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Capability of Filling Systems to Dispense Micro-Doses of Liquid Pharmaceutical Product

This article presents a study to determine the accuracy and precision of four major liquid dosing systems running at high speeds.

by Al Peterson, Eric Isberg, and Alison Schlicht

Introduction

The potency of new drugs continues to increase, particularly in the area of biopharmaceuticals and other biotech drugs. An increase in drug potency often results in a decrease in the volume required per dose. Therefore, equipment used for final filling is being used to fill decreasing volumes of liquid pharmaceuticals. It is not uncommon to dose liquid volumes below 1.0 ml using high speed filling systems. Another strong trend is the filling of parenteral liquid pharmaceuticals directly into final administration devices like prefilled syringes. In addition to being convenient for caregivers and patients, administration devices eliminate product waste attributed to the use of vials and separate syringes to prepare and deliver product doses.

Combining the two trends leads to the requirement to fill decreasingly small volumes of drug products into final administration devices. Executing this scenario correctly requires the highest level of dosing accuracy and precision. This is particularly true when performed at high speeds, as any errors will affect a large number of doses in a very short time period.

This study was an investigation to determine the accuracy and precision of four major liquid dosing systems running at high speeds: a rolling diaphragm pump, piston pump, peristaltic pump, and time pressure filler. It was important to perform the study at high speed, as speed has a large potential affect on performance. At high speeds, filling needle movement can cause unwanted release of liquid droplets from the needle tip between dosing events. This can lead to intra-container filling volume fluctuations. Certain filling systems can compensate for this by creating 'suck-back' of liquid droplets on the needle tip before the needle is moved to the next container. High speed applications also can test the performance limits of certain systems. For example, the peristaltic pump systems tested ran at a maximum of approximately 40 cycles per minute for certain fill volumes, due to physical limitations of the drive system.

The percent deviation from setpoint was

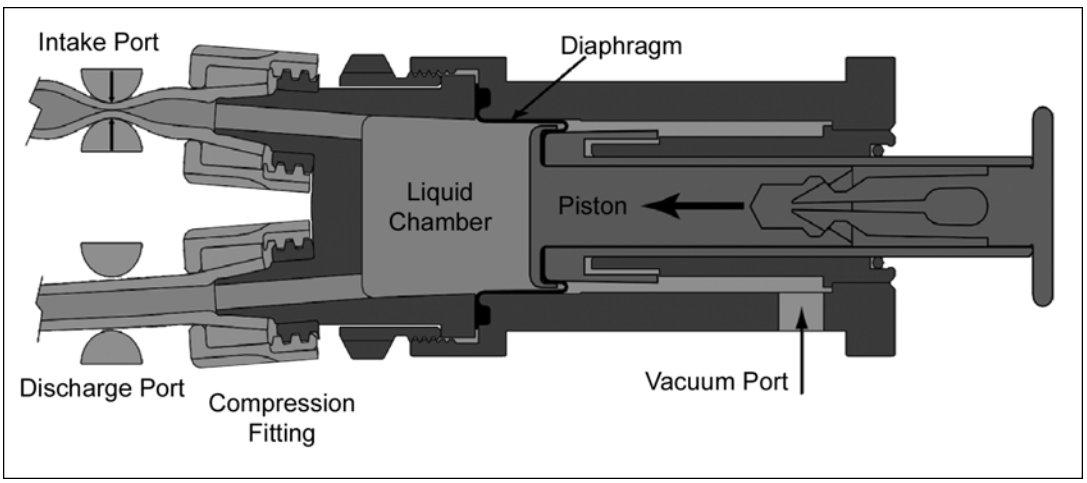

Figure 1. Rolling diaphragm pump cross section.

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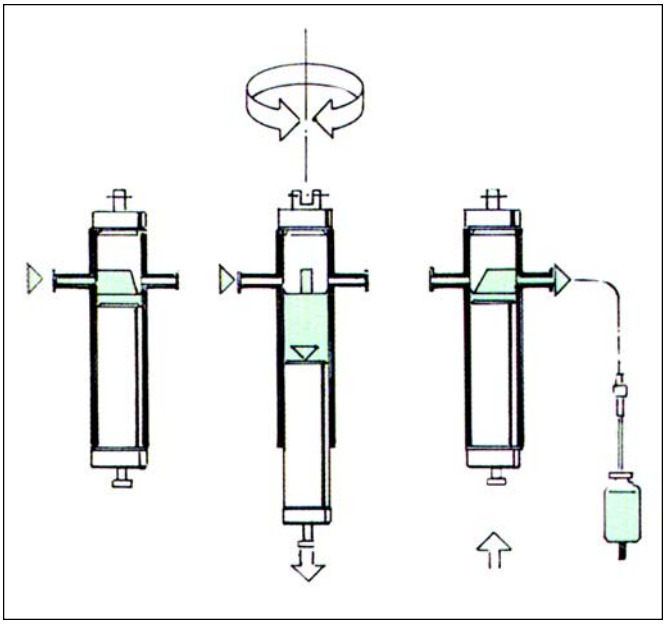

Figure 2. Piston pump cross section.

calculated for each dosing system configuration and each volume dosed. This deviation was used to both determine the relative performance of each system and to determine the 'point of failure' for each scenario. It was hypothesized that the performance limitation of each system will be shown by a definitive increase in percent deviation. This limitation will be volume dependent. At a certain dose volume set point, each dosing system will fail the acceptance criteria and will not recover at smaller dose volumes. It also was hypothesized that reasonable system adjustments will not counteract the effect of volume at the true 'point of failure.'

This article describes in detail how the study was performed. The results for each dosing system are reported and compared to determine which systems are appropriate for micro-dosing applications. An additional study to quantify drift caused by tubing distortion in peristaltic dosing systems was performed. Results from this study also are included in this article.

Study Method

All testing was performed with high speed filling systems using a single filling needle run at approximately 50 cycles per minute. Weight data was gathered using a calibrated scale from 10% of the dispensed cycles over an approximate 20 minute period for a minimum of 100 total samples (of the 1000 total doses) for each scenario tested. The dispensed volumes tested were 1.00 ml, 0.70 ml, 0.50 ml, 0.30 ml, 0.10 ml, 0.07 ml, and 0.03 ml. Deionized water and 1X Phosphate Buffered Saline (PBS), made with PBS 10X solution diluted with deionized water, were the liquids used for the testing. It was significant to run the tests with PBS solution in addition to deionized water because the increased ion concentration has the potential to affect the accuracy of the tests.

Four unique types of dosing systems were evaluated in this study:

1. Rolling Diaphragm Pump with Servomotor Piston Actuation

The rolling diaphragm pump is a positive displacement pump using a diaphragm located between the piston and outside cylinder. A vacuum is pulled on the back side of the diaphragm to maintain diaphragm shape and dosing accuracy. Pinch valves are used on the flexible tubing inlet and outlet - *Figure 1*.

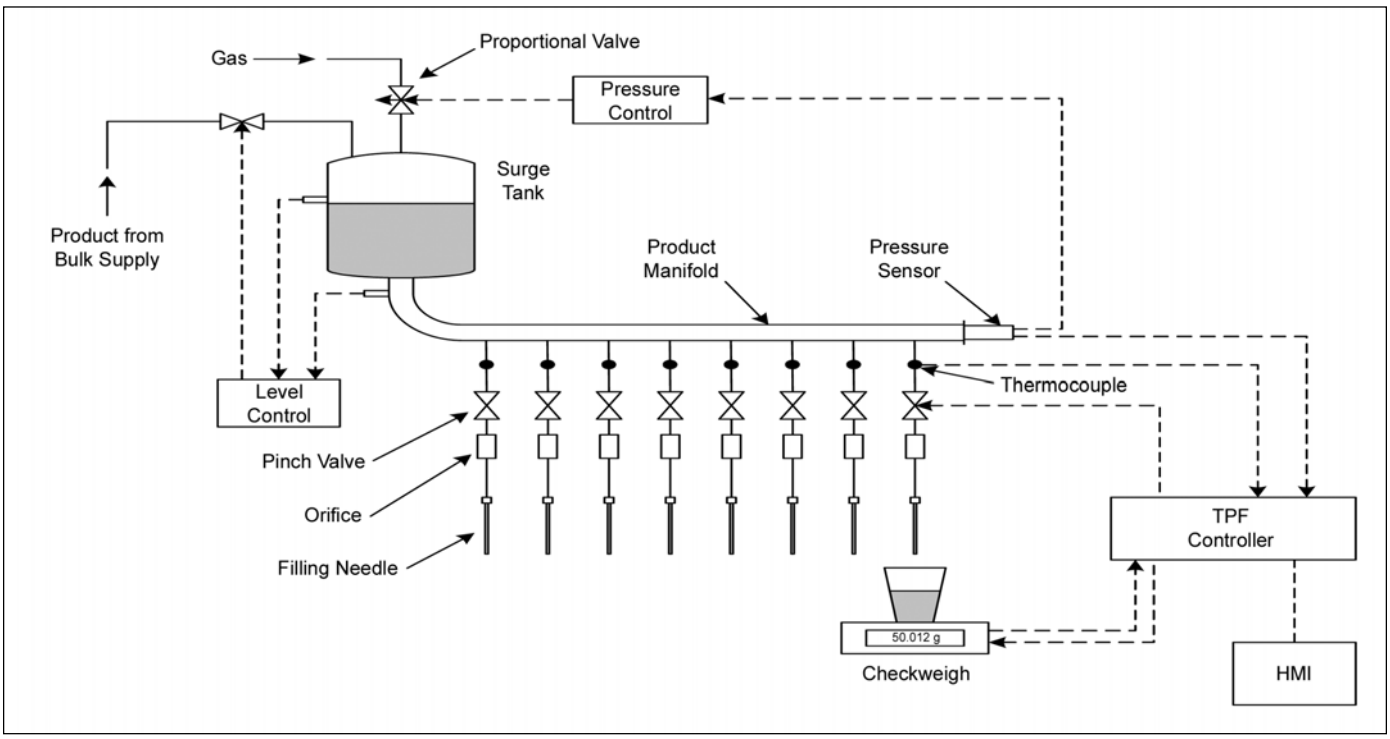

Figure 3. Typical time pressure filling system.

The rolling diaphragm pump system used for the study was a two-pump filler with servomotor pump piston and servomotor valve actuators. This system was tested with both 2 ml and 6 ml pump sizes.

2. Piston Pump (lapped) with Servomotor Piston and Valve Actuators

The piston pump is a positive displacement pump using an internal piston. The pump body is mounted rigidly. The pump piston moves up and down while a valve rotates above the piston. The piston and the valve are lapped to the body inside the diameter so that no seals are required.

Valve actuation for this study used a main drive and cam with servomotor from a production filling machine. A 1.5 ml pump size, with a normal operating range of 0.3 to 1.5 ml, was used for the testing.

3. Programmable Peristaltic Pump

A peristaltic pump was used for the study. It uses one or two heads. Two continuous lengths of silicone rubber tubing pass from the product supply reservoir, between moving rollers and a stationary shoe within the pump head, and then to the filling needle. The two pieces of tubing used through the pump head were connected into a single piece of tubing with a "Y" connector, both upstream and downstream of the pump head. The tubing used for this pump was non-silicone pump tubing with a 0.5 mm I.D. and non-silicone pump tubing with a 1.6 mm I.D.

4. Time Pressure Filler (TPF)

A time pressure filler test machine was used for this study. Product flows out of a pressurized manifold and through flexible tubing past pinch valves that are used to turn flow on and off. The product then moves through flow orifices which help regulate flow rate. Two major parameters are the time the pinch valves are open and the manifold pressure: increasing either of these factors also will increase the amount of product that is dispensed. The third parameter is the orifice size. The smaller the orifice used, the greater the pressure drop; therefore, the slower the product flow. The 0.5 mm and 0.7 mm orifice sizes were used for this study. Product temperature also can have an effect on dosing accuracy. Thermocouples can be used at each control valve to track temperature, which is fed back to the control system. Temperature compensation was not used in this study.

The product was gravity fed at a pressure of 1 psig (27" height above the pump) to the rolling diaphragm and peristaltic pump systems. The supply pressure target was regulated at 0.2 to 0.35 bar using compressed air for the TPF system. The supply pressure was 0.0 to 0.3 psig for the piston pump system.

The range of fill volumes required the use of different size parts for proper system operation. All systems required the use of several filling needle sizes to allow the most accurate dosing possible. See Table A and Table B for a summary of the size parts used in this study.

The acceptance criterion for the fill data generated in this study is based on historical data for the rolling diaphragm pump system.[1] The percent deviation from fill target, at 3s (3 X standard deviation), was to be 5% or less for fill volumes of 0.03ml to 0.10ml and 1% or less for fill volumes of 0.30ml to 1.00ml. The acceptance criterion was used to:

1. Make interventions to optimize tests that do not meet the criteria.
2. Determine the "point of failure" for each system.

Once a test scenario was optimized, 100 weights were recorded with no further changes to the setup. Outside influences (such as air flow around the electronic balance) were minimized during the collection of data. Precision of values at each fill volume target required that all 100 samples from each system tested meet the acceptance criteria.

Fill Volume (ml)	RD Pump Sizes	Piston Pump Size (ml)	Peristaltic Tube Size (mm ID)	TPF Orifice Size (mm)
0.03	2 ml, 6 ml	1.5	0.5	0.5
0.07	2 ml, 6 ml	1.5	0.5	0.5
0.10	2 ml, 6 ml	1.5	0.5	0.5
0.30	2 ml, 6 ml	1.5	1.6	0.5
0.50	2 ml, 6 ml	1.5	1.6	0.5
0.70	2 ml, 6 ml	1.5	1.6	0.7
1.00	2 ml, 6 ml	1.5	1.6	0.7

Table A. Tested filling system sizes.

