figure 3. Input data grouped together for ease of use.

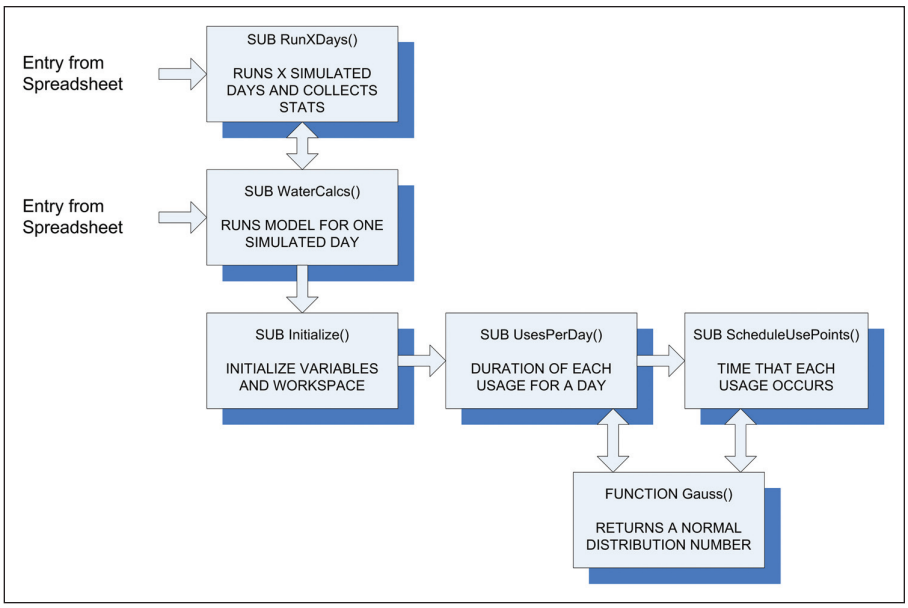


Figure 4. VBA subroutine flow diagram.

```
Option Explicit
Dim OutputData, OutputStart, OutputHourly As Range
Dim i, j, k, L, m As Integer      ' pointers and counters
Dim HourlyConsumption(24, 25)     ' hour of day, use point number
Dim UsePointParameters(25, 15)    ' Holds Parameter data (i,j)
    ' where i = the Use Point number
    ' and j = the following parameters
    '   0 = Number of usage starts per day
    '   1 = Description
    '   2 = Draw Rate
    '   3 = Priority (not currently used)
    '   4 = Schedule (Day, Evening, Night, Day & Evening, or Anytime)
    '   5 = Duration, minutes
    '   6 = Standard Deviation of Duration
    '   7 = Distribution of Duration (NA or Normal)
    '   8 = Usage Starts, minimum number per day
    '   9 = Usage Starts, maximum number per day
    '  10 = Distribution of Usage Starts (NA, Uniform, or Normal)
    '  11 = Starting time for first usage
    '  12 = Number of hours available for usage
Dim MaxDraw, TankSize, GenerationRate
Dim Temp, SD, TotalConsumption, Rate, Duration
Dim Upper, Lower As Integer
Dim Sanitize As Boolean
Dim SanitizeTime, SanitizeDuration
```

Listing A. Defining the variables used in the VBA subroutines.

```
Sub UsesPerDay()
' Step 1: Decide how many starts per day for each of the usage points
' Use k to keep track of the maximum number of starts
10 k = 0
‘ Cycle through all of the Use Points (i)
20 For i = 1 To UsePointParameters(0, 0)
30 Lower = UsePointParameters(i, 8)
40 Upper = UsePointParameters(i, 9)

50 Select Case UsePointParameters(i, 10)
     Case "NA"
       UsePointParameters(i, 0) = Int((Lower + Upper) / 2 + 0.5)
     Case "Normal"
       ' for this case, "Normal" is assumed to mean
       ' truncated to 2 SD on each side of the mean
       ' therefore, SD = 1/4 times the range
       SD = (Upper - Lower) / 4
       UsePointParameters(i, 0) = Int(gauss * SD + (Lower + Upper) / 2 + 0.5)
       If UsePointParameters(i, 0) < Lower Then UsePointParameters(i, 0) = Lower
       If UsePointParameters(i, 0) > Upper Then UsePointParameters(i, 0) = Upper
     Case "Uniform"
       UsePointParameters(i, 0) = Int((Upper - Lower + 1) * Rnd + Lower)
     Case Else
       ' should never be here, but if so,
       UsePointParameters(i, 0) = Int((Lower + Upper) / 2 + 0.5)
   End Select
60 If UsePointParameters(i, 0) < 0 Then UsePointParameters(i, 0) = 0
70 If UsePointParameters(i, 0) > k Then k = UsePointParameters(i, 0)
80 Next i

' Display starts per day on the spreadsheet
90 For i = 1 To UsePointParameters(0, 0)
100 OutputData.Offset(3, i - 1).Value = UsePointParameters(i, 0)
110 Next i
' List Use Starts
120 For i = 1 To k
130   OutputStart.Offset(i, 0).Value = i
140 Next i

' Step 2: Calculate the duration for each usage
150 TotalConsumption = 0
160 For i = 1 To UsePointParameters(0, 0)
170   Rate = UsePointParameters(i, 2)
180   For j = 1 To UsePointParameters(i, 0)
190     Select Case UsePointParameters(i, 7)
          Case "NA"
            Temp = UsePointParameters(i, 5)
          Case "Normal"
            SD = UsePointParameters(i, 6)
            Temp = Round(gauss * SD + UsePointParameters(i, 5), 1)
            If Temp < 0 Then Temp = 0
          Case Else
            ' should never be here, but if so,
            Temp = UsePointParameters(i, 5)
        End Select
200     OutputData.Offset(3 + j, i - 1).Value = Temp
210     TotalConsumption = TotalConsumption + Temp * Rate
220   Next j
230 Next i
240 Range("Consumption").Offset(0, 1).Value = TotalConsumption
End Sub
```

Listing B. Subroutine to perform Steps 1 and 2.

Engineers cite “ease of use” as one of the strong advantages of Excel and plant modeling software (such as SuperPro Designer). When the software’s toolbox contains the function needed and makes it accessible and intuitive, then people are impressed with the ease in using the software. However, that accessible tool may not be the best one for the job. Use engineering judgment to assess results. It is up to the user to ensure the work is easy for others to understand by using good development practices, including clear documentation. In the author’s experience, at least 80% of the time spent developing a spreadsheet is devoted to formatting, testing, and documentation. It’s interesting that this axiom was true when mainframes were programmed in FORTRAN using punch cards and it still applies today with Excel and VBA.

The VBA module contains five subroutines and one function. It could easily be combined into a single subroutine, but it’s easier to develop, debug, and maintain when divided into pieces. Figure 4 shows the relationship of the routines in the module.

Most of the variables that are used in the code are dimensioned at the beginning of the module. This makes them available to all of the subroutines - *see Listing A.*

The Initialize subroutine takes care of all of the housekeeping needed to facilitate the calculations. It clears variables and declares initial values. It also erases old data from the worksheets, where the calculation subroutines will write new intermediate results.

The first two steps of the algorithm, calculating the duration for each instance of a use point utilization for a day, are performed by the UsesPerDay subroutine - *Listing B.* The array called “UsePointParameters” holds data for each of the use points as defined in the remarks - *Listing A.*

Step 1 is to decide how many starts to assign to each usage point for this random day. From our input parameters, it is seen that the minimum and maximum number of usages are known and there is a distribution model (i.e., uniform or normal distribution). In

Lines 30 to 40, variables Lower and Upper are assigned to the minimum and maximum number of usages. Then, in Line 50, the kind of distribution to apply is selected.