Study Results

Rolling Diaphragm Pump System

A rolling diaphragm pump test rig with two pumps was used for the 2 ml and 6 ml rolling diaphragm pump study. This rig is used to simulate a multiple head manufacturing scale filling system and includes precise servomotor pump actuation. Only one of the pumps was activated during testing. Silicone tubing led from an elevated liquid source to the pump head, and from the pump head to a filling needle. The filling needle was suspended on a ring stand above a waste container. Test samples were pulled using a small sampling cup.

Optimization of the rolling diaphragm systems prior to testing required "suck-back" adjustments to avoid drop formation on needle tip between filling cycles. It was assumed

Fill Volume (ml)	RD Pump Needle Size (mm)	Piston Pump Needle Size (mm)	Peristaltic Pump Needle Size (mm)	TPF System Needle Size (mm)
0.03	0.81	0.81	0.41	0.41
0.07	0.81	0.81	0.41	0.41
0.10	0.81	0.81	0.41	1.00
0.30	0.81	0.81	0.81	1.00
0.50	0.81	0.81	0.81	1.00
0.70	0.81	0.81	0.81	1.00
1.00	0.81	0.81	0.81	1.00

Table B. Tested filling needle sizes.

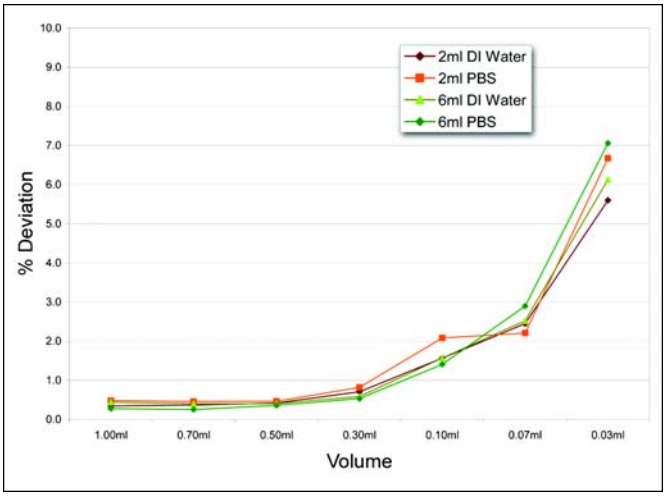

Figure 4. Rolling diaphragm pump results.

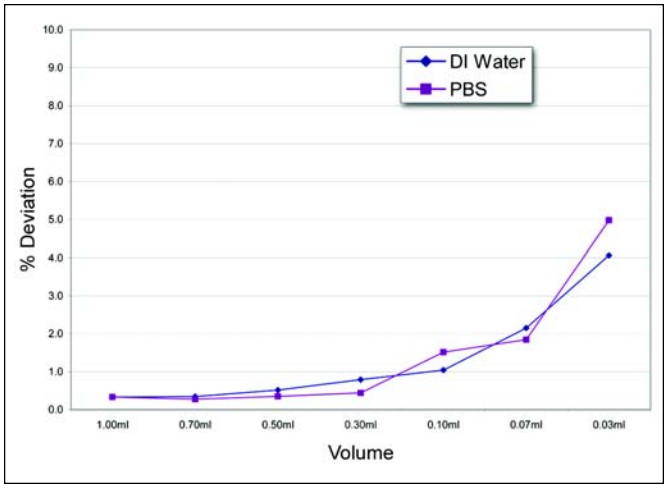

Figure 5. Piston pump results.

that any drops seen would fall during normal needle movement, thus negatively effecting fill accuracy. The final "suck-back" settings used in the study were dependent on dose volume with an increase in set point percentage as the dose volume decreased.

The results of the testing indicate that the 2 ml and 6 ml rolling diaphragm pumps in a standard setup meet the accuracy criterion down to the 0.07 ml dose volume. A significant increase in percent error is seen at the 0.03 ml volume. It is interesting to note that there was no significant difference in percent error between the two pump sizes. See Figure 4 for a summary of the pump results. No significant difference was seen when dosing 1X PBS compared to deionized water with this dosing system.

Piston Pump System

A piston pump from a commercial two pump nested syringe filling system was used for the testing. Silicone tubing led from the liquid source to the pump head, and from the pump head to a filling needle. The liquid bottle was kept at the same level as the pump head, thus, the liquid was fed at ambient pressure. The filling needle was suspended on a ring stand above a waste container. Test samples were pulled using a small sampling cup.

Optimization was required to eliminate liquid droplets from the filling needle between fills. When the speed of the pump stroke and the "suck-back" were increased, the droplet on the end of the needle was eliminated and the results were accurate and repeatable. Faster pump stroke speeds reduced the size and frequency of droplets forming on the end of the needle.

The results indicate that the 1.5 ml piston pump met the accuracy criteria down to the 0.03 ml dose volume. A significant increase in percent error is seen at the 0.03 ml volume, but was still within the acceptance criteria. See Figure 5 for a summary of the pump results. No significant difference was seen when dosing 1X PBS compared to deionized water with this dosing system.

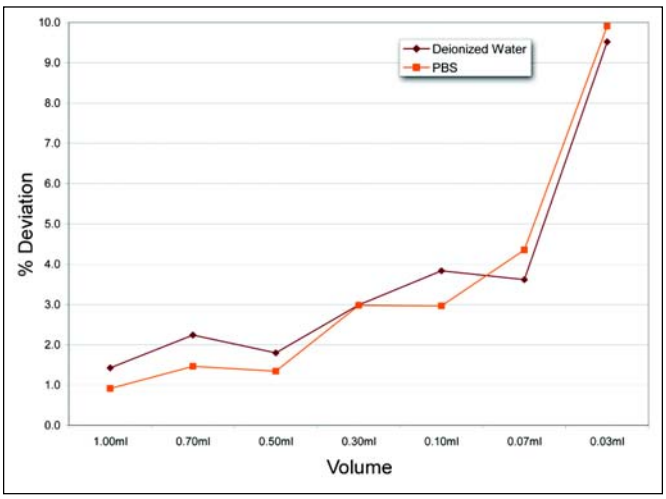

Figure 6. Peristaltic pump results.

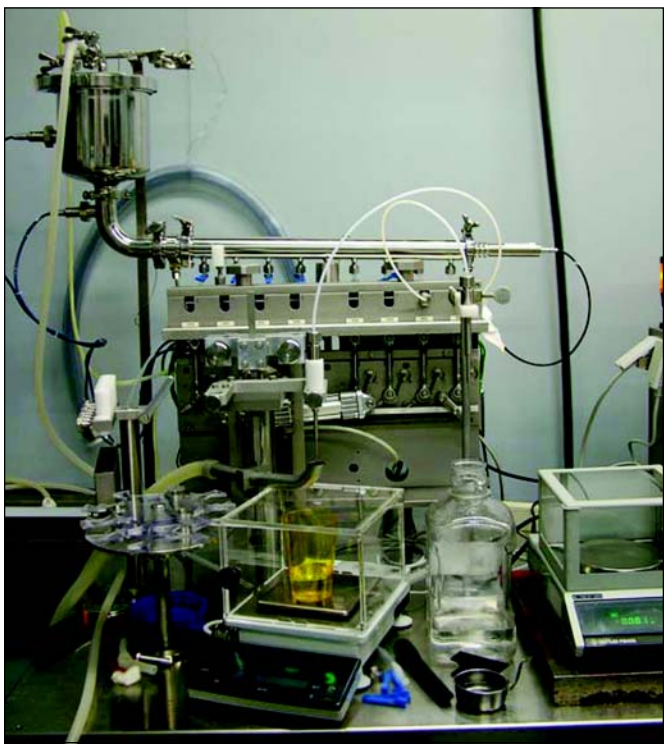

Figure 7. Time pressure setup.

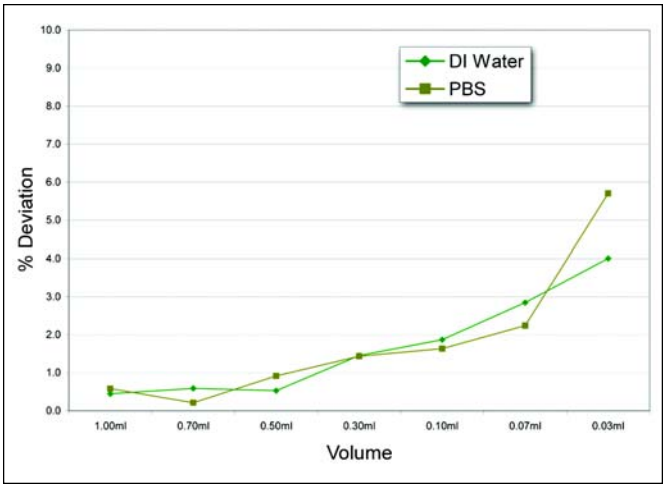

Figure 8. Time pressure results.

Peristaltic Pump System

Peristaltic tubing led from an elevated liquid source to the pump head, and from the pump head to a filling needle. The two pieces of tubing used through the pump head were connected into a single piece of tubing with a "Y" connector, both upstream and downstream of the pump head. Rigid tubing led from the pump head to a filling needle. The filling needle was suspended on a ring stand above a waste container. Test samples were pulled using a small sampling cup.

After completing the programmable peristaltic pump 0.03ml fill test with two heads, the same fill level was tested with only one pump head. There no significant change in percent error.

The results indicate that the peristaltic pump met the accuracy criteria down to the 0.07 ml dose volume. A significant increase in percent error is seen at the 0.03 ml volume. See Figure 6 for a summary of the peristaltic pump results. No significant difference was seen when dosing 1X PBS compared to de-ionized water with this dosing system.

Time Pressure Fill System

A TPF test rig was used for this study. This rig is used to simulate an eight-head manufacturing scale filling system and includes stepper motor valve actuation. Only two of the ports were activated during testing. One port was used to tune the system and a second was used to pull samples for the study. Rigid tubing led from the flow orifices to the filling needles to ensure pressure stability, as pressure fluctuations after the orifice will lead to dose variability. The filling needles were suspended on ring stands above the waste containers. Test samples were pulled using a small sampling cup. The needle used for tuning the system was suspended above a separate scale that automatically downloads data to the control system. The setup is shown in Figure 7.

A significant pressure drop can occur through the flow orifices in the TPF system depending on the pressure set point of the supply tank and manifold. Bubbles can form in this area, in particular with dosing solutions that are prone to foaming. PBS is more prone than water to the formation and increased lifetime of bubbles, due to the presence of

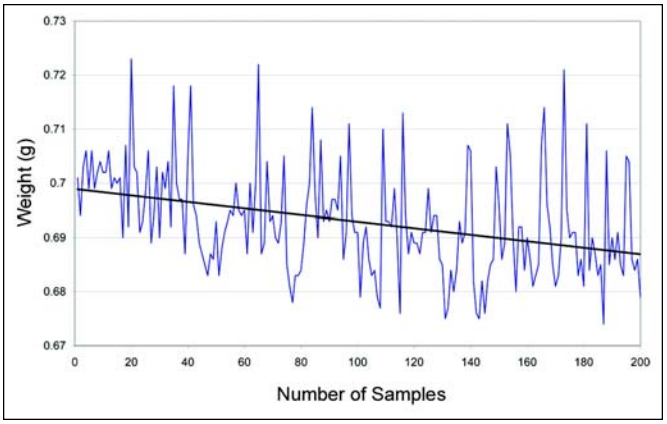

Figure 9. Silicone tubing drift test results.

Sodium Chloride.[2,3] These bubbles can significantly affect the accuracy of the system when dosing volumes below 1.0 ml. Whereas the distilled water did not bubble during the testing, the PBS solution bubbled readily at the orifice at pressure set points above 0.35 bar. Therefore, 0.35 bar was the maximum pressure set point used during the study.

The results indicate that the TPF system met the accuracy criteria down to the 0.07 ml dose volume for water and PBS. Although the system met the accuracy criteria down to the 0.03 ml dose volume for water, a significant increase in percent error is seen for PBS at this volume. This is likely due to bubble formation in the PBS solution. Further system tuning can likely reduce the error to acceptable levels. See Figure 8 for a summary of the TPF system results.

Additional Study: Peristaltic Tubing Drift

It was hypothesized that peristaltic pump systems can be prone to dosing inaccuracies over time due to tubing shape changes caused by distortion. A study was performed to quantify the change in dosing accuracy over time. Testing was initiated on a programmable peristaltic pump with a 505L head. The unit uses tubing with a wall thickness of 2.4mm (.094"). The tubing used for this test was silicone rubber tubing with a 0.5mm I.D. Dose testing was performed over a 100 minute period with 10 samples taken every five

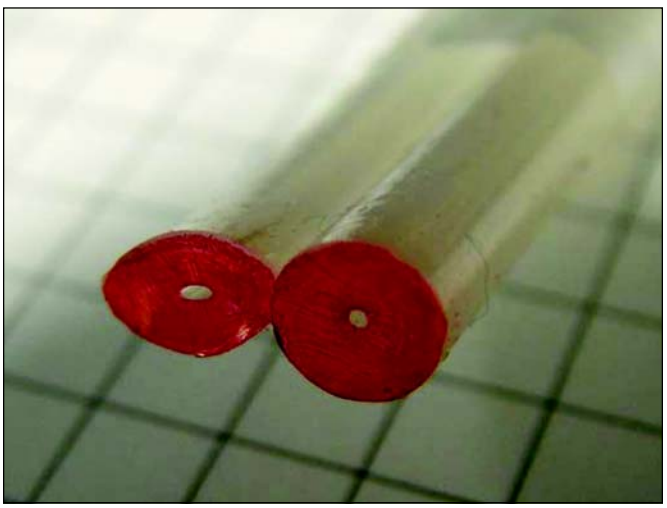

Figure 10. Used vs. new silicone tubing shape.