Function Gauss() returns a normally distributed random number - *Listing C.* Calculate the value by multiplying the standard distribution by the random number (gauss * SD) then adding to the mean [(Lower+Upper)/2]. Round the result to the nearest integer since there cannot be a partial usage. Then, since about 5% of the values lie outside two standard deviations from the mean, move those outliers to the stated minimum or maximum values.

Now that there is a count for the number of times each usage point is used in the day, turn to Step 2 which determines the duration for each of those usages. Line 160 begins a loop through each of the usage points. Within that loop, Line 180 cycles through the uses for a usage point as determined in Step 1. For each usage, calculate a duration using the rules established by the input parameters. It is convenient to collect the total water consumption for the day, which is done in Line 210.

When the UsesPerDay subroutine executes, it saves the results on the worksheet called "UseDurations" - *Figure 5.* Notice the button called "Run 1 Day." Clicking it enters the VBA Module at the WaterCalcs subroutine and executes the model once. It is placed here to make it convenient to step through the model and assess whether the intermediate results make sense. This is part of the testing process. Having this kind of visibility into the calculations is extremely useful; in this case, it helps to reality test the input parameters for usage starts and variability.

These intermediate results are the input values to Step 3, which determines the time of day each usage occurs - *Listing D.*

As before, the subroutine cycles through each of the use points. It takes the number of uses determined above and assigns them to a time of day. To keep this relatively simple, it starts at a random hour within the allowed range (i.e., day, evening, anytime), then just marches forward. If the end of the range is reached, it wraps around to the beginning. If there are more usages than hours, the subroutine assigns multiple uses per hour.

At Line 500, water consumption is calculated using the Duration and Rate of an instance. The results are compiled on another intermediate results worksheet, called "UseAmounts" - *Figure 6.* Again, a button is provided that when clicked, executes the model for a single day. This facilitates reality checking the results.

The tank level material balance is compiled on the "Inputs and Results" worksheet using Excel formulas - *Figure 7.* Again, there is a button that executes the model for one day. The tank level is graphed over the simulated day.

That completes the model for simulating one random day. The final subroutine, RunXDays, runs the model for as many days as desired. In addition, it selects between two cases: 1) start each day with the tank level set to a specific value or 2) start each day with the tank level equal to the last value from the previous day. This is interesting because the tank level change during any one day is limited. If it is always

```
Function Gauss()
' Function returns a normal distribution random number
' Source: http://www.anthony-vba.kefra.com/
Dim fac As Double, r As Double, V1 As Double, V2 As Double

10  V1 = 2 * Rnd - 1
    V2 = 2 * Rnd - 1
    r = V1 ^ 2 + V2 ^ 2
    If (r >= 1) Then GoTo 10
    fac = Sqr(-2 * Log(r) / r)
    Gauss = V2 * fac

End Function
```

Listing C. Function returns a normally distributed random number.

```
Sub ScheduleUsePoints()
' Step 3: Establish schedule
' Block out sanitization time
310 For j = 0 To 23
320   If HourlyConsumption(j, 0) = "X" Then
330     OutputHourly.Offset(j, 3).Value = "X"
340   End If
350 Next j

' For each use, populate the consumption table
360 For i = 1 To UsePointParameters(0, 0)
370   Lower = UsePointParameters(i, 11) 'Lower means the earliest starting hour for
usage
380   Upper = Lower + UsePointParameters(i, 12) - 1 'and Upper means the latest hour
390   Rate = UsePointParameters(i, 2)
400   Temp = OutputData.Offset(3, i - 1).Value 'number of usage starts
410   k = Temp / UsePointParameters(i, 12) + 1 'integer number of usage starts per
hour
420   j = Int((Upper - Lower + 1) * Rnd + Lower) 'start at a random hour
430   Do
440     If j > 23 Then j = Lower
450     For m = 1 To k
460     L = 0
470     If HourlyConsumption(j, 0) <> "X" And Temp > 0 Then
480       Duration = Round(OutputData.Offset(Temp + 3, i - 1), 0)
490       If Duration <= 60 Then
500         HourlyConsumption(j, i) = HourlyConsumption(j, i) + Duration * Rate
510         OutputHourly.Offset(j, i + 3).Value = HourlyConsumption(j, i)
520        Else ' this applies for very high volume uses
530         Do
540           If j + L = 24 Then L = L - 24 'Wraps around the clock
550           HourlyConsumption(j + L, i) = HourlyConsumption(j + L, i) + _
              ((Duration >= 60) * (-60) * Rate) + ((Duration < 60) * (-Duration) *
Rate)
560           OutputHourly.Offset(j + L, i + 3).Value = HourlyConsumption(j + L, i)
570           Duration = Round(Duration - ((Duration >= 60) * (-60)) - _
              ((Duration < 60) * (-Duration)), 0)
580           L = L + 1
590         Loop While Duration > 0
600       End If
610       Temp = Temp - 1
620       j = j + L
630     End If
640     Next m
650     j = j + 1
660     If j > Upper Then j = Lower 'wrap around
670   Loop While Temp > 0
680 Next i
End Sub
```

Listing D. Subroutine performs Step 3.

assumed that the level starts the day at 50% full, then the model indicates a tank size that accommodates that limited level change. However, running the model with the selected tank size, but with the level already at say, 20% full may result in the simulated tank running dry. By stringing days together (or alternatively, just starting with a random tank level at the beginning of each day) the effect of the usage variability is fully visualized.

Figure 8 shows the results for a simulated 30 days of running, also charted in Figure 1. See also the inputs to control the simulation – tank level case selection and number of days. Clicking the button initiates the run. This simulation requires the user to propose a tank size and water generation rate. The results of those proposals are seen when the simulation is run, and it is an iterative process to adjust the decision inputs until the user is happy with the results. It is possible to write additional program steps to "optimize" the tank size and generation rate without user intervention, but this would take the user one more step away from the decision process with consequent insulation of the user's engineering judgment.

The water tank example shows how to create a model that incorporates variable input data. Whenever input data varies, consider whether it is important to model it this way by doing a sensitivity analysis. Build the model first assuming a fixed set of inputs. Then observe the effect on the results by varying those inputs individually or in groups. Consider input modeling if a there is a significant change in the results. Playing the "what if…" game often gives new insight into a system's behavior and may lead to more robust design decisions.

This simulation, using variable inputs with statistical results, is an example of a "stochastic" simulation, also called a "Monte Carlo" simulation. This type of simulation is very useful for modeling pharmaceutical processes and gives better understanding of the process than a model that uses fixed inputs (called "deterministic").

It took about eight hours to fully develop, debug, and test the example spreadsheet. This included time to formulate the problem, design the algorithm, create the worksheets, and write the VBA subroutines. Tackling the problem in steps and using a modular approach eased the creative process.