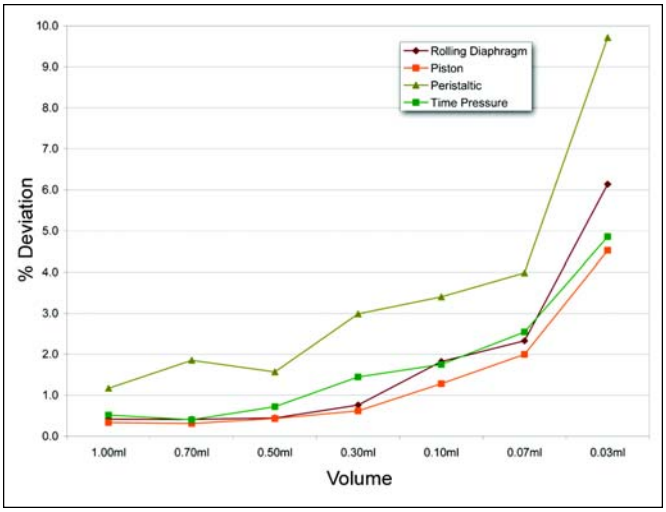

Figure 11. Average test results by system type.

minutes for a total of 200 samples. The 0.70 ml dose point was chosen for the testing.

Results of the testing are shown in Figure 9. As can be seen, there is a trend toward smaller volumes over time. It was noted that the silicone tubing was flattened from the rollers of the pump after use, and even one week after the tests, the tubing had not regained its circular shape - *Figure 10*. The fills began at or above the target set points and decreased below the target toward the end of the test. However, the drift seen may level off over time. Drift over time is likely not a characteristic of silicone; in theory, all tubing types show drift. The dosing system can be made to compensate if the drift is fully characterized. More data is needed to determine if different tubing types display different drift characteristics at these small dose volumes.

Discussion

The dose volumes used in this study tested the accuracy and precision limits of the filling systems used. As can be seen in Figure 11, all of the filling systems tested were able to repeatedly meet the acceptance criterion down to doses of 0.07 ml. Two of the systems, piston pumps and time pressure, met the criteria down to 0.03 ml. This is a testament to the amount of technical achievement that has occurred with each type of system over the last decade.

The piston pump filling system was arguably the most accurate and precise for the doses tested. However, there are system attributes that may not make it the best system for biopharmaceuticals and other biotech drugs. Product is used as the piston lubricant and creates the pump seal. The use of such open pump systems with highly potent products that must have a fully sealed product path is not possible. Products like proteins that are sensitive to shear, or products that are prone to crystallization, also may not work with this system.

The rolling diaphragm system closely matched the piston pump and time pressure system down to the 0.07 ml volume. It has attributes that make it attractive, including a completely closed product path and the ability to use one pump size to dose a range of dose volumes. However, the study showed a slightly higher error than the piston pump and time pressure system at 0.03 ml. Previous data from the rolling diaphragm system showed a filling error of 5% or less down to 0.03 ml, which would more closely match the results from the piston pump system. The decreased error seen during the earlier study is likely due to the much smaller sample set of 40 samples, and the fact that the samples were pulled consecutively to yield 40 total doses. The study described here pulled 100 samples from a set of 1000 total doses.

The Time Pressure system was the most complicated to set up, required the most tuning prior to use, and was the most sensitive to the chemical differences between products. It requires the most complicated control system because of the number of variables involved. However, system accuracy was better than expected for this testing, and closely matched the piston pump and rolling diaphragm pump down to the 0.03 ml volume. The system also has a high potential for conversion to a 100% disposable product path. One technical challenge for this is conversion of the supply tank, manifold, and orifice to a disposable system that still meets the pressure and fluid flow needs.

The results seen with the peristaltic system tested is particularly interesting. Data for the system tested showed successful fills down to 0.07 ml at a rate of 40 cycles per minute. In addition to being the most cost-effective type of dispensing system, peristaltic systems also have the highest potential for conversion to a 100% disposable product path. Therefore, development in the near future of commercial-speed, micro-dosing, and disposable filling systems are possible. However, further work to characterize and compensate for tubing conformational changes is necessary before a commercial system that meets our accuracy and precision requirements would be successful.

Drift was seen with both the peristaltic and time pressure systems. Compensation for the drift was made using manual adjustments to control parameters during the tuning process. Results during testing were then verified based on a 10% sampling rate. On commercial machines, automatic adjustments to compensate for drift are made real time using data from check weigh systems, which normally sample one to three percent of filled containers. The filling systems tested in this study also used a single filling needle. Commercial high-speed systems typically have eight to 12 filling needles. Intra-needle error, which has an effect on filling results, is additive in nature. Individual needle adjustments can help reduce the effect, but will not totally eliminate it. For this reason, there is a greater potential error in a high speed commercial filling system.

Summary

This article quantified the accuracy and precision of four types of pharmaceutical filling systems to dispense liquid micro-doses at production speeds. Results demonstrate that all systems were able to repeatedly meet the acceptance criterion down to doses of 0.07 ml. Several systems met the criterion down to the 0.03 ml dosage level. No significant

difference was seen when dosing 1X PBS compared to deionized water using the rolling diaphragm pump, piston pump filler, and peristaltic pump systems. Bubble formation in the flow orifice of the time pressure filler, which is exacerbated by PBS, can be controlled by using a lower liquid supply pressure, but still likely affected fills at the 0.03 ml dosage level. From the data obtained, it can be concluded that accurate and precise high speed micro-dosing of typical pharmaceutical products can occur at volumes as low as 0.03 ml.

References

1. Bostrom, C., "FLM RD Pump Prototype, Fill Data, 0.030g - 1.000g," Bosch Packaging Technology internal technical report, (2003).
2. Hofmeier, U., Yaminsjy, V., Christenson, H.K., "Observations of Solute Effects on Bubble Formation," *Journal of Colloid and Interface Science,* (1995), 174(1), 199-210.
3. Craig, V.S.J., Ninham, B.W., Pashley, R.M., "The Effect of Electrolytes on Bubble Coalescence in Water," *Journal of Physical Chemistry,* (1993), 97, 10192-10197.

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Outsourcing and Contract Manufacturing in the Pharmaceutical Industry

by Magdalena Nannei and Sandra Rumiano

This article reviews the considerations involved to decide whether to outsource any manufacturing activity. Some basics for successful outsourcing are considered. The challenges and benefits of outsourcing, the company's areas that should be involved in the process, and the activities to be developed are discussed.

The pharmaceutical industry is facing new challenges. The need for continually increasing investment both to develop new products and to maintain them in the market following regulatory approval often conflicts with the requirement to keep costs low.

At some point, outsourcing may become a strong candidate for improving the business, and sourcing strategies could allow the pharmaceutical company to focus on its core activities or products. In addition, the technology required may be so specialized that there is no in-house knowledge and expertise and it is more convenient to obtain this from outside the organization.

The possibility of increased cost benefits when a product or process is manufactured by a third party provider should be balanced against the risk that a contract manufacturing organization will not satisfy expectations. Therefore, risk analysis is one of the major activities when establishing an outsourcing manufacturing strategy.

What is Outsourcing?

The FDA indicates in its Guidance for Industry, Quality Systems Approach to Pharmaceutical cGMP Regulations, that *"Outsourcing involves hiring a second party under a contract to perform the operational processes that are part of a manufacturer's inherent responsibilities."*[1]

Why Outsource?

There can be many reasons why an organization would outsource, some of which may be planned, including:

- optimizing and controlling operating costs
- strengthening the focus on core business initiatives
- freeing resources
- reducing the time to market

Frequently outsourcing is a consequence of merger and acquisition activities without a clear strategy on the possibility for outsourcing in a continuous operating environment. This could be considered as an example of an unplanned outsourcing strategy.

Gaining focus is one of the major drivers for outsourcing. The "two-digit growth factor" is essential when developing a commercial and manufacturing strategy for a pharmaceutical company. Focus should be applied to the fastest growing products which provide the company with the highest return on investment.

Companies usually have a list of 10 or 20 top molecules on which they prefer to concentrate their commercial efforts, capital investments, and resources utilization. Regardless of the importance of other products to the commercial portfolio, they will not provide significantly to future growth. This is why an outsourcing manufacturing strategy could be designed to maintain them at the necessary regulatory and commercial requirements, while avoiding further capital investments.

Recently, offshoring (substituting foreign for domestic labor) has become a highly interesting alternative when coupled to a Contract Manufacturing Organization (CMO) since substantial savings can be obtained. Currently, Latin America, China, and India represent valid alternatives for global manufacturing with Argentina, Brazil, Colombia, and Mexico as the main contributors within Latin America. These countries have developed all the conditions

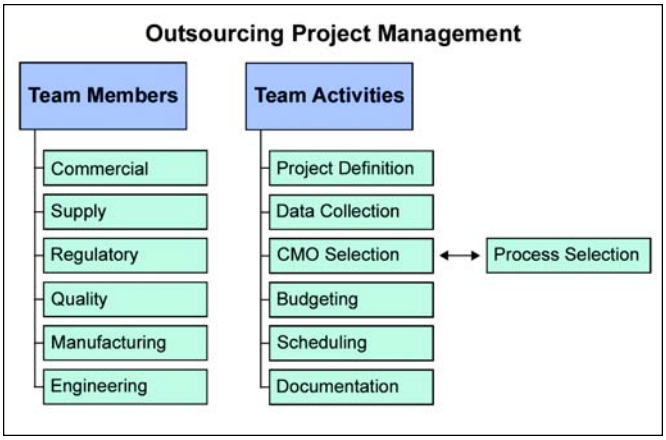

Figure 1. Main areas and activities that are involved in an outsourcing project.

required to become reliable outsourcing alternatives.

Some of the conditions which the countries should possess, in order to be selected as potential countries for manufactured products, are related to a reliable macroeconomic environment and include:

- stable democracy system
- no conflicting borders
- tax and duty benefits (inside the country plus regional benefits like a common trade area)
- a developing and healthy economy
- placid trade unions
- low labor costs
- a high educational level (particularly)

It is not considered reasonable under the current scientific, regulatory, and investment environment to have manufacturing sites designed to manufacture everything. Both capital investment, in areas and services, and significant numbers of highly educated personnel, needed to keep the site updated and compliant, are required when several different areas of expertise are involved.

When asking the question "make or buy?" in the pharmaceutical industry, necessary considerations include:

- the successful experience of other industries, like the automotive industry that is outsourcing 70% to 80% of its total value
- dissatisfaction with outsourcing, due to failures in the outsourcing relationships within short to mid periods of time

An impressive figure in favor of using a CMO is shown in the pharmaceutical outsourcing market, which today is valued at $22.5 billion, and this is estimated to more than double by 2010.[2]

What to Outsource?

Practically everything that is manufactured also can be outsourced. From APIs and their intermediates to drug products, bulks, or filled and packaged drug products, the complete manufacturing chain or single processes, or unit operations, including analytical and QA, as well as distribution and inventory management. With creative thinking, there are many ways to resolve manufacturing constraints using outsourcing[3]. Usually outsourcing comes after situations like:

- supply chain analysis (bottle necks, non added value activities)
- new products requiring unavailable expertise inside the company
- strong changes in demand requirements
- cost issues

Filling and packaging operations are activities that are commonly outsourced. New packaging configurations and materials often require equipment not available inside a company, and contract manufacturing is a satisfactory solution to overcome the problem without significant issue.

Another regular outsourcing activity is the manufacture of gelatin soft elastic capsules that it is performed at highly specialized sites. Effervescent tablets or powders, lyophilized and sterile products, eye drops, aerosol formulations, and medical shampoos are some of the pharmaceutical forms that are usually manufactured at dedicated manufacturing sites since the processes involved in their production require specialist knowledge, equipment, and facilities.

Penicillins and *beta-lactam* antibiotics, high potent compounds, and hormones are usually manufactured by third parties when they do not belong to the core product list since these products require separate buildings and expensive room classifications.

Another popular outsourcing activity in the pharmaceutical (and other industries) is the logistics function. During the 1980s, the outsourcing in this regard was related only to some elements of the whole range of the logistics operation and it was delegated to one specialist. Then this figure was changed for a more complex environment involving the development of strategic alliances. Thus, the situation turned into "the strategic alliance with service providers."[4] In the logistics world, this refers to "logistics service providers," including functions such as:

- warehousing
- transportation
- electronic information exchange
- packaging process of the goods
- identification (labeling)
- custom clearance

The figure in this case is increasing and was doubled only during the 1990s.[5] In that way, Kuehne Nagel, Caterpillar, TNT Contract Logistics, are very good international examples.

How to Outsource?

There are many strategies for contract manufacturing for

products, processes, and organizations. However, there are some basic elements that are present, regardless of the selected strategy. Figure 1 provides a summary of the main areas involved and the activities to be performed when selecting a CMO. The participants in the different areas can be either team members or have a type of technical advisory role. There is a tendency to increase the number of team members as a project develops, primarily based on the project complexity. This may cause the transfer of a project to be very difficult to handle.

The commercial departments may not be part of the transfer team or organization although their involvement is necessary. There are many commercial issues affecting a project, like packaging configuration or batch size changes, which in turn can affect shelf life, mainly in low volume products. Response time to peak demand periods also will have an important effect on the commercial areas. Commercial departments are key players since actions taken by the other functional areas are based on their input, needs, and long range forecasts. Without proper feedback, the technical areas might continue to work on a project without an updated perspective:

- what has been developed is no longer sufficient for the company's needs
- does not meet required standards
- the product is no longer of commercial interest

The financial analysis could be led by manufacturing or supply, but many organizations may prefer to have it as a separate group. Financial analysis determines whether the transference to a CMO is justified and it may be more convenient to have an independent member of the transfer team performing this task.

The basic process for implementation of a CMO consists of four principle activities, including:

1. Project definition
2. Collection of data
3. CMO/Process Selection
4. Generation of data

Project Definition

"A project is a sequence of unique, complex, and connected activities having one goal or purpose and that must be completed by a specific time, within budget, and according to specification," as defined by Robert K. Winsock in his book, *Effective Project Management.*[6]

In the case of the CMO, the purpose is to find the most suitable supplier for a specific service or product. Once cost calculations are involved, the specifications for the product and process must be clearly defined.

The Project Overview Statement will summarize the requirements, costs estimations, capital needs, risk, and gap analysis, timelines and milestones, resources allocations, etc. The signatures of the top management of the regulatory, QA, supply, manufacturing, and commercial areas of a company will reinforce the strategic plan described in the Project Overview Statement.

Table A summarizes some of the possibilities for defining an outsourcing project. Several reasons may combine to strengthen the rationale for implementing an outsourcing project. Tax and cost benefits, mergers and acquisitions, capital related matters, or regulatory issues are various significant factors. However, gaining flexibility and reducing time to market are increasingly key factors for implementing a CMO project.

Collect Data

This is the most critical activity to decide why, what, and when to outsource a product or process.

Data collection implies a significant effort for the entire organization in order to avoid unexpected omissions that could affect progress of the contract manufacturing project. Data collection provides the background for the data generation activities and for the filing process. Regulatory agencies, generally, require more and more data comparisons between the current and the new source to evaluate the impact on product.

All too often, the inadequate background information is handed over to the CMO, and the outsourcing company fails to provide a satisfactory product comparison.

The *ISPE Good Practice Guide: Technology Transfer*, provides valuable guidance for product or processes transfers applicable to contract manufacturing.[7] Industrial manufacture is the transfer from an R&D area or from one industrial site to another. The Guide's fundamental goal *"is to provide value added guidance to industry, which will facilitate timely and cost effective transfer of technology between two parties. Advice and guidance is provided which may be applied to analytical methods, APIs, and dosage forms, and takes ac-*

Business Strategy	Operational	Finance	Regulatory
Not a Core Product	Plant Capacity Constraints	Cost Savings	Need to Separate Products
Niche Product	Reduce Time to Market	Avoid Capital Investments	Compliance Issues
Commercial Uncertainty	Packaging Design Issues	Tax/Duty Benefits	Other Regulatory Issues
Political Unrest	Production Technology not Available	Increase Capital Rentability	
Capital Rentability	Rationalization		
Mergers and Acquisitions	Lack of Expertise		
Worldwide Planning	Increase Production Flexibility		
Consolidation and Specialization			

Table A. Some factors to consider in the "make or buy" decision process.

count of requirements in the US, Europe, and Asia." The value of this Guide has been demonstrated in transfer projects within Latin America since many countries closely follow US or European regulations. The value of the Guide also is related to the need to speak a common language with a CMO, and even within an organization.

Regulatory and compliance evaluation should be one of the first steps. In addition, when the project also involves offshoring, the revision of the regulatory status of the receiving country should be evaluated.

As they will affect both the product owner and the CMO, one of the most challenging topics is the post marketing regulatory compliance issues. In the case of contract manufacturing compliance, managing the changes has the potential to increase risk for both organizations. The due diligence process should highlight the characteristics of a manufacturing organization, as well as the risks associated with its business environment. The quality agreement signed between both companies should highlight the need for the owner company to have access to all relevant data and systems. It should be emphasized that any change or issue within the CMO has the potential to impact in the product owner. The quality agreement should clearly identify the method by which both companies will handle product recalls, complaints, change control management, quality reviews, etc. Regardless of how many details are described in the Quality Agreement, the culture of an organization will make a difference when problems arise.

Stability issues and process statistics should be carefully evaluated to focus on potential production problems. In the case of offshoring, transportation times can have an impact on products with short expiration dates.

Collection of data is not only an in-house activity since it also affects the potential sourcing companies. The data collection should start as soon as possible in a selected CMO.

In FDA Guidance for Industry, Quality Systems Approach to Pharmaceutical cGMP Regulations, there is a section dedicated to make some short observations on outsourcing, Control Outsourced Operations, IV, B, 4. One very significant comment is that "*Under a quality system, the manufacturer should ensure that a contract firm is qualified before signing a contract with that firm. The contract firm's personnel should be adequately trained and monitored for performance according to their quality system, and the contract firm's and contracting manufacturer's quality standards should not conflict. It is critical in a quality system to ensure that the management of the contractor be familiar with the specific requirements of the contract. However, under the cGMP requirements, the manufacturer's QU is responsible for approving or rejecting products or services provided under a contract (§ 211.22(a)).*" (QU stands for Quality Unit). It is clear from this recommendation that the quality systems for both organizations should be carefully reviewed and gaps and risks identified and ranked. This Guideline is only applicable – as a recommendation – for the US, but the statement on the evaluation of conflicting interests in the quality system is of universal

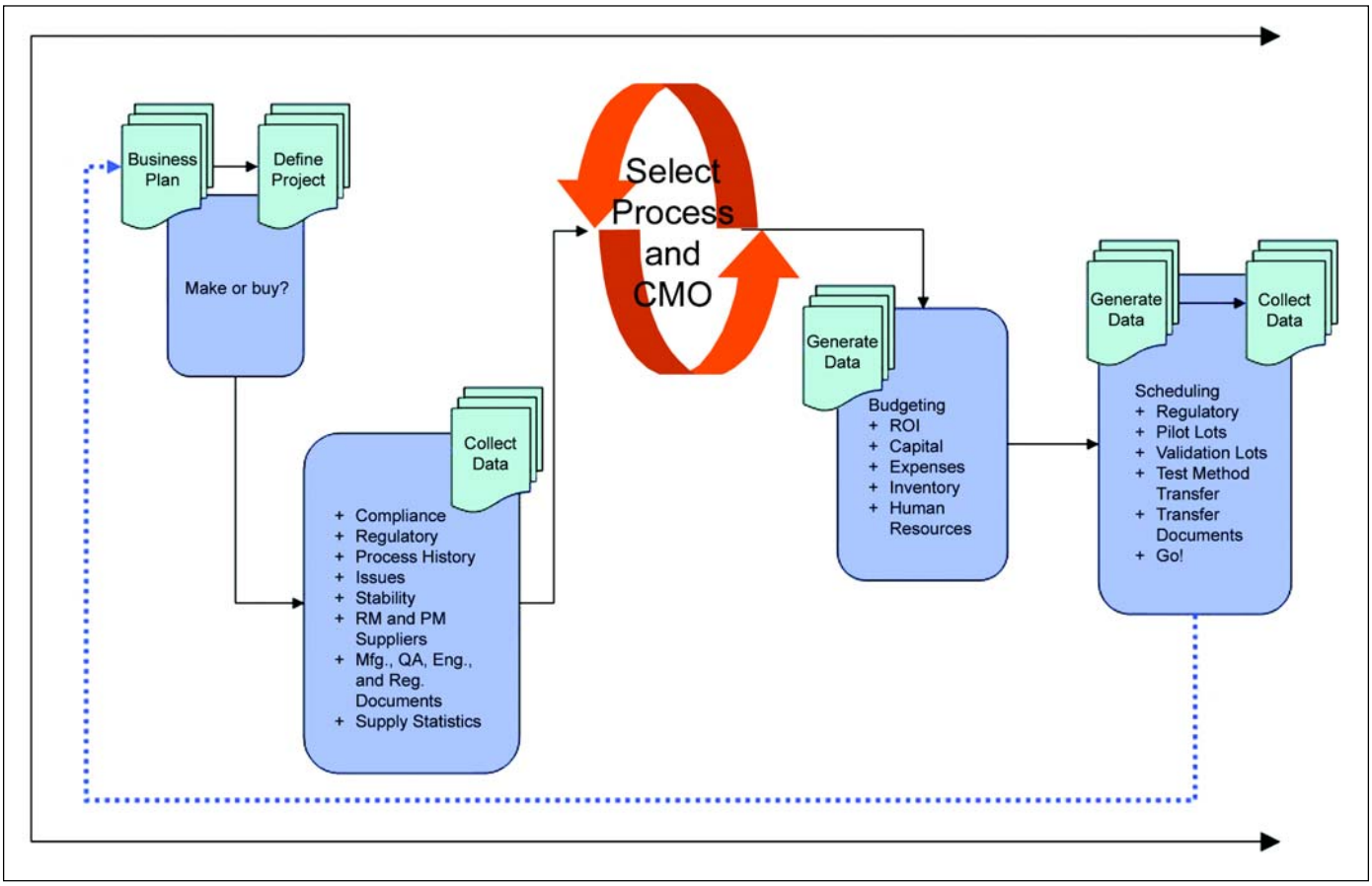

Figure 2. Scheme of the process flow for data generation and data collection pre and post CMO selection.

value. This is a point not easily resolved since it implies challenges for training when cultural or regulatory behavior is very distinct. Therefore, a basic recommendation is to consider the differences carefully in the risk assessment process.

Other documents of very high value to be used as reference are the guidance documents published by the FDA, like the SUPAC-MR: Modified Release Solid Oral Dosage Forms, which have the scope to provide "*recommendations to pharmaceutical sponsors of New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), and Abbreviated Antibiotic Drug Applications (AADAs) who intend to change (1) the components or composition, (2) the site of manufacture, (3) the scale-up/scale-down of manufacture, and/or (4) the manufacturing (process and equipment) of a modified release solid oral dosage form during the post approval period.*"[8] When multiple changes are required, which can happen easily in an outsourcing project, the document indicates that "*changes not addressed in this guidance, or for multiple changes submitted at one time or over a short period of time, sponsors should contact the appropriate CDER review division or consult other CDER guidance's to obtain information about tests and application documentation.*" Similar documents exist for other pharmaceutical forms. Other countries also use SUPAC as guidance documents or similar types of recommendation papers with some variations. In the case of offshoring, where the sourcing country and receiving country follows different guidelines, this could be an added complication.

From the manufacturing, QA, analytical, and regulatory point of view, the following elements that are always present, materials, methods, machines, measures, environment, and equipment, are the key factors to consider in the review process.

Materials: materials of natural origin can have a wide variation in their specifications. The Pharmacopeia requirements are usually met for materials of different sources, but the issues are generally related to some physical properties, such as particle size, shape or bulk density; therefore, data should be generated to highlight the differences and estimate the dissimilarity for chemical or physical properties.

Method of manufacture: the selected manufacturing method will be used to generate pilot lots, stability lots, and the technical knowledge and expertise in the CMO. The SUPAC guidelines, mentioned above, help to provide strong support for the selected strategy.

Measurements and analytical techniques: analytical equipment or methodology can be an endless source of conflict. Very small differences can generate large differences in the results and be the cause of delays and conflicts. The test method transfer process starts with the data collection, to review and compare equipment, methodologies, and training, in preparation for the moment of data generation when the transfer is actually performed. The sending laboratory should provide the experience and analytical know-how to ensure regulatory compliance.

Machines and equipment: the SUPAC guidelines are again a very good reference to be used for the comparison work. Many countries, such as Brazil and Mexico, are developing similar types of guidelines. Both companies should establish the strategy to evaluate any potential difference within written guidelines, since regulatory requirements could have a detrimental impact on the project cost.

Environment: the environment can have a decisive influence, mainly in the case of offshoring. As an example of the influence of the environment in the regulatory strategy, it is interesting to note that there are some regulatory agencies located in tropical areas that could accept previously generated stability data from zone IV areas, but they would ask to repeat the studies if the data was generated in zone II areas.

People: cultural, language, training, experience, and motivation differences are important factors to be considered in an outsourcing project.

Figure 2 attempts to summarize all the activities for data collection and data generation.

Select the Process and the CMO

Once the data has been collected in the manufacturing company and in the CMO, there should be a continuous flow of more data and information to gain a deep understanding of the pros and cons of each explored alternative until a final decision is made and a CMO is selected.

In this selection, the process itself is selected. It may be desirable to change the technology, e.g., the current technology is old and less cost effective. Filing and bioequivalence requirements may prevent the desired change, but the alternative should still be considered. Packaging configuration poses an extra challenge due to the differences in the commercial chain (blisters or bottles). In global sourcing, the CMO should be able to fill and package the products according to the requirements of different customers.

Risk Analysis

Risk analysis is a specific activity that it is present both during data collection and also during data generation activities. ICH Q9 provides, in Annex II, a complete list of activities and issues to consider during the risk evaluation such as: documentation, training and education, design and facilities, flow of material, and personnel. Carney has pointed out that "*there is an expectation that a pharmaceutical company will proactively and systematically identify risks that might negate some deliverable quality attribute of a product and have a program in place to prevent or minimize these identified risks.*"[9]

Outsourcing involves the usual risks of any product trans-

fer project, plus the risks of doing the work through a vendor. The company risk analysis, generally, considers what happens within its organizational boundaries and investigates possible sources of risk in the CMO with the help of auditing and reviewing tools. However, some risks could be completely unknown for activities performed outside the company. Similarly, the CMO should perform the corresponding risk analysis for the impact of the new process or product inside its operation.