**Intermediate Results from Steps 1 and 2**

This sheet simply provides a list of the duration of uses from each use point for one day
It uses the data for usage starts minimum, maximum, and distribution from the Parameters section
and the time and distribution for each usage
The sheet is calculated and filled in with the VBA macro "UsesPerDay"

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Generated | 21,600 | liters | Use Point | | | | | |
| | | | | Consumec | 19,646 | liters | 1 | 2 | 3 | 4 | 5 | |
| | Number of Usages | | | VBA | | | Duration | | | | | |
| | | Usage Data | | | | | 2 | 2 | 12 | 18 | 20 | |
| | | | 1 | | | | 80 | 135 | 3.8 | 21.8 | 7.7 | |
| | Run 1 Day | | 2 | | | | 80 | 135 | 16 | 7.8 | 4.9 | |
| | | | 3 | | | | | | 13.5 | 21.3 | 6.1 | |
| | | | 4 | | | | | | 9.7 | 10.7 | 4.7 | |
| | | | 5 | | | | | | 17.7 | 14.8 | 3.9 | |
| | | | 6 | | | | | | 13.9 | 18.3 | 5.2 | |
| | | | 7 | | | | | | 18.9 | 13.8 | 5.4 | |
| | | | 8 | | | | | | 13.2 | 19.8 | 5 | |
| | | | 9 | | | | | | 10.6 | 12.1 | 5.3 | |
| | | | 10 | | | | | | 20.3 | 23.1 | 6.9 | |
| | | | 11 | | | | | | 10.7 | 21.4 | 6.2 | |
| | | | 12 | | | | | | 13.9 | 19 | 2.4 | |
| | | | 13 | | | | | | | 24.8 | 3.7 | |
| | | | 14 | | | | | | | 9.9 | 4.5 | |
| | | | 15 | | | | | | | 30 | 5.3 | |
| | | | 16 | | | | | | | 9.7 | 5.6 | |
| | | | 17 | | | | | | | 23.9 | 4.4 | |
| | | | 18 | | | | | | | 7.4 | 3.8 | |
| | | | 19 | | | | | | | | 3.5 | |
| | | | 20 | | | | | | | | 4 | |

Figure 5. Intermediate results worksheet for Steps 1 and 2.

**Intermediate Results from Step 3**

This sheet spreads the uses within the time of day limits parameters
The sheet is calculated and filled in with the VBA macro "ScheduleUsePoints"

| | | | Generated (liters) | Hourly Consumption | Sanitized | Consumed (liters) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1 | 2 | 3 | 4 | 5 |
| Midnight | 0 | 900 | 350 | | | | | | 350 | |
| | 1 | 900 | 340 | | | | | | 340 | |
| | 2 | 900 | 450 | | | | | | 330 | 120 |
| | 3 | 900 | 440 | | | | | | 320 | 120 |
| Run 1 Day | 4 | 900 | - | X | | | | | | |
| | 5 | 900 | - | X | | | | | | |
| | 6 | 900 | - | X | | | | | | |
| | 7 | 900 | 465 | | | | | | 300 | 165 |
| | 8 | 900 | 120 | | | | | | | 120 |
| | 9 | 900 | 2,220 | | | | 2100 | | | 120 |
| | 10 | 900 | 2,530 | | | | 2100 | 250 | | 180 |
| | 11 | 900 | 2,485 | | | 1500 | 525 | 310 | | 150 |
| | 12 | 900 | 955 | | | 500 | | 320 | | 135 |
| | 13 | 900 | 2,585 | | | | 2100 | 320 | | 165 |
| | 14 | 900 | 4,035 | | | 1500 | 2100 | 240 | | 195 |
| | 15 | 900 | 1,225 | | | 500 | 525 | 200 | | |
| | 16 | 900 | - | | | | | | | |
| | 17 | 900 | 310 | | | | | | 310 | |
| | 18 | 900 | 400 | | | | | | 400 | |
| | 19 | 900 | 350 | | | | | | 350 | |
| | 20 | 900 | 400 | | | | | | 400 | |
| | 21 | 900 | - | | | | | | | |
| | 22 | 900 | - | | | | | | | |
| | 23 | 900 | - | | | | | | | |

Figure 6. Intermediate results worksheet for Step 3.

## Further Reading


1. Albright, S.C. *VBA for Modelers: Developing Decision Support Systems Using Microsoft® Excel.* 2nd ed. South-Western College Pub; 2006.

2. Anthony's VBA Page provides help for VBA programmers. http://www.anthony-vba.kefra.com/

3. Powell S.B. and Baker K.R. *Management Science: The Art of Modeling with Spreadsheets, Excel 2007 Update.* 2nd ed. Wiley; 2008.

4. Ragsdale C. *Spreadsheet Modeling and Decision Analysis: A Practical Introduction to Management Sci-*

*ence.* 5th ed. South-Western College Pub; 2007.

5. Savage, S.L. and Danziger, J. *The Flaw of Averages: Why We Underestimate Risk in the Face of Uncertainty.* Wiley; 2009.

5. Winter Simulation Conference, www.wintersim.org.

## Excel Add-In Tools for Simulation and Analysis

1. @Risk, "Complete risk and decision analysis toolkit," http://probilitech.com/.

2. Crystal Ball, "Application Suite for Predictive Modeling, Forecasting, Simulation, and Optimization," http://www.oracle.com/appserver/business-intelligence/crystalball/.

3. Ersatz, "A Bootstrap Add-in for Microsoft Excel for Windows. It allows you to do uncertainty analysis (aka 'risk analysis,' 'Monte Carlo simulation,' 'probabilistic sensitivity analysis,' 'bootstrapping') and microsimulation in Excel," http://www.epigear.com/index_files/Ersatz.htm.

4. ModelRisk, "Best and Most Advanced Spreadsheet Sim Currently on the Market," http://www.vosesoftware.com.

5. SimTools, "Adds Statistical Functions and Procedures for doing Monte Carlo Simulation and Risk Analysis in Spreadsheets," free download from http://home.uchicago.edu/~rmyerson/addins.htm.

6. Simulación, "Fully Developed in VBA, Created to Bring a Flexible and Easy to Use Simulation Tool to Excel," English and Spanish versions, free download from http://www.ucema.edu.ar/~jvarela/.

7. XLSim 3, "A Monte Carlo Simulation Package," http://probilitech.com/.

| | A | B | C | D | E | F | G | H | I | J |
|---|---|---|---|---|---|---|---|---|---|---|
| 22 | | | | | | | | | | |
| 23 | **Results** | | | | | | | | | |
| 24 | | | | Time (hour) | Generation (l/m) | Consumption (liters) | Avg Draw Rate (l/m) | Net (liters) | Level (liters) | Percent |
| 25 | | | | 0 | 900 | 350 | 6 | 550 | 13,800 | 46% |
| 26 | | Run 1 Day | | 1 | 900 | 340 | 6 | 560 | 14,360 | 48% |
| 27 | | | | 2 | 900 | 450 | 8 | 450 | 14,810 | 49% |
| 28 | | | | 3 | 900 | 440 | 7 | 460 | 15,270 | 51% |
| 29 | | | | 4 | 900 | - | - | 900 | 16,170 | 54% |
| 30 | | | | 5 | 900 | - | - | 900 | 17,070 | 57% |
| 31 | | | | 6 | 900 | - | - | 900 | 17,970 | 60% |
| 32 | | | | 7 | 900 | 465 | 8 | 435 | 18,405 | 61% |
| 33 | | | | 8 | 900 | 120 | 2 | 780 | 19,185 | 64% |
| 34 | | | | 9 | 900 | 2,220 | 37 | (1,320) | 17,865 | 60% |
| 35 | | | | 10 | 900 | 2,530 | 42 | (1,630) | 16,235 | 54% |
| 36 | | | | 11 | 900 | 2,485 | 41 | (1,585) | 14,650 | 49% |
| 37 | | | | 12 | 900 | 955 | 16 | (55) | 14,595 | 49% |
| 38 | | | | 13 | 900 | 2,585 | 43 | (1,685) | 12,910 | 43% |
| 39 | | | | 14 | 900 | 4,035 | 67 | (3,135) | 9,775 | 33% |
| 40 | | | | 15 | 900 | 1,225 | 20 | (325) | 9,450 | 32% |
| 41 | | | | 16 | 900 | - | - | 900 | 10,350 | 35% |
| 42 | | | | 17 | 900 | 310 | 5 | 590 | 10,940 | 36% |
| 43 | | | | 18 | 900 | 400 | 7 | 500 | 11,440 | 38% |
| 44 | | | | 19 | 900 | 350 | 6 | 550 | 11,990 | 40% |
| 45 | | | | 20 | 900 | 400 | 7 | 500 | 12,490 | 42% |
| 46 | | | | 21 | 900 | - | - | 900 | 13,390 | 45% |
| 47 | | | | 22 | 900 | - | - | 900 | 14,290 | 48% |
| 48 | | | | 23 | 900 | - | - | 900 | 15,190 | 51% |
| 49 | | | | | | | | | | |
| 50 | | | Results for 1 Day | Total, liters | 21,600 | 19,660 | | | | |
| 51 | | | | Minimum | 900 | - | - | (3,135) | 9,450 | 32% |
| 52 | | | | Maximum | 900 | 4,035 | 67 | 900 | 19,185 | 64% |
| 53 | | | | Average | 900 | 819 | 14 | 81 | 14,275 | 48% |