The risk description for a regular transfer could be the shift to a new technology, the safety risks in the new areas, the supply delays as the project moves forward, or inadequate yields, etc. The additional risk of an outsourcing project is related to infrastructure and project management skills in the CMO, but also it should consider some issues in the organization like risk of service level reduction, lack of cultural fit, loss of technological connections. In the case of offshoring, the risk analysis should include additional subjects, such as:

- geopolitical stability
- risk of being subject to different laws in another jurisdiction
- language skills
- work culture
- union issues

In the case study, described under "The Value of the Right CMO," the serious issues that arose as a consequence of improper vendor selections are detailed, as well as the solution with the switch to a convenient contract manufacturing organization where the cultural model was in agreement with that of the owner company.

Generation of Data

When the CMO has been selected, a program of activities is detailed, and the above mentioned *ISPE Good Practice Guide: Technology Transfer* can be used as an example for the information required to prepare for manufacture. The outsourcing company, when located offshore, should be prepared to handle differences that arise in the regulatory requirements of the receiving country.

The project could involve the manufacture of pilot lots, feasibility studies, stability, and bioequivalence studies, API impurity profiles in the case of source change for an API, and thorough evaluation of the manufacturing differences between the original and new source since this difference will be challenged by many regulatory agencies. Transportation studies, and the evaluation of any difference in the temperature profile during transportation, should be addressed and evaluated. The final runs will be the validation lots that, upon approval, will be put into the market.

The Value of the Right CMO - a Case Study

A European company with sales offices in one Latin American country decided to move all the production located in that country from different manufacturing contract organizations to a single organization because of compliance issues.

The "owner" company did not have local technical support to help with the process and neither did headquarters since the formulations were developed several years ago for the specific needs of that affiliate. The formulations were developed in headquarters.

The "new" CMO was requested to handle the transfer, as well as the technical work to bring products under compliance. The products were several uncoated and film coated tablets.

The review of the available documentation by the "new" CMO showed lack of compliance between the manufacturing, QA, and regulatory documents. Reasons for changes were not available and the change control system in the different companies involved in this transfer was very poor. The evaluation of the lack of compliance made clear that several minor differences were introduced throughout the years in the processes, in the formulations, and in the analytical methods, without proper supporting data or filing updates. Fortunately, the original documents were available as a reference source.

The revision also indicated that the filings were in agreement with the original documents. The differences in the analytical methods were minor and could easily be resolved. There were clearly two possibilities:

1. to build adequate data with the current manufactured formulations
2. to go back to the original products since there was no strong evidence to support the changes

In the first case, the products did not reflect the filed formulation and processes although again it should be stressed that the differences were minor. In the second case, the formulations could be immediately brought under compliance, but the risk could be an unexpected manufacturing failure.

The "owner" and the "new" CMO decided to start the work with the evaluation of the original filed formulations, as the risk analysis pointed out strong evidence in favor of this solution. The main factor was that the original documentation developed at headquarters was clear and adequately supported the formulations, while there was no reason to trust the documents presented by the CMO, which initiated the changes.

It is probably that bad management, inadequate training, and lack of investments were the main reasons to explain the changes. One of the most common differences found was the screen size change for the milling operation: the correct size had been replaced for a closely related screen to avoid expenses.

One pilot lot of each formulation was manufactured and stress stability studies were performed for a short period of time to identify potential failures. The results confirmed the results already filed, thus supporting the alternative selected.

The analytical method validations were updated by the "new" CMO, given that there were analytical equipment

differences and there was no possibility of doing a satisfactory Test Method Transfer with the several former CMOs.

The next step was the manufacture of the engineering runs and the validation lots, which was performed satisfactorily.

The compliance issue was mostly an internal issue since the regulatory requirements did not request so many details of the manufacturing or analytical methods. The "owner" company also was concerned by the lack of a controlled situation and any potential regulatory or manufacturing implication in the future.

This example from real life is not an uncommon situation and emphatically stresses the need of a very good process of selection of a CMO for pharmaceutical products. In this particular case, the "new" CMO took the ownership of the whole project, but it should be noted that the headquarters for both companies, the "owner" and the "new" CMO, belonged to the same European country and they were able to understand each other fairly easily.

Conclusion

The outsourcing activity is a challenging and exciting opportunity to improve the way of doing things for pharmaceutical companies. The economic figures involved in the outsourcing trade have continuously increased during the last few years and the forecasts are more than promising.

The key factors for success are to establish the outsourcing activity as a permanent strategic tool to develop "inbound" confidence in it, to generate a clear and complete Project Overview Statement, and to develop close partnership with the outsourcing company.

Many years ago, it was unthinkable that some activities could be handled outside the manufacturing company, while today there are some companies that outsource all their manufacturing activities. This change in the manufacturing paradigm is giving a strong signal to the market and that market should be listening in order to profit from it.

References

1. Guidance for Industry, Quality Systems Approach to Pharmaceutical CGMP Regulations, FDA, September 2006.
2. The Economic Times, Pharmaceuticals, Times News Network, April 2006.
3. Stockdale, Douglas, and others, "Ready to Use Stoppers: A Novel Outsourcing Alternative," *Pharmaceutical Engineering*, March/April 2002.
4. Roberson and Copaccino, The Free Press, 1994..
5. idem.
6. Wysocki, R.K., with contributions McGary, R., "Effective Project Management," Wiley Publishing Inc., Third edition.2003.
7. *ISPE Good Practice Guide: Technology Transfer*, International Society for Pharmaceutical Engineering (ISPE), First Edition, March 2003, www.ispe.org.
8. Guidance for Industry, SUPAC-MR: Modified Release Solid Oral Dosage Forms, FDA, September 1997.
9. Carney, Defining and Managing Risk for Projects with a Contract Manufacturing Organization, *Pharmaceutical Technology*, August 2006.

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"Offshoring" Life Science Production is not the Only Answer

by Roger S. Benson, FREng

This article presents an analysis of the manufacturing and supply chain costs and suggests that for true commercial stage manufacturing, offshoring is not the only option for products that are sold in Europe and other Western countries.

Introduction

The life science industry of Western Europe is an important source of wealth, jobs, and a large export success. As with all Western European manufacturing industries, it has to produce the right product at the right price and the right time, while satisfying all the environmental, safety, and product regulatory control requirements. Maintaining true commercial manufacturing of life science products in Western Europe increasingly faces a specific challenge from low labor rate countries. The published average wage rates in Western Europe[1] of Germany €23/hr ($29.90/hr) and the UK of €13.70/hr ($17.81/hr) compare unfavorably with Poland €2/hr ($2.60/hr), India €0.85/hr ($1.11/hr), and China €0.61/hr ($0.79/hr). However, note that the low labor cost countries often encourage the use of labor rather than automation, hence the effective difference is nearer a fifth to a half of Western European rates.

Life science manufacturers also face a number of other challenges, including:

- stringent regulatory pressures such as GMP, QA, and QC validation requirements, moving to "real time release"
- increasing taxes in Europe
- growing buying power of governments and pharmaceutical intermediaries used to decrease prices – this pressure works down the supply chain to the manufacturers.
- rising oil, energy, and other raw materials prices, which pass through the supply chain to manufacturers
- the growing presence of generic drug manufacturers who do not have the research overhead of the major drug companies – with no patent protection, they focus on ensuring a very competitive delivered cost.

Given these pressures, it is hardly surprising that many Western European life science manufacturers have already established commercial manufacturing facilities in low labor cost countries, particularly India and China, to satisfy both the large indigenous market and export to Europe. They also are considering "offshoring" additional manufacturing. In addition, the low

Table A. Life science manufacturing benchmarks.

KPI	Life Science Industry	A Winning Life Science Plant	A World Class Process Plant
Added Value/Emp	€94,000 ($122,200)	€185,000 ($240,500)	€297,000 ($386,100)
Total/Added Value Emp	2.6	1.6	1.3
Supply Chain Costs % Sales	22%	14%	5.3%
Customer OTIF	98.5%	99.5%	99.8%
Finished Goods Days	54	30	3
Supplier OTIF	88.1%	99%	99.8%
Stock Turn	4	14	50
RFT	95%	96%	99%
Plant Availability	46%	86%	97%
OEE	30%	74%	97%
Cycle Time Hours	720	48	8

labor rates and high education standards offshore also are encouraging the relocation of the development-stage manufacturing, though often the proximity of research and technology is a reason for retaining development stage manufacturing in Western Europe.

This article presents an analysis of the manufacturing and supply chain costs and suggests that for true commercial stage manufacturing, offshoring is not the only option for products that are sold in Europe and possibly other Western countries.

Lean Manufacturing in Life Science

The analysis refers to the concept of "lean operations."[2,3] To clarify, this does not directly mean less people. It does mean driving out the following seven wastes:

- overproduction, e.g., minimum batch sizes in excess of immediate product demand
- off specification products and service, e.g., second quality product that is destroyed
- unnecessary motion, e.g., moving an intermediate to another site only to return for final processing
- unnecessary inventory anywhere in the supply chain, while ensuring that the patient's course of treatment is never put at risk through supply interruptions or delays
- inappropriate or unnecessary processing of material and information
- unnecessary transport, e.g., moving a product past a customer to a central warehouse only to then ship it back to the customer
- waiting in manufacture and the supply chain, e.g., time from raw material arriving to product being shipped significantly longer than the actual manufacturing time

In the life science industry, this journey is often described as Lean Six Sigma.[4]

Benchmarking Life Science Manufacturing

A starting point for any improvement journey is to benchmark the existing performance[5] - *Table A*.

While the very high customer On Time In Full delivery (OTIF) rate of 98.5% is excellent, the high number of Finished Goods Days of cover, low Added Value per Employee, high total /Added Value Employees plus the low Overall Equipment Effectiveness (OEE) are all indicators of potential waste.[6]

For those unfamiliar with the term OEE, it is the product of three components:

$$\text{Product rate} - \frac{\text{average production rate}}{\text{best ever achieved production rate}}$$

Quality rate – % of production that is Right First Time (RFT)

$$\text{Availability} - \frac{\text{hours the plant is producing saleable product}}{\text{8760 hours per year}}$$

Manufacturing	Western European Plant	Low Labor Cost Plant	
Sales = Plant Capacity	100,000	85,714	
Raw Material Costs	18%	15%	
Energy, Waste, Purchased Cost	20%	16.3%	
Labor and Other Fixed Costs	41%	10.25%	
Depreciation	21%	15%	
Interest: Stock and Cash Time	4.0%	4.6%	
Total	**104%**	**61.6%**	
Supply Chain			
Shipping	2%	2%	
Other Supply Chain Costs	14%	6%	
Import/Export Duties	0	3%	
Total	**120%**	**72.6%**	
Cost/Ton in Europe	€120 ($156)	€85 ($111)	
Performance			
OEE	35	30	
Stock Turn	4	3	
Cash to Cash Days	90	90	

Problem as life science products may be flown and labor costs high

Table B. Analysis of the delivered cost/unit comparing a European life science manufacturer and a competitor in a low labor cost country.

The best ever achieved production rate is typically that achieved over a one week period when the plant was fully operational. Note that it is not the design rate. This is based on the premise that if the plant has achieved the rate for one week, it should target to achieve it every week. Similarly, the Right First Time percent is the figure direct from the plant. In availability, the figure of 8760 is the number of hours in a year. If a plant has annual shutdowns for maintenance of holidays, these all reduce the OEE. While it is a very demanding measure as it is the product of three percentages, it is increasingly being used in the life science industries and other process industries to measure asset effectiveness.

Analyzing the Effect of Low Labor Cost

Life science manufacture has two key characteristics, which are significantly different from other process manufacturers.

1. Much higher requirements of QC, QA, and documentation control as the manufacturing process is not normally directly controlled. Thus, the quality has to be assessed through testing. This results in relatively high numbers of people employed in the laboratories and QC area. The consequence is a typical labor cost of 41% of manufacturing costs compared to 20% in a typical specialty chemical company.

2. The high value and low physical volume of the products makes air freight a competitive option for all manufacturers. Other process industry products have higher physical

volumes and much lower prices. For these industries, the cost and working capital implications of shipping the product half way across the world may add 7% plus costs to the importer and provide a little protection from lower manufacturing cost imports.

The key to analyzing the threat and opportunity is to focus on the delivered cost of the product to the customer in Europe, not the cost of the product exiting the manufacturing plant. This is the cost that determines the final selling price and the customers' buying decisions. If this delivered cost is greater than the price set by the market or by the regulators in respective countries, the sale is potentially made at a loss.

To analyze the impact, Table B provides a simple way for a typical life science operation using the benchmarking approach developed in references six and seven. The first column analyzes a Western European life science manufacturer and the cost breakdown is based on true figures. The analysis is dimensionless and considers a plant manufacturing 100,000 units of product. These could be blister packs or consignments. The cost breakdown as a percent of manufactured product cost is: raw materials 18%, energy 20%, and labor 41%. As a relatively new and expensive plant its depreciation is high at 21%. The manufacturing performance is the average for the life science industries as presented in Table A and analyzed[5] with an Overall Equipment Effectiveness (OEE) of 35% and a Stock Turn of four. The Cash to Cash time of 90 days is the total number of days between the manufacturer paying for the raw materials and the customer paying for the products. In some parts of the life science industries, it may be even longer. Shipping costs are low at 2% as most products are sold locally, but the other supply chain costs like storage, transport, marketing, insurance, administration, IT, etc., are high at 14% of delivered costs.

Using an 8% interest rate on money to fund the stock and the cash to cash days, this performance results in a delivered cost of **€120/unit ($156/unit)** for a Western European plant.