Figure 7. Results for one simulated day.

| | A | B | C | D | E | F | G | H | I | J |
|---|---|---|---|---|---|---|---|---|---|---|
| 49 | | | | | | | | | | |
| 50 | | | Results for 1 Day | Total, liters | 21,600 | 19,660 | | | | |
| 51 | | | | Minimum | 900 | - | - | (3,135) | 9,450 | 32% |
| 52 | | | | Maximum | 900 | 4,035 | 67 | 900 | 19,185 | 64% |
| 53 | | | | Average | 900 | 819 | 14 | 81 | 14,275 | 48% |
| 54 | | | | | | | | | | |
| 55 | | | | | | | | | | |
| 56 | | | Results for 30 days | | Generation (liters) | Consumption (liters) | Avg Draw Rate (l/m) | Net (liters) | Level (liters) | % Full |
| 57 | | | | Minimum Daily | 20,935 | 5,935 | | | | |
| 58 | | | | Maximum Daily | 21,600 | 29,615 | | | | |
| 59 | | | | Average Daily | 21,578 | 20,056 | | | | |
| 60 | | | | | | | | | | |
| 61 | | | | Minimum Hourly | 235 | - | - | (4,050) | 2,170 | 7% |
| 62 | | | | Maximum Hourly | 900 | 4,950 | 83 | 900 | 30,000 | 100% |
| 63 | | | | Average Hourly | 899 | 836 | 14 | 63 | 16,188 | 54% |
| 64 | | | | | | | | | | |
| 65 | | | | | | | | | | |
| 66 | **Simulation Parameters** | | | | | | | | | |
| 67 | | | | Case 1: | Tank starting level is a fixed value | | | | | |
| 68 | | | | Case 2: | Tank level is carried over from previous day | | | | | |
| 69 | | | | | | | | Run Multiple Days | | |
| 70 | | | | Which case: | 2 | | | | | |
| 71 | | | | Number of days to simulate: | 30 | | | | | |

Figure 8. Results for many simulated days.

## About the Author

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## Europe

### *Denmark*

#### Danish Medicines Agency Publishes Notification to Medicines Manufacturers about Reduced Testing of Starting Materials[1]

In response to some uncertainty about the possibility of using reduced testing of raw materials, including Active Pharmaceutical Ingredients (API), the Danish Medicines Agency outlined the conditions for introducing reduced testing of raw materials at companies that manufacture finished products in Denmark.

To introduce reduced testing of raw materials, including APIs, it is generally a condition that this option is accounted for either in the marketing authorization application for the medicine concerned or in connection with a subsequent application for a change of the marketing authorization (variation application).

However, the European pharmaceutical authorities have different views on the conditions required to introduce reduced testing of raw materials at manufacturers of finished products. The Danish Medicines Agency has therefore taken steps to ensure that this matter is handled at EU level.

Until the European pharmaceutical authorities have reached a common understanding, the Danish Medicines Agency accepts reduced testing of raw materials if the qualified person at the finished product manufacturer based on a risk assessment has developed and documented a plan for ongoing testing of raw materials.

### *European Union*

#### Eighth Supplement to the 6th Edition European Pharmacopoeia Takes Effect[2]

Supplement 6.8 to the 6th Edition European Pharmacopoeia and its cumulative Internet and CD ROM versions became effective 1 July 2010. The list of current monographs included in the national pharmacopoeia has been updated by including the additions and changes required under Supplement 6.8. New terms have been added to the Standard Terms list.

#### European Medicines Agency Launches New Web Site[3]

The European Medicines Agency unveiled its new corporate Web site at www.ema.europa.eu. The site has been completely redesigned and rebuilt to optimize usability for the Agency's key online audiences and build on existing activities to improve openness and transparency.

#### European Medicines Agency Publishes Policy on Communicating Safety Issues for Human Medicines[4]

A new policy on communicating safety-related issues on medicines for human use has been published by the European Medicines Agency. The policy describes the various communication tools that are used. This includes the criteria for communicating on specific issues, the preparation and publication of communication material (including roles and responsibilities), the timing of the publication, how they work with the EU Regulatory Network and how they share communications material with other regulatory authorities both in Europe and beyond.

#### European Medicines Agency and European Commission Start Reflection Process on Way Forward for the Agency and the Network[5]

The European Medicines Agency and the European Commission held a joint one-day conference on 30 June 2010 to discuss the outcome of the recent evaluation of the Agency and how the findings of the exercise can be used in preparing the Agency for future challenges.

In 2009, the European Commission engaged Ernst & Young to carry out a comprehensive assessment of the effectiveness and efficiency of the European Medicines Agency and the European medicines system as a whole in delivering high-quality scientific opinions on medicines for human and veterinary use. Following publication of the outcomes of the evaluation in April 2010, the conference brought together some 150 partners and key stakeholders from the European Commission, the national competent authorities for medicines regulation in the EU Member States, patients and healthcare professional associations and the pharmaceutical industry associations. The conference focused on the architecture of the Agency's scientific forums, ways to assure long-term availability of scientific resources of the network and the coordinating role of the Agency. Reflection on issues specific for veterinary medicines and an exchange of views about the funding of the Agency concluded the discussion on outcomes of the evaluation.

### *Finland*

#### Generic Substitution Appears to Have Increased Competition in the Finnish Pharmaceutical Market[6]

A comparison of average pharmacy sales before and after generic substitution (in 1995–2002 and 2004–2008) showed that both the number of companies marketing pharmaceuticals and the number of pharmaceutical brands increased by about 25%, even though the number of active substances remained almost unchanged. However, the indicators used in the comparison showed that the increase actually started before the generic substitution system was introduced.

Wholesale pharmaceutical sales in Finland totalled about 2.7 billion euros in 2008. As compared with the situation in 1995, pharmacy sales had increased by 35% (hospital sales by 23%), the number of active substances by 19% (20%), the number of brands 50% (30%) and the number of packages 29% (11%). The number of active substances increased steadily between 1995 and 2008, and generic substitution does not appear to have influenced this trend.