The second column considers an identical plant operating in a low labor rate country. While raw materials and energy costs per unit are assumed to be the same, the low labor costs reduce manufacturing labor costs to a quarter and all other supply chain also will be lower at an estimated 6% for the same reason. A slightly lower OEE of 30% is assumed. Since all products are air freighted, the cash to cash time, shipping costs, and duties remain unchanged. The comparable delivered cost into the European markets on this basis is a very competitive **€85/unit ($111/unit)** after all the transport costs. This 30% delivered cost difference is exactly what many Western European life science companies are experiencing.

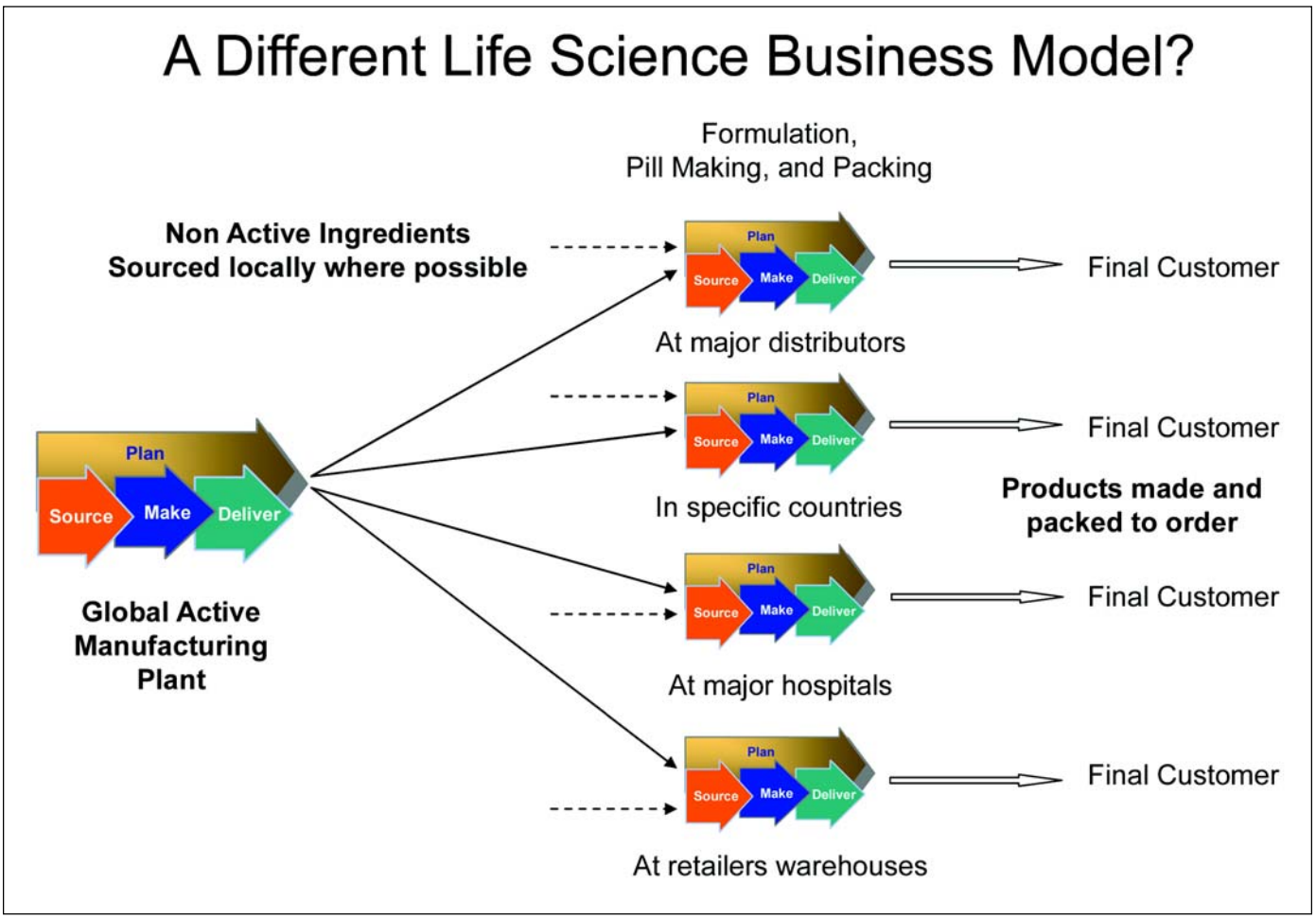

Figure 1. Illustration of a distributed life science manufacturing model.

Exporting from Europe becomes very difficult for the same reason, plus the additional export costs incurred.

Impact of Applying "Lean Manufacturing" Principles

The journey to "lean manufacturing" may take from two to five years depending on the starting position. Reference 3 describes the route to deliver "lean manufacturing" in life sciences, while ensuring the regulatory demands are satisfied. A key and common component is to focus on significantly reducing all equipment change over times applying techniques from other industries such as Single Minute Exchange of Die (SMED). In the author's experience, this is always beneficial. Reducing change over times not only increases plant availability, but the shorter times encourage smaller batch runs, which potentially reduce working capital levels. While working capital levels are often determined by business priorities to never let a customer down, experience has often demonstrated that as confidence in manufacturing increases, coupled with continuous pressure to lower costs, working capital levels are reduced.

In the best "lean" batch operations in the process industries, the OEE has been driven up to 90%. For life sciences, this would effectively increase the manufacturing output by 246%. For those unfamiliar with OEEs, this is calculated by dividing the best experienced OEE for a life science operation of 74% by the average value of 30%. It does not follow at all that the extra output may be sold as markets will not increase by the same amount if at all. Hence, one immediate consequence of such actions will be excess manufacturing capacity and sites within the business. This will lead to the closure of the less efficient manufacturing sites. The Western European press is already reporting evidence that this is happening.

The third column in Table C presents the analysis after the Western European manufacturer has successfully applied and delivered the principles of "lean operations" to both manufacturing **and** the supply chain.

Raw materials and energy usage per unit of product remain unchanged, while labor is reduced significantly as people contribute fully, automation is increased, and real time release is delivered. Much improved reliability and quality, reduced change over time, and even better OTIF allow the stock turn to increase to 15 and cash to cash time to reduce to 40 days. The other supply chain costs also are reduced to 9% as the operation moves more to an electronic mode of servicing the customers. This alone would release much of the cash to fund the journey to "lean."

The resulting delivered price per unit falls to **€60 ($78)**. This is 30% less than the imported cost. It is very competitive in Europe and may even enable products to be exported. This is exactly what the winning process plants in Western Europe are delivering; growing market share and ensuring the manufacturing stays in Western Europe.[9]

However, the journey to "lean operations" is well documented.[2,3,4] There is no fundamental reason why plants in low labor cost counties should not also adopt "lean operations." Column 4 applies the benefits of "lean manufacturing" in a low labor cost country. While the OEE achieved is slightly less at 85% and the stock turn is less as they may have more shipping delays which also increase cash to cash days, the result is that they again become competitive with a delivered price of **€45 ($59)**.

Manufacturing	Western European Plant	Low Labor Cost Plant	Lean Western European Plant	Lean Low Labor Cost Plant	
Sales = Plant Capacity	100,000	85,714	257,143	242,857	
Raw Material Costs	18%	15%	46%	44%	
Energy, Waste, Purchased Cost	20%	16.3%	48.9%	46.1%	
Labor and Other Fixed Costs	41%	10.25%	25%	3%	
Depreciation	21%	15%	21%	4%	
Interest: Stock and Cash Time	4.0%	4.6%	1.4%	2.3%	
Total	104%	61.6%	142.6%	99.2%	
Supply Chain					
Shipping	2%	2%	2%	2%	
Other Supply Chain Costs	14%	6%	9%	5%	
Import/Export Duties	0	3%	0	3%	
Total	120%	72.6%	153.6%	109.2%	
Cost/Ton in Europe	€120 ($156)	€85 ($111)	€60 ($78)	€45 ($59)	Competitive Again
Performance					
OEE	35	30	90	85	
Stock Turn	4	3	15	12	
Cash to Cash Days	90	90	40	80	

Table C. Impact of lean manufacturing and supply chain.

Moving Beyond "Lean" to Distributed Agile Manufacturing

Is there a route beyond "lean" that would allow Western European manufacturers to remain competitive?

The bottleneck preventing additional cost reductions is often the existing plant equipment and business model. The trend has been to build even larger reactors and mixers feeding ever faster "tablet" machines and packing lines. These have the following three disadvantages:

- Increase supply chain costs as all feed stock and products have to be shipped to and from the central location. This is waste and increases both transport and working capital costs and is not good sustainability practice.
- While high speed tablet lines are very impressive when operating, any breakdowns are very significant and changeovers are often complicated and very time consuming.
- As the products for many different countries are often packed on one line the number of Stock Keeping Units (SKUs) increases due to different languages and sizes with all the consequential problems and non value added time of more changeovers.

These are not "Agile" plants capable of manufacturing to a "unit of one." This term was first described in a 1999 United Kingdom Manufacturing Foresight study on the future of manufacturing in the United Kingdom in 2020.[10] The concept of a "unit of one" is that the manufacturing plant only manufactures exactly what the customer orders, no more or no less. To achieve this agile state, the plant would need to:

1. operate at a rate and time determined by the customers
2. become fully automated
3. distribute adjacent to the customer's premises or market
4. size according to adjacent customer requirements
5. possibly manage from a central remote control room

Much of the potential process technologies required to deliver such a plant is already available today in other industries such as food, gas liquefaction, and some parts of the chemical industries who have already responded to similar cost pressures from their customers. While life science manufacturing has specific requirements, such as temperature controlled environments, GMP practices, and others, reducing the size of the plants and potentially operating at slower speeds than today's fastest plants, will allow exploitation of proven reliable process technology. In addition, today's proven advanced process control and multi-variate data monitoring techniques makes such plants a practical proposition. While all this process technology also is available in low labor cost countries, it is the author's experience that, due to the very low cost of labor, they tend at this time to use labor rather than automation as it is less expensive. In Western Europe, automation is usually less expensive than people. As labor costs inevitably increase in today's low labor cost countries, this balance between automation and labor will change.

Distributed Life Science Manufacture

With manufacturing processes capable of manufacturing to a "unit of one," it is suggested that the business model will evolve more to one of distributed life science manufacturer as illustrated in Figure 1.

This business model has been successfully adopted in air liquefaction for many years and other parts of the process

Manufacturing	Western European Plant	Low Labor Cost Plant	Lean Western European Plant	Lean Low Labor Cost Plant	Agile Western European Plant	
Sales = Plant Capacity	100,000	85,714	257,143	242,857	274,286	
Raw Material Costs	18%	15%	46%	44%	40%	
Energy, Waste, Purchased Cost	20%	16.3%	48.9%	46.1%	40%	
Labor and Other Fixed Costs	41%	10.25%	25%	3%	15%	
Depreciation	21%	15%	21%	4%	3.75%	
Interest: Stock and Cash Time	4.0%	4.6%	1.4%	2.3%	0.9%	
Total	104%	61.6%	142.6%	99.2%	99.6%	
Supply Chain						
Shipping	2%	2%	2%	2%	1.5%	
Other Supply Chain Costs	14%	6%	9%	5%	4%	
Import/Export Duties	0	3%	0	3%	0	
Total	120%	72.6%	153.6%	109.2%	105.1%	
Cost/Tonne in Europe	€120 ($156)	€85 ($111)	€60 ($78)	€45 ($59)	€38 ($49)	Very Competitive
Performance						
OEE	35	30	90	85	96	
Stock Turn	4	3	15	12	40	
Cash to Cash Days	90	90	40	80	30	

Table D. The potential impact of agile distributed life sciences manufacture.

industries are beginning to explore. Effectively, the life science business model is changed to an "agile" distributed model. The primary API is manufacturing at one or more major manufacturing sites. Due to its relatively small volume, it is air distributed for final secondary processing, particularly blending and packaging, adjacent to the major customers. These may be countries, large pharmaceutical distributors or even hospitals.

Such a business model could potentially increase OEE to 96%, deliver improved energy efficiency and process yield, increase stock turn to 40 with cash to cash down to 30 days or less, and reduce shipping costs to 1% and other supply chain costs to 3% due to much reduced central overhead functions, storage, and shipment. The resulting impact is calculated in Column 5 of Figure D. The result is that the delivered cost to the customer reduces to **€38/unit ($49/unit)**!

Note that the delivered cost/unit has effectively reduced by **69%** without any change in raw material costs. This illustrates the impact on delivered cost of significantly reducing all the existing supply chain costs and operating expensive assets much harder. This business model is even potentially robust against lower cost raw materials being available in low labor cost countries.

At this point the low labor cost threat no longer exists as it is very difficult for a low labor cost country to compete with a fully automated lean agile manufacturing and supply chain situated on the customer's site when the costs of importing and transport have to be absorbed.

Conclusions

While it is recognized that several assumptions have been made in this analysis, the conclusion is that it is possible for life science manufacturers in Western Europe to compete with low labor cost manufacturers.

The analysis suggests that the key steps are:

- Continuously invest and deliver "lean" manufacturing and supply chains.
- Automate as much as possible to reduce impact of Western European wages.
- Actively invest in developing and building the "agile plant after next" that is potentially distributed to the customer's sites.
- Consider moving to a distributed manufacturing business model.
- Focus on providing outstanding product quality and service to customers at a competitive delivered cost.

This is not an easy journey, but it is winnable and on the way the capacity of existing assets will almost double and productivity will increase dramatically.