The data are based on a poster by Henna Kannisto and Vesa Jormanainen, presented at the European Conference on Health Economics 2010 (ECHE 2010) in Helsinki on 7 to 10 July 2010.

### *Germany*

#### BfArM Updates Content Management System – Several Web Site Links Change[7]

Due to a technical update of the underlying content management system, sever-

al Web site and RSS links have changed. Please check your bookmarks.

### *Iceland*

#### The Icelandic Medicines Agency Has Moved to New Premises[8]

The new address for the Icelandic Medicines Agency is Vínlandsleið 14, 113 Reykjavík.

### *Netherlands*

#### Dutch Medicines Evaluation Board Publishes Annual Report[9]

The Dutch Medicines Evaluation Board has presented its Annual Report 2009. The theme of this report is "the life cycle of a medicine is our care." This refers to the fact that development, assessment and pharmacovigilance of medicines is a cyclical process.

### *Sweden*

#### Sweden's MPA is Reorganizing[10]

As a result of the reorganization, many employees will be changing rooms. The new organization, with partly new units, will be in operation from 1 September 2010.

### *United Kingdom*

#### Britain's MHRA Annual Report and Accounts 2009/10[11]

The MHRA Annual Report and Accounts 2009/10 were laid in Parliament on 8 July 2010. The Annual Report and Accounts give a selective overview of the events that have had most impact on the Agency during the past year, highlighting the landmark events and the safety issues the Agency has had to deal with, including the rise and global spread of pandemic influenza H1N1.

#### Britain's Heads of Medicines Agencies Drafts Strategy 2011-15 Consultation[12]

The Heads of Medicines Agencies (HMA) has launched a consultation on its draft strategy for the period 2011-2015. The aim of the consultation process is to give the HMA's stakeholders an opportunity to feed into the strategy by commenting on existing content, and also by suggesting new areas for inclusion if they feel that anything substantial has been missed. The consultation will run for three weeks from 9 July to 30 July 2010. Comments on the draft strategy should be sent to hma-strategy-consultation@infarmed.pt.

#### Britain's MHRA Publishes New Enforcement Strategy[13]

A new enforcement strategy has been published by the Inspection, Enforcement and Standards Division of the MHRA. The document sets out the MHRA strategy for the enforcement of medicines and medical devices legislation. It reflects Government Better Regulation initiatives, as well as the recommendations contained in the Hampton Review, and the Regulators' Compliance Code, which set out the principles and characteristics to be applied in the enforcement of regulations.

As part of the strategy, the MHRA also is actively considering extending its existing toolkit of sanctions, based on the recommendations of the Macrory Review, which found that the range of sanctions available to regulators was too limited and predicated on criminal prosecution.

## Asia/Pacific

### *Australia*

#### Review of the Australian Regulatory Guidelines for Over-The-Counter Medicines[14]

The TGA has begun a project which will review and amend the current Australian Regulatory Guidelines for Over-The-Counter Medicines (ARGOM), published in 2003. This project will bring the ARGOM up to date to reflect the current TGA regulatory environment and business practices for Over-The-Counter (OTC) Medicines. The project is called ARGOM Review Project. The ARGOM 2003 is being updated to:

- ensure that the guidelines reflect current legislative regulatory requirements;
- streamline processes where possible;
- improve the usability and consistency of the information available to stakeholders in relation to the Australian regulatory requirements for OTC medicines;
- provide increased transparency about decision making processes; and
- clarify post-market monitoring of OTC medicines.

It is anticipated that, during the ARGOM update process, the TGA will initiate additional longer-term projects to consider particular aspects of the current regulatory requirements and business processes related to OTC medicine regulation. The updated ARGOM will be drafted in liaison with industry stakeholders. The TGA will work with the following organizations:

- the Australian Self-Medication Industry (ASMI);
- the Generic Medicines Industry Association (GMiA);
- the Australian Association of Cosmetic Chemists (ASCC); and
- the Advocate for the Consumer, Cosmetic, hygiene and specialty products sector (ACCORD).

Each new draft of an ARGOM chapter will be published on this Web site to enable broader public consultation. ARGOM 2003 will remain as the guidance document until it can be fully replaced by the updated ARGOM.

### *China*

#### China's SFDA and the Ministry of Health to Take Further Actions to Curb Non-drug Substance Being Simulated as Drug[15]

In order to crack down on the illegal activities of non-drug substance being simulated as drug and safeguard the public's health, recently, the State Food and Drug Administration and the Ministry of Health jointly issued a notice on further taking actions to curb non-drug substance being simulated as drug, determining to intensively carry out the second phase actions on curbing non-drug substance being simulated as drug from June to the end of October this year.

The second phase actions will include continuous consolidation of the achievements in the first phase, tracing and investigation of the origins of discovered problems and serious punishment in ac-

cordance with laws. Special efforts shall be made to regulate the use of drugs in grassroots medical and health institutions and private medical institutions, regulate drug distribution and use and ensure drug safety for the public.

### SFDA Requires Re-licensing the Enterprises Engaged in the Production and Distribution of Pharmaceutical Precursor Chemicals[16]

In order to strengthen the supervision of pharmaceutical precursor chemicals and prevent them from flowing into illegal channels, Provisions for Pharmaceutical Precursor Chemicals (Order No.72 of the Ministry of Health) was issued by the Ministry of Health and went into effect on May 1, 2010. On June 4, 2010, the State Food and Drug Administration (SFDA) issued a notice, requiring that enterprises approved by the SFDA to be engaged in the production and distribution of pharmaceutical precursor chemicals before the Provisions took effect shall reapply for the production and distribution licenses within three months as of the issuing date of the notice.

### SFDA and the Ministry of Health Jointly Launch Supervision and Examination of Vaccine Supervision[17]

In order to enforce the quality supervision over the biological vaccines, improve the quality assurance in vaccine production, circulation and inoculation and ensure safety and effectiveness of the vaccine, the State Food and Drug Administration and the Ministry of Health decided to jointly launch the supervision and examination program to the supervision of the vaccine production, circulation and inoculation and the implementation of relevant measures and recently issued a notice on the relevant issues.

This supervision and examination program is launched specially for the supervision enforcement of the local food and drug administrations and the health administrative departments in the vaccine production, circulation and inoculation, to learn about the actual situation of the supervision over the vaccine production, circulation and usage, specify the weakness and problems in the process, and deliberate measures enforcing the vaccine supervision. The program started in June 2010.

### SFDA Issues Announcement on Relevant Issues Concerning the Implementation of 2010 Chinese Pharmacopoeia[18]

The 2010 edition of Chinese Pharmacopoeia has been promulgated by the Ministry of Health and will be enforced from 1 October 2010. The State Food and Drug Administration recently issued an announcement on relevant issues concerning the implementation of 2010 Chinese Pharmacopoeia.

### Singapore's Health Science Authority Signs Memorandum of Understanding with Korea Food and Drug Administration and Memorandum of Information Exchange with Japan's Pharmaceutical and Medical Device Agency[19]

In signing an MOU, the HSA and the KFDA seek to protect the public health and safety of their respective nations by ensuring the safety, quality and efficacy of health products manufactured in, imported into and exported from Singapore and Korea. This MOU formalizes the bilateral exchanges and deepens the engagement of both agencies in the area of health products regulation.

In signing a Memorandum of Information Exchange with Japan, the participants intend to cooperate through exchanging more regulatory information including advance drafts of legislation and/or regulatory guidance documents as well as information related to authorization and supervision of medical products for human use in accordance with their respective national laws and regulations. Since this type of information may include information of a non-public nature, participants assure that they will keep the information exchanged confidential.