Standing still is not an option as it will inevitably lead to closure due to either:

- excess capacity arising from Western European competitors who do make the journey
- off-shore and generic manufacturers

If Western European life science manufacturers do not make the journey, many of the commercial manufacturing plants could be closed within 10 years with the critical mass of manufacturing skills, support services, and product supply chains in decline. It has already happened to other industries like cotton and electronics. Why not life science?

The solution is in the hands of all the technologists, engineers, and business managers of the Western European industry.

References

1. "The Economist Intelligence Unit," Euromonitor; S&P DRI; Department of Labour; BCG Analysis, 2004.
2. Womack, J.P., Jones, D.T., and Roos, D.; "The Machine That Changed the World: The Story of Lean Production," Published by Rawson Associates 1990; ISBN 0-06-097416-6.
3. Page, J., "Implementing Lean Manufacturing Techniques: Making Your System Lean and Living with It," Published by Hanser Gardner; March 2004. ISBN-13: 978-1569903537.
4. Chatterjee, B., and Green, J., "Eight Steps to PAT: Using the Design for Lean Six Sigma Toll-Gate Process as Best Practice," *Pharmaceutical Engineering,* March/April 2007, Vol. 27, No. 2.
5. Benson, Professor R. S., "From Good Manufacturing Practice to Good Manufacturing Performance," ISPE Conference, Manchester, October 2003.
6. Ahmed, Prof. M., Benson, Prof. R.S., "Benchmarking In The Process Industries," Published by the Institute of Chemical Engineers, May 1999. ISBN 0 85295 411 5.
7. Benson, R.S., "Off Shoring production is not the only answer," *Specialty Chemicals Magazine,* April 2006.
8. Competitiveness of the UK Process Industries, April 2003; www.picme.org.
9. 2005 CIA Awards report, Outstanding Progress, Available from PICME Office: www.picme.org
10. Manufacturing 2020: We Can Make It, http://www.foresight.gov.uk/Previous_Rounds/Foresight_1999__2002/Manufacturing_2020/Reports/Reports.html.

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Managing Offshore Outsourced Software Development

by Jan Villumsen

This article focuses on how to run offshore outsourced projects – what makes these projects different, what to be aware of, and how to get organized in an offshore outsourced setup.

Introduction

Offshoring and outsourcing have been in the headlines for some years now, and this trend seems to continue. It is facilitated by factors such as cheaper transport of goods and people, internet, and optical sea cables changing the virtual distances, plus liberalization of international trade opening markets in both directions. The drivers are numerous – access to scarce competencies or more people, reduction of captive investments, and cost savings, to mention some of the predominant ones.

A tour at one of the Indian IT hubs will show sites from most of the big IT companies and also an impressive, ongoing construction of new facilities. Doing offshore outsourcing involves big risks. It is easy to find literature on how to select offshore destinations, supplier evaluations, and contractual matters – but when this is done, the work is just about to begin. Transfer of tasks/projects/products has to be prepared, including training in domain, products, and processes. Infrastructure has to be established, the actual transfer must be implemented, and the progress of projects monitored.

This article focuses on how to run offshore outsourced projects – what makes these projects different, what to be aware of, and how to get organized in an offshore outsourced setup. It is based on experience from software development, but the majority of the recommendations are generally applicable in offshore outsourcing setups involving design and development.

Overview

First an overview is presented of different kinds of offshore outsourcing setups with focus on multi-site development and contract development, which are the two extreme or pure models discussed in the rest of this article. A brief guidance is given on when to choose which model.

A fundamental aspect of offshore outsourcing is the distance. This article discusses how it affects projects and how to address it. How to run multi-site projects constitutes the main section: communication, trips (purpose, agenda, frequency), follow-up on status and progress, and finally technical support are the primary subjects. The IT infrastructure covers both development tools and communication tools and is an important platform for the day-to-day

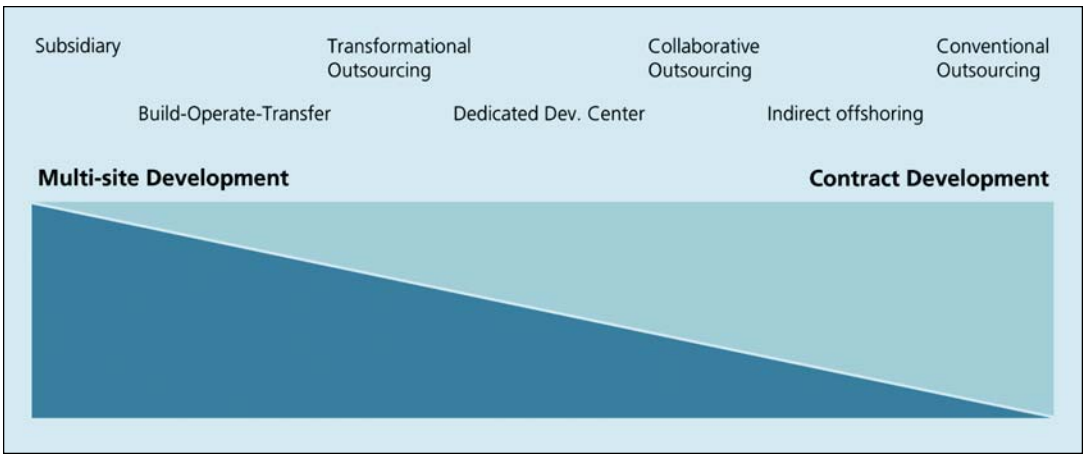

Figure 1. Various offshore outsourcing setups.

operation. The performance and stability of this platform should contribute to increased efficiency and reduction of the sensed distance. Contract development is the second and smaller main section. It covers such topics as contractor competencies, contractual matters, and requirements for implementation and delivery. Culture is an important aspect of offshoring. This article gives a brief introduction and generic guidance in the section "Communicating Across Cultures." The opportunities and risks in offshore outsourcing are discussed in the conclusion.

Two Different Project Models

The variety in nature of offshore outsourced projects is huge, and there is an individual terminology for a number of these setups. To make things simpler and more operational only two different ways of managing projects are addressed in this article - multi-site development and contract development.

Contract development is another term for conventional outsourcing. The term outsourcing is generally used for a contractor delivering products or services to a company to which the contractor is not a subsidiary. The focus in this article is on the way projects are managed and not on ownership relations; hence, the term contract development is used for managing both internal contractors (including subsidiaries) and external contractors. Thus, the project management tools in contract development are the same as in conventional outsourcing - and offshoring elements are outside the scope.

Multi-site development addresses offshoring. Again focus is on the way projects are managed; therefore, the offshore entity can be a subsidiary or it can be a contractor with a contract based on a time and material consumption (the actual outsourcing element being outside of scope).

Characteristics of the two setups are:

Multi-Site Development:

- full control
- time and material-based costs
- all financial risks
- all project risks and consequently lower prices
- more exposed to multiculturalism due to direct interaction with the offshore destination

Contract Development:

- no direct control – arm's length relationship
- very elaborate contracts
- risks taken by contractor
- higher prices as contractor takes the risks

Figure 1 illustrates the gradual change between different setups. The terminology in the top row describes the degree of outsourcing, while the second row describes the degree of offshore outsourcing. The figure is solely meant to give an overview and illustrate the gradual change and does not provide an absolute rating of the different setups.

Collaborative outsourcing is a flexible relationship where the scope may change. It is an ongoing company-to-company interaction where the cost is not necessarily the primary concern. One example is IT outsourcing.

Transformational outsourcing is a committed and ongoing relationship; it can be a joint venture.

In Indirect Offshoring, the contractor has an onshore legal entity that makes the legal agreements with the customer. The onshore entity also may be the interface to the remote site, making things simpler for the customer who has to pay for this, but benefits from having contractual terms according to onshore laws and traditions.

A Dedicated Development Center is a contractor's entity that is dedicated to work for a specific customer. The site has an IT infrastructure dedicated to this specific customer and customer branding of the site.

Build-Operate-Transfer is an agreement starting as a Dedicated Development Center, and after a certain time, the customer will, or has the right to, take over the entity.

The combination of the two extremes – multi-site development and contract development – offers the complete palette of additional project management tools, enabling a project manager to choose the right tools in any of the setups in Figure 1.

Selection of offshore outsourcing model is a strategic choice. A brief general guidance on how to select a model would be: multi-site development is suitable for long-term engagements and complex projects with many deliverables/dependencies across projects (typically products with many interfaces) or a short time-to-market requirement, which rules out an up-front elaborate contract (focus is on training the remote site rather than specifying every single bit and byte). Contract development is well suited for maintenance and porting projects plus development of stand-alone products, i.e., low risk projects. Typically, contract development is for non-strategic technologies and for projects where it is feasible to write specifications upfront.

The main focus of this article will be on multi-site development with a briefer description of contract development since many other sources exist on contract development.

How Distance Matters

The fundamental factor in multi-site projects is that participants are placed in different locations - which means that transport and communication become issues. It is a well-known fact that performing projects in a multi-site setup increases the risks. Co-location of personnel is often mentioned as a key factor for successful projects.

Distance dramatically changes the way we communicate. A lot of communication is in writing such as e-mails, and the written word is strong and may lead to misunderstandings when using irony or writing in anger. Mail can be too short. Be aware that mail constitutes a form of communication that falls between a telephone conversation and a letter. It is fast and dialog-oriented, but without the tone of the voice that enables the listener to observe whether the sender has a good or a bad day. E-mails should start and end with some small talk – it may be as short as "have a nice weekend."

The general amount of small talk is reduced considerably

Welcome Presentation • News from headquarters – organization, revenue ... • Accomplishments since last trip and their contribution • Status of ongoing projects • Roadmap and plans – a vision for their role • Kick-off of new projects • Project Evaluation of completed projects • Training, new procedures/processes, ... • Agenda for this trip
Joint Meetings with Local Manager • Status meetings with local manager and each development team • Project Evaluation with local manager and each developer
Miscellaneous Meetings • Small talk plus formal talk about current tasks and issues at each developer's desk • Meeting various key people • Group photo
Optional Meetings • Participation in job interviews with new candidates
Wrap-up Meeting • Accomplishments during the trip • Updated Project Evaluation • Priorities for tasks the next few months

Table A. Generic agenda for visits to remote site.

by the fact that colleagues do not meet informally in the kitchen for tea or have lunch together. Reality at the other site is watched through a keyhole.

Usually people will try to do their best. The old Greeks talked about Etos, Patos, and Logos as the natural flow in communicating with and convincing other people.[1] Etos is building trust and integrity, Patos is about understanding the other part and showing empathy, while Logos is being understood and to convince the other part.

Participants who understand the nature and importance of communication tend to make a project more successful as they prioritize the coordination between sites. On a module staffed across sites where staffing changed slightly between releases, it was obvious that the quality was affected by the team's changing communication skills.

Language might be another issue – English is not just English. Key people and preferably everybody must be able to communicate with one another both orally and in writing, making it possible to conduct reviews as teleconferences. Despite the language problems it is important that the parties call one another. If necessary, people might confirm what they have agreed on by e-mail afterward. Small talk is a serious issue. By showing some interest and respect for the other site's culture, participants will get a lot in return. It is important to have some fun together.

Running Multi-Site Projects

Vital aspects of multi-site projects are communication, giving feedback, and having well-defined processes.

Regular and frequent trips (e.g., quarterly) between sites are highly recommended in order to build trust and relationships with key people at the other site. Valuable information and buy-in will be obtained and relations will be established that the project is likely to benefit from if it experiences a crisis. In case of trouble, a remote site on another continent is far, far away. The remote site also should be encouraged to build relationships with key staff at the onshore site - help them build a local network, introduce them to colleagues etc. This will relieve onshore staff from acting as simple messengers on many questions.

The most important and powerful aspect of communication is mindset and attitude. A multi-site mindset and good attitude should be enforced, making people understand that they will only become successful if the other site becomes successful. One site should not leave it to the other to make things happen as they are highly dependent on one another. When disagreements between the sites pop up, the heads of both teams have a common problem. If they start blaming one another, they are sure to be in trouble.

Multi-site development inherently has a lower communication bandwidth due to the distance. This easily results in lack of trust, even if both sites have the best intentions. Offshore teams should be considered as equal stakeholders and as being just as committed as the onsite team. It is essential to build relations with people who are trustworthy, and to get to know the offshore team members by communicating as often as possible by phone or other means. The delay in the feedback cycle related to long distance and time difference should be fought.

It is recommended to empower the remote team – to give them freedom to try new things (invent better practices and techniques) and freedom to use all their skills. Multi-site development is a careful balance between being in control and empowering the remote team. The remote site's loss of context – both business-wise and technically – is an obstruction for empowering. Training sessions on domain knowledge should be conducted, either by remote sessions or face-to-face.

Visitors to offshore sites should keep in mind that they are usually the messengers of the information that the onshore team gets at regular town hall meetings. Additionally, visitors are an essential part of the "glue" between the sites, i.e., visitors must promote the team spirit across sites as sites often have separate kick-off activities and team events. The headlines for headquarters' trips to offshore sites should be to provide feedback and visions and to strengthen personal relationships. This is reflected in the generic agenda in Table A.

Project evaluation is an important part of communication. The distance from the onshore development team to the customers is usually an issue – from the remote site it may be even more difficult. Visitors from headquarters might be the only ones telling the staff at the offshore site face-to-face about the importance of doing a quality job.