## North/South America

### *Canada*

### Health Canada Publishes Draft Guidance Document – Labeling of Pharmaceutical Drugs for Human Use[20]

The purpose of this document is to provide guidance to sponsors to facilitate compliance with the labeling requirements pursuant to sections 3, 9, and 10 of the Food and Drugs Act as well as related provisions of the Food and Drug Regulations, the Controlled Drugs and Substances Act, and its related Regulations including the Narcotic Control Regulations, Parts G and J of the Food and Drug Regulations and the Benzodiazepines and Other Targeted Substances Regulations. Once finalized, adherence to this guidance is expected to support the safe and effective use of drugs by health care professionals, patients, and consumers.

### *USA*

### FDA Requests Comments on Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements[21]

FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Submit either electronic or written comments on the collection of information by September 13, 2010.

### FDA Issues Draft Guidance on the Judicious Use of Medically Important Antimicrobials in Food-Producing Animals[22]

This draft guidance outlines the FDA's current thinking on strategies to assure that antimicrobial drugs that are important for therapeutic use in

humans are used judiciously in animal agriculture. The FDA acknowledges the efforts to date by various veterinary and animal producer organizations to institute guidelines for the judicious use of antimicrobial drugs, but the agency believes additional steps are needed.

The draft guidance summarizes a number of published reports on antimicrobial resistance and states that the overall weight of evidence available to date supports the conclusion that using medically important antimicrobial drugs for production or growth enhancing purposes (i.e., non-therapeutic or subtherapeutic uses) in food-producing animals is not in the interest of protecting and promoting the public health.

### FDA Marks First Anniversary of Tobacco Control Act[23]

Under the Tobacco Control Act, the U.S. Food and Drug Administration obtained authority to regulate tobacco products, with a special emphasis on preventing their use by children and youth and reducing the impact of tobacco on public health. The Act authorizes the FDA, among other things, to set tobacco product standards, require product listing and registration, revise health warning labels, create manufacturing standards, and review products intended to modify the risk of tobacco use.

Since the law's passage, the FDA has taken several important steps in a coordinated effort to prevent children from becoming the next generation of Americans to die prematurely from tobacco use and ultimately reducing death and disease associated with tobacco use.

### FDA and Other Federal Agencies Collaborate to Improve Chemical Screening[24]

The US FDA has joined the U.S. Environmental Protection Agency, the National Institute of Environmental Health Sciences National Toxicology Program and the National Institute of Health Chemical Genomics in the Tox21 collaboration. The Tox21 collaboration merges federal agency resources (research, funding and testing tools) to develop ways to more effectively predict how chemicals will affect human health and the environment. The collaboration was established in 2008 to develop models that will be able to better predict how chemicals will affect humans. FDA will provide additional expertise and chemical safety information to improve current chemical testing methods.

## International

### *World Health Organization*

### WHO Adopts GMP for APIs from the ICH Q7 Guideline – additional explanations added[25]

During the revision of the WHO's Technical Report Series in June 2010, "Good manufacturing practices for active pharmaceutical ingredients" was revised. This revised Annex 2 replaces the annex dating back to the year 1992 and is identical to the ICH Q7 Guideline. However, the WHO added two more appendices to this Annex 2:

- A list with references to a number of corresponding WHO guidelines or Technical Report Series
- A list of explanations and clarifications on various paragraphs of Annex 2

It is a fact that the wording of Annex 2 is absolutely identical to that of the ICH Q7 Guideline. However, the recently conducted revision of Part II of the EU GMP Guide, which came into force on 31 July 2010 and will afterwards no longer be identical to ICH Q7, has not been taken into account. This means that Paragraph 2.19 requiring the application of the quality risk management principles, which has recently been introduced into Part II, will not be present in the new WHO Annex 2.

### *PIC/S*

### Taiwan's Food and Drug Administration, the United Kingdom's Veterinary Medicines Directorate, and New Zealand's Medicines and Medical Safety Authority Apply for PIC/S Membership[26]

With the application of TFDA, four Asian Competent Authorities are currently being assessed for joining PIC/S. Other Asian applications are expected, soon. Recently, the Health Department of Hong Kong also announced its intention to apply for PIC/S membership in the near future. According to PIC/S rules, several Competent Authorities from the same country can apply for membership.

After the accession to PIC/S of the Czech Institute for State Control of Veterinary Biologicals and Medicines (ISCVBM) in 2005 and the French Agency for Veterinary Medicinal Products (ANMV) in 2009, UK's VMD is the third veterinary authority to apply for PIC/S membership.

### International Collaboration for the Quality of APIs[27]

PIC/S was invited by the European Commission to participate in an initiative for enhanced international co-operation in the field of APIs. PIC/S believes that the proposal is a recognition of its important role in the field of APIs, in particular with regard to:

- the assessment of Competent Authorities;
- training (through the PIC/S Expert Circle on APIs) and;
- sharing of information related to APIs inspections.

On 22 June 2010, the PIC/S Chairman sent a positive response to the Commission regarding PIC/S' involvement.

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# Discover "What's Next" at Annual Meeting

How will we know "what's next" in our industry? How do we prepare for it? **Discovering What's Next: Reality, Retooling, Growth** is the theme of this year's ISPE Annual Meeting, to be held 7-10 November in Orlando, Florida, USA.

Attendees will hear from regulators and industry leaders and get critical first-hand understanding and information needed to face the future successfully. The following are highlights of what to expect at the Keynote Session and in education and training:

## Keynote Session

- This year's Keynote Speaker is **Bruce G. Gellin, MD, MPH,** Deputy Assistant Secretary for Health and Director of the National Vaccine Program Office (NVPO), Office of Public Health and Science, Office of the Assistant Secretary for Health, US Department of Health and Human Services. Dr. Gellin is one of our nation's top experts on vaccines and infectious diseases. NVPO was created by Congress to provide leadership and coordination among federal agencies and other immunization stakeholders, including states and municipalities, health care providers, and private-sector entities such as vaccine manufacturers.

- The Keynote session also will feature a speaker from the **Disney Institute**. In "Leading through Turbulent Times," attendees will explore the proven best practices that underlie the Disney approach to sustaining excellence during turbulent times and be provided with creative strategies to weather the economic climate and effectively meet the challenges of today's business environment. These strategies can easily be adapted to any organization or industry to help retain customers, engage employees, and position an organization for future ongoing success.

- The **Overall Winner of the 2010 Facility of the Year Awards** program will be announced. The Overall Winner will be selected from this year's six Category Winners as determined by an independent panel of global representatives from the pharmaceutical design, construction, and manufacturing sectors. This year's Category Winners include:

  - Biogen Idec
  - Genentech
  - MannKind Corporation (two categories)
  - Pfizer Biotechnology Ireland
  - Pfizer Ireland Pharmaceuticals


## Education Sessions

Education sessions will be featured in each of the following tracks. Please visit www.ispe.org/2010annualmeeting for a listing and detailed descriptions of sessions in each track.

- Facilities and Equipment
- Outsourcing
- Retooling for Operational Excellence
- Successful Delivery
- Regulatory
- Young Professionals
- Information Systems
- Hot Topics
- Sustainability
- Project Management
- Investigational Products

## Training Courses

The following Training Courses will be available at Annual Meeting. Please visit http://www.ispe.org/2010annualmeeting for a detailed description of each course.

- Basic Principles of Computerized Systems Compliance: Applying the GAMP® 5 Guide: A Risk-based Approach to Compliant GxP Computerized Systems (T07)
- Cleaning Validation Principles (T17)

# ISPE to Develop PQLI Guides

Product Quality Lifecycle Implementation® (PQLI®) is ISPE's global industry initiative for a practical approach to implementation of International Conference on Harmonization (ICH) guidances Q8 (R2), Pharmaceutical Development; Q9, Quality Risk Management; and Q10, Pharmaceutical Quality System, as well as the more recently initiated topic, Q11, Development and Manufacture of Drug Substances.


Through PQLI, ISPE is spearheading the effort to provide "how to" Good Practice Guides and training materials supported by case studies for the implementation of these guidelines, including a better understanding of the "enhanced, Quality by Design (QbD) approach." Roll out of the first in a series of ISPE PQLI Guides is on track for a late 2010 release and will continue through 2011.

The first ISPE PQLI Guide to be released, "Overview of Product Design, Development, and Realization: A Science- and Risk-Based Approach to Implementation," will provide an outline of the application of Quality by Design (QbD) to product realization and acts as a top level roadmap for subsequent separate PQLI Good Practice Guides, covering various topics.

Subsequent PQLI Good Practice Guides will describe:

- the relationship possibilities between Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs),
- options and opportunities for using design space, and
- development of control strategies.

A small molecule case study developed by a PQLI team will be used to exemplify some of the options and this will be issued as a separate Guide. Subsequent Guides will be produced on important topics relevant to introduction and operation of a modern pharmaceutical quality system particularly supporting products and processes developed using enhanced approaches. Consideration also will be given to developing Guides for existing products, and small molecule and biotechnology-derived drug substances related to the ongoing ICH topic Q11, Development and Manu¬facture of Drug Substances.

**For further information, visit the PQLI section at www.ISPE.org.**

# ISPE-CCPIE China Conference 2010 to Focus on the Internationalization of China's Pharmaceutical Industry

The ISPE-CCPIE China Conference will be held 26-29 October at the China National Conference Center in Beijing. The conference is a joint effort between ISPE and the China Center for Pharmaceutical International Exchange (affiliated with the State Food and Drug Administration of China). This year's theme is Facilitating the Internationalization of China's Pharmaceutical Industry. Sessions will focus on how to further facilitate the internationalization of China's pharmaceutical industry and understanding of WHO and new GMP regulation in China, Europe, and the USA. Topics will include:

- Cleaning Validation
- Solid Dosage Forms
- PQLI®
- Technology Transfer from R&D to Production
- Commissioning and Qualification
- Sterile Drug Manufacture
- GAMP®

For more information about the Conference, please visit: www.ispe.org/2010chinaconference or contact ISPE China china@ispe.org.

ENGINEERING PHARMACEUTICAL INNOVATION

# *Pharmaceutical Engineering* Now Accepting Articles for 2011

## Publish your work in *Pharmaceutical Engineering*, the Global Information Source for Pharmaceutical Manufacturing Professionals

ISPE's recognized industry magazine, *Pharmaceutical Engineering*, is looking for industry case studies demonstrating advanced technologies, manufacturing efficiencies, and solutions to regulatory compliance issues with a global perspective.

Articles must be noncommercial in nature, describe new developments or work, and significantly contribute to the body of knowledge relating to pharmaceutical manufacturing, quality management, and technology.

*Pharmaceutical Engineering* is now accepting articles for its 2011 Editorial Calendar. For further information, please visit us on the Web site at www.ISPE.org/pharmaceuticalengineering, and then connect to the following links: How to Submit an Article, and then Author Guidelines.

## 2011 Editorial Calendar

### JANUARY/FEBRUARY 2011

*Theme: Risk Management and Quality Systems*

Manuscripts Due: 4 Oct 2010 Publishes: 21 Jan 2011

Articles in this issue will include implementation of risk management and quality systems through the use of ASTM 2500, GAMP, Risk-MaPP, ICH Q9 and Q10 methodology and standards. Following the release of the much anticipated ISPE Baseline® Guide, Risk-Based Manufacturing of Pharmaceutical Products (Risk-MaPP), where principles are laid out for a scientific risk-based approach to managing the risk of cross contamination to achieve and maintain an appropriate balance between product quality and operator safety. Articles will include case studies of how companies implemented these principles and how regulatory bodies globally have reacted to this approach. Articles and case studies also will include risk management relating to laboratories, facilities, utilities, and R&D as well as cross contamination and operator exposure. Note: The January/February issue will also feature the 2010 FOYA winner.

### MARCH/APRIL 2011

*Theme: Disposables and Sterile Manufacturing*

Manuscripts Due: 1 Nov 2010 Publishes: 18 Mar 2011

This issue will focus on Disposables. The use of single-use disposables is becoming a major factor in biotechnology manufacturing. The disposable issues of waste management and bulk refuse can be discussed. Focus on disposable technologies may include bag systems, filters, connectors, aseptic transfer, controlled freeze-thaw, tubing, and many other types of equipment for bioprocessing in single-use format.

### MAY/JUNE 2011

*Theme: Green Pharma*

Manuscripts Due: 3 Jan 2011 Publishes: 20 May 2011

This issue will cover environmental and energy issues as it relates to the pharmaceutical industry. Topics that may be covered include sustainability, LEED design, energy optimization and efficiency, waste reduction, disposables, manufacturing waste handling, recycling opportunities, and lessons learned from other industries.

### JULY/AUGUST 2011

*Theme: Computer and Control Systems*

Manuscripts Due: 2 Mar 2011 Publishes: 22 Jul 2011

This issue will focus on computers and controls. The advent of sophisticated tools has depended on the usage and integration of computers, computerized systems, and control strategies to enhance production. Mechanisms for the automation of manufacturing are dependent of the data produced, archived, and retrieved. The Pharmaceutical and Biotechnology industry is more dependent on computers, data, and controls strategies than ever before. Articles can be focused on computers, computer validation, GAMP, CGMP, control schemes, MES, LIMS, data acquisition, data management, data warehousing, data integration, discernible computerized records, etc.

### SEPTEMBER/OCTOBER 2011

*Theme: Project Management and Operational Excellence*

Manuscripts Due: 2 May 2011 Publishes: 23 Sep 2011

This issue will focus on Project Management and Operational Excellence. Effective implementation of Project Management and Operational Excellence programs and tools is an ongoing issue in which many organizations are focusing their efforts. Approaches, tools, case-studies and creative ideas can be shared in this issue. Project Management topics could include case studies of success projects, creative implementation of project management tools, project execution tools, organization of project management departments and processes or other aspects of the Project Management profession. Operational Excellence topics could range from instruction on the selection, implementation and use of measurement mechanisms and key process indicators to program-level subjects such as implementation of electronic batch records, six-sigma or other lean programs at a site, company or enterprise-wide level.

### NOVEMBER/DECEMBER 2011

*Theme: Utilities*

Manuscripts Due: 1 Jul 2011 Publishes: 21 Nov 2011

This issue will be centered on Critical Utilities used in Pharmaceutical and Biotechnology facilities. Innovations and new approaches are being instituted by reducing energy costs, minimizing carbon footprints, and consolidation of older systems. Integration and design with intrinsic usage of critical utilities complements the manufacturing environment. Articles can be submitted on pharmaceutical waters, gases, compressed air, electrical, cost savings, green usage, recycle, reclaim, and reuse of critical utilities.

# Open Volunteer Positions

You can take part in helping drive innovation in pharmaceutical manufacturing by volunteering your time to ISPE programs, activities, and committees. While one of the most common ways to share your knowledge and expertise is to volunteer on an ISPE committee, other possibilities to volunteer include:

- Writing or reviewing a technical article
- Participating in a focus group
- Responding to a survey
- Serving in a leadership position or being active on an Affiliate or Chapter Board or Committee

The following volunteer positions are available. Please visit www.ispe.org/open_volunteer_positions for more details and contact information.

- New Search Engine Review and Feedback
- Subject Matter Experts - CPIP Exam Item Writer
- Online Training Course Content Developer
- Membership Development Committee (MDC) Member
- Marketing Intelligence Subcommittee
- Recruitment Marketing Position
- Volunteers Subcommittee
- Value Proposition Subcommittee
- Critical Utilities COP
  - Webinar Coordinators
  - Knowledge Brief Writers
  - Online Community Facilitators
- Engineering Standards Benchmarking COP
  - Survey Data Analysis Task Team
  - Logistic Task Team
- Operations Management COP
  - Improvement Tools Task Team
  - Operations Strategies Task Team
  - Performance Indicators Task Team
  - Supply Chain Task Team
- COP Online Facilitators
  - API
  - Disposables
  - ESB
  - GCLP
  - OSD
  - Packaging
  - PPD
  - SPP
  - Sustainable Facilities
- Calling All Young Professionals
  - Young Professionals

# New to the Industry?

ISPE launched a new section under the Career Solutions category at www.ISPE.org featuring resources for young professionals or anyone new to the industry. The section includes links to resources on fundamental knowledge, networking, and career development.

ISPE also has developed a Young Professionals Committee (YPC) to promote young professional involvement in ISPE locally and internationally. The 2010 ISPE Annual Meeting, 7-10 November in Orlando, Florida, USA will feature a Young Professionals track that will include sessions that are applicable across the industry and contain information that can be beneficial to individuals at any stage in their career, but are of particular benefit to professionals who are new to the industry.

For further information on the Young Professionals track, **visit http://www.ispe.org/2010annualmeeting**.

For more information on Young Professionals and other networking resources, visit **http://www.ispe.org/newtoindustry/buildyournetwork**.

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## Architects, Engineers – Constructors

CRB Consulting Engineers, 7410 N.W Tiffany Springs Pkwy., Suite 100, Kansas City, MO 64153. (816) 880-9800. See our ad in this issue.

EI Associates, 8 Ridgedale Ave., Cedar Knolls, NJ 07927. (973) 775-7777. See our ad in this issue.

NNE Pharmaplan, Vandtarnsvej 108-110, 2860 Søborg, Denmark. +45 44447777. See our ad in this issue.

Pharmadule, 500 Hills Dr., Suite 120, Bedminster, NJ 07921. (908) 470-1023. See our ad in this issue.

## BioProcess Manufacturing

Alfa Laval Inc., 5400 International trade Dr., Richmond, VA 23231. (804) 222-5300. See our Ad in this issue.

## Cleanroom Products/Services

AES Clean Technology, 422 Stump Rd., Montgomery, PA 18936. (215) 393-6810. See our ad in this issue.

Perfex Corporation, 32 Case St., Poland, NY 13431. (800) 848-8483. See our ad in this issue.

Plascore, 615 N. Fairview, Zeeland, MI 49464. (800) 630-9257. See our ad in this issue.

## Consulting

NNE Pharmaplan, Vandtarnsvej 108-110, 2860 Søborg, Denmark. +45 4444 7777. See our ad in this issue.

## Containment

Esco, 21 Changi South Street 1, 486 777 Singapore. +65 65420833. See our ad in this issue.

## Dust Collectors

Camfil Farr Air Pollution, 3505 S. Airport Dr., Jonesboro, AR 72401. (866) 530-5474. See our ad in this issue.

## Employment Search Firms

Jim Crumpley & Associates, 1200 E. Woodhurst Dr., Bldg. B-400, Springfield, MO 65804. (417) 882-7555. See our ad in this issue.

## Instrumentation

Ametek, 37 N. Valley Rd., Bldg. 4, P.O. Box 1764, Paoli, PA 19301. (610) 647-2121. See our ad in this issue.

Hach Ultra Company., 5600 Lindbergh Dr., Loveland, CO 80539. (970) 663-1377. See our ad in this issue.

## Life Science Solutions

Telstar, Josep Taapiolas 120, 3 Bajo, 08223 Terrassa Barcelona, Spain. +34 0937361600. See our ad in this issue.

## Marking, Coding and Package Printing

Videojet Technologies Inc., 1500 Mittel Blvd., Wood Dale, IL 60191. (630) 860-7300. See our ad in this issue.

## Micro Leak Detection Machines

Bonfiglioli Pharma Machinery, Via Rondona, 31, 44018 Vigarano Pieve (Fe), Italy. Tel: +390532715631 Fax: +390532715625 WEB: www.bonfiglioli pharma.com Email: h.carbone@bonfiglioliengineering.com. Manufactures of Laboratory or High Speed Leak Testing Machines for ampoules, vials, blister packs, BFS, HDPE containers and any other type of pharmaceutical packaging.

## Packaging

Bosch Packaging Technology, 8700 Wyoming Ave. N., Minneapolis, MN 55445. (763) 424-4700. See our ad in this issue.

## Passivation and Contract Cleaning Services

Cal-Chem Corp., 2102 Merced Ave., South El Monte, CA 91733. (800) 444-6786. See our ad in this issue.

## Processing Systems

Intelligen, 2326 Morse Ave., Scotch Plains, NJ 07076. (908) 654-0088. See our ad in this issue.

Pharmaceutical Online, 5340 Fryling Rd., Suite 101, Erie, PA 16510. (814) 897-7700. See our ad in this issue.

## Processing Systems (cont.)

Software Element, 14000 Tahiti Way, #313, Marina del Rey, CA 90292. (310) 880-5459. See our ad in this issue.

## Rupture Discs

Fike Corp., 704 SW 10th St., Blue Springs, MO 64015. (816) 655-4546. See our ad in this issue.

## Sterile Products Manufacturing

Bausch + Stroebel Machine Company, Inc., 21 Commerce Dr., P.O. Box 206, North Branford, CT 06471. (203) 484-9933. See our ad in this issue.



## Tanks / Vessels

Safety Storage, Inc. 855 N. 5th St., Charleston, IL 61920. (800) 344-6539. See our ad in this issue.

## Validation Services

Commissioning Agents, Inc., 1515 N. Girls School Rd., Indianapolis, IN 46214. (317) 710-1530. See our ad in this issue.

Emerson, 8000 W. Florissant Ave., St Louis, MO 63136. (314) 553-2000. See our ad in this issue.

GxP Manager, 74 Rue de Bonnel, 69003 Lyon, France. +33 042610810. See our ad in this issue.

Pharmadule, DanviksCenter 28, SE – 131 30 Nacka, Sweden. + 46 858742000. See our ad in this issue.

## Valves

Gemu GmbH & Co., Fritz-Mueller-Str. 6-8, D-74653 Ingelfingen, Germany. +49 7940123-0. See our ad in this issue.

## Water Treatment

Elettracqua Srl, Via Adamoli 513, 16141 Genova, Italy. +39 0108300014. See our ad in this issue.

MECO, 12505 Reed Rd., Suite 100, Sugar Land, TX 77478. (800) 421-1798. See our ad in this issue.

Siemens AG, I IA VMM P Siemensallee 84, 76187 Karlsruhe, Germany. +49 7215952591. See our ad in this issue.

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