Before conducting a visit, the remote site should be requested to complete project evaluation reports. Simple metrics will be a good starting point for a discussion. It may be as simple as the number of error reports per working hour - *Figure 2*. The essence of the evaluation reports should be abstracted. What are the lessons to learn? What more would be interesting to know? It can be addressed in the welcome presentation and discussed both at the presentation and with individual team members. Afterward, conclusions might need adjustments, which should be included in the wrap-up pre-

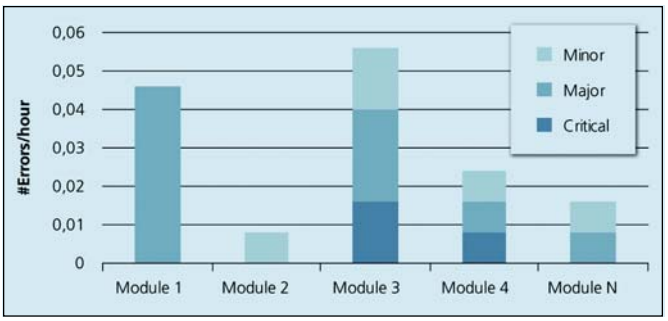

Figure 2. Metric on error reports per working hour.

sentation. Attention should be paid to cultural barriers to address. In some cultures, people find it difficult to apply a critical approach to their own and their colleagues' performance, especially in the presence of visitors from headquarters. Focus should be on the positive experiences as well as emphasizing that the goal is not to criticize one another, but to identify lessons to learn when striving for continuous improvement.

Multi-site development requires more formality to ensure that both sites are aligned. One option could be to organize it around well-defined points of contact with weekly teleconferences and to have weekly updates of the common Development Plan, Status Report, and Action List - *Figure 3*. Frequent deliverables make things more visible.

There will always, to some extent, be a lack of visibility of project status in multi-site projects.[2] This may be addressed by having a clear strategy with goals and priorities, taking into consideration that onshore management representatives are not there all the time to guide them.

Technical Support can be shared by a number of people in order not to overload a few people, as long as the agreed roles and responsibilities are in place. Teams should be composed of emphatic professionals who are able to communicate well when providing technical support. Different setups for technical support might be applicable at different stages. On an old legacy system, the onshore project manager provided most of the technical support and involved additional competencies when needed. In the early stages of remote participation in development on a new platform, the support load was huge and distributed among all the team members to avoid overloading a few. When the remote team had been trained to a level of self-support, the need for support was reduced, and the support that was then needed was high-level support usually handled by either the project manager or the system engineering department supplemented with support from senior developers.

Well-defined processes supported by procedures and standards with defined inputs and outputs (quality gates) have to be in place as illustrated in Figure 4 – and they have to be supported by detailed document plans and cookbooks. Document Plans have to be much more detailed than usual in order to ensure that documents get reviewed - and reviews get documented. Due to this, document plans should include review reports. Cookbooks describe "how to" and support the developers on how to carry out their tasks.

Inspection readiness is an important aspect for GxP-regulated companies, but is not covered by this article.

IT Infrastructure

When it comes to everyday life, teams depend heavily on the IT infrastructure. The quality and costs of telecommunication and data connections to many places have improved dramatically over the last decade. If the offshore site is not a subsidiary, security has to be balanced versus efficiency - the more integrated the company gets, the more efficient. There is not much added value in copying data to special areas dedicated to the remote team.

An efficient IT infrastructure includes development tools and communication tools. Preferably the same tools should be used at both sites to ease support.

Development tools include identical development environments, access to servers and test equipment, and access to document control systems, configuration management, and error tracking. Servers containing large volumes of data frequently needed by many people should be replicated nightly in order not to load the link during working hours. Organize things to benefit from time zone differences (for example sharing test equipment and round-the-clock-engineering).

Communication tools include tools used for communicating and sharing information. In the starting phase, which is a

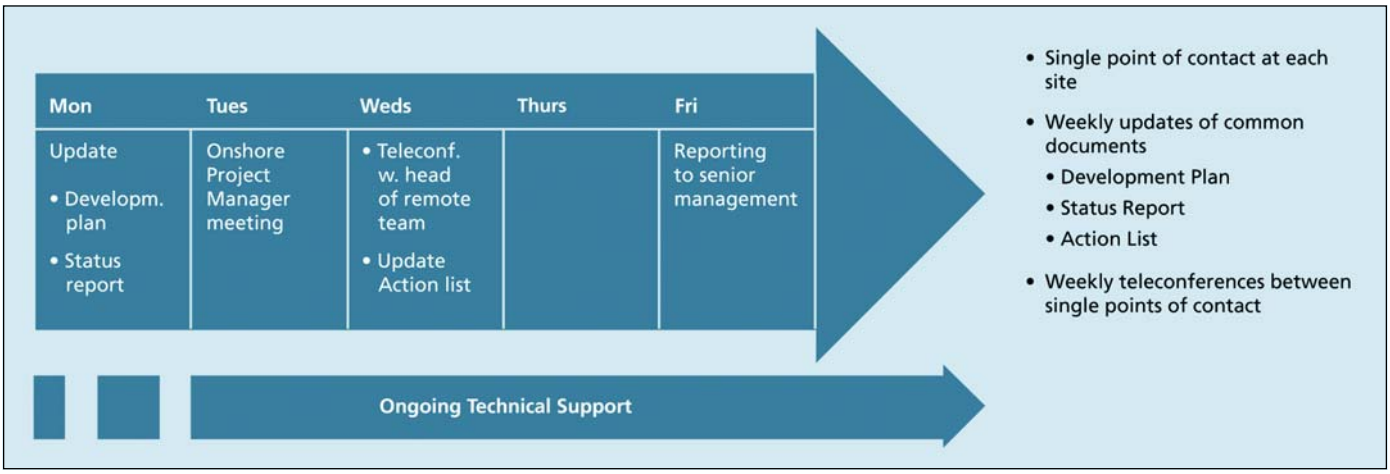

Figure 3. Follow-up process aligned across sites.

learning phase, many people ask the same questions. Discussion groups and news groups are, for example, good ways to disseminate information to everybody. Teleconferences are an efficient, but costly way of solving many problems compared to e-mails, due to the long turn-around times of e-mails because of time zone differences. An example is a product family which for years had been generated from the same code base. Suddenly there was a consistent problem on one of the products despite the fact that the issue was reported as solved several times, and there were daily mails discussing the problem. A short telephone call revealed a simple lack of communication regarding the specific content of one of the products triggered by a small general change to the entire product family. Over the phone, it is generally easier for people to recognize if they are talking past each other.

PC tools are available that operate across data links and enable users to have teleconferences, use Web-cams, chat, and to give somebody at the other site access to some of their applications or full access to their PC. This is very handy for troubleshooting.

The intranet is a good focal point for sharing information such as information on staff members with photos (who-is-who), procedures and guidelines, documents and links, information on projects, and test environments. Current update is very important.

As a matter of course, the remote site depends heavily on the link. Not all kinds of links are equally robust. In case of a VPN via the internet to an entity that is not covered by the onshore IT organization, who is then responsible for solving link problems? The consequences of link problems may be reduced by getting local servers and test setups; thus, this also improves performance and efficiency at the remote site. Not all applications are tuned for performing across intercontinental links with big delays.

The importance and urgency of an integrated IT infrastructure simply cannot be exaggerated.

Contract Development

In the case of contract development, the onshore organization is still responsible for the contractor meeting the requirements of the user.[3] The contractor has to be on the list of approved suppliers.

Contract Development is about managing settings, scope, and outputs rather than detailed task management. It can be divided into the following areas:

- contractor competencies
- contractual matters
- requirements to implementation and delivery

Regarding competencies the questions are: Does the contractor master the technology, i.e., programming language, de-

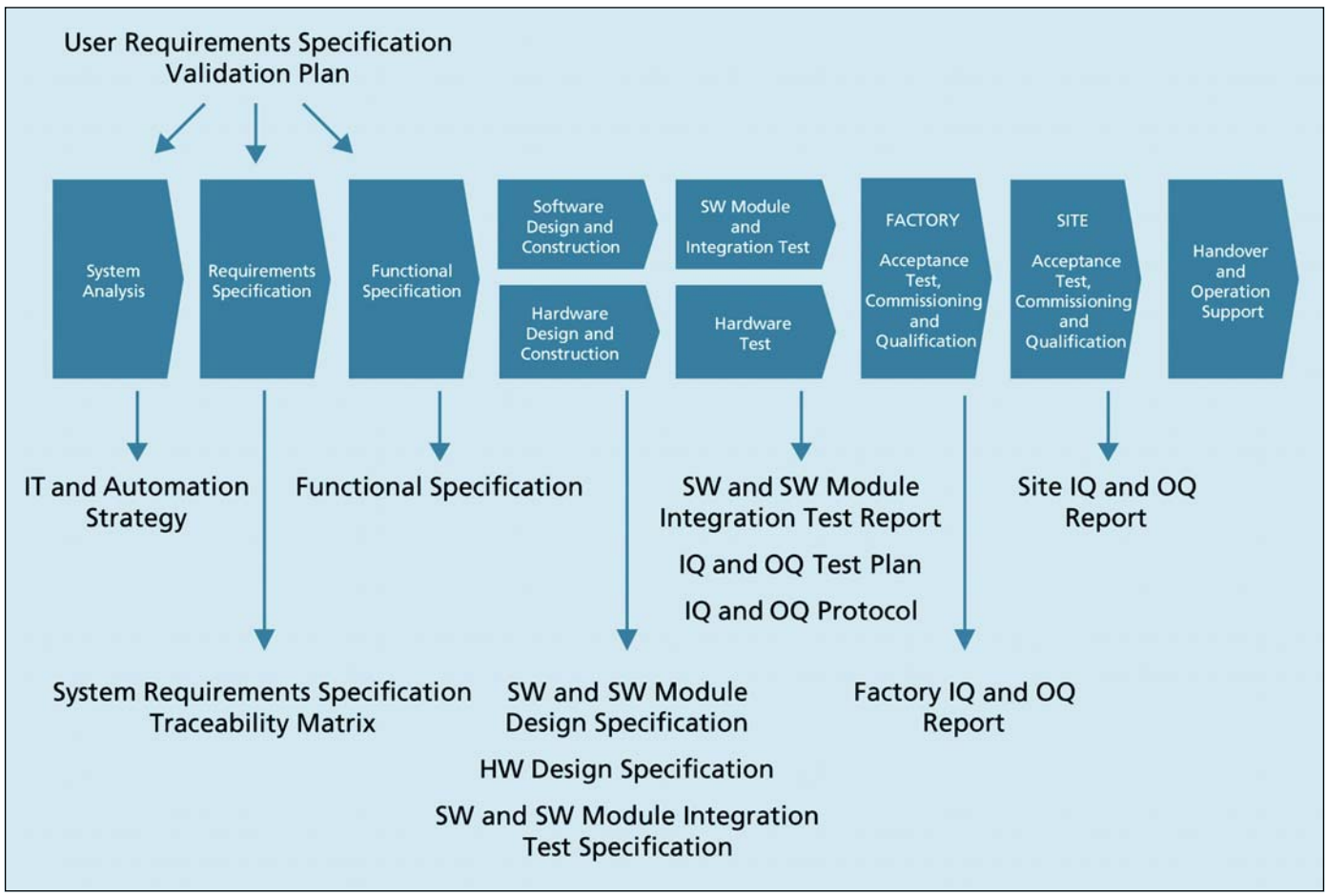

Figure 4. Process model for development of IT systems.

velopment environment, design for maintainability, and performance? Does the contractor have domain knowledge, that is, does the contractor understand requirements and deliver applicable solutions? An issue to follow up on via requirement reviews. How about process maturity? Does the contractor have a formal quality management system (e.g., based on ISO 9001) fulfilling the requirements, i.e., is the contractor able to organize teams with predictable quality, time, and resources and to deliver documented solutions? Some otherwise capable contractors are not knowledgeable about validation, its terminology, and applicable regulations.[4] This may limit the source of contractors unless ways of addressing the problem are found.

Continuous follow-up on the competencies is recommended via regular visits to the contractor and formal audits of said contractor.[5] But choosing contractors having top maturity might trigger other challenges if the onshore organization does not have an equal maturity level. The contractor will win every dispute as they are able to document their case.

When making a contract with an offshore company, competent legal advice is needed since traditions, and what is accepted, can differ considerably from country to country. On the other hand, bringing a lawyer to an opening meeting where participants are supposed to build relations with one another might be regarded as offending in a relation-based culture. Standards and force majeure can differ greatly – in some countries, contractors will accept taking certain actions in case of force majeure as force majeure is much more likely to occur in some countries than others.

A user requirement specification is part of the contract as well as agreed quality plans and project plans. All metrics on contractor performance should be defined and documented with penalties for poor performance and incentives for excellent performance. Intellectual Property Rights (IPR), responsibilities, service, and maintenance are basic components of IT contracts besides many traditional legal issues.

Change management and organization, including communication are important issues as well. Who are members of a joint steering committee, when is who meeting whom, and what is the agenda, status reporting, and how are conflicts solved? Both parties having a common interest in the contract becoming a success is more important than a long contract, especially in countries where the legal system is useless for any practical matters.

Requirements to implementation are important if it is essential to ensure the ability to maintain the product in a specific environment. These are typical requirements to development environment, configuration management, and error reporting.

Delivery requirements specify acceptance criteria (e.g., FAT and SAT), documentation, prototypes, and early deliveries.

Communicating Across Cultures

In offshore outsourced projects, there are cultural differences between the sites. They might be small differences or huge differences - nevertheless investigating and understanding the culture of the remote site is strongly recommended. As culture is dynamic, professionals have to keep observing it and adapting to its new forms. This section offers some generic guidelines on how to address these cultural differences.

Trust, respect, and comfort are universal relationship elements and they are communicated differently. Westerners prefer to keep a long distance when talking, which might be interpreted as being untrustworthy by people from the Middle East. Silence is ok in Japan, while it makes people feel uncomfortable in North America. Close supervision indicates distrust in North America, while in India it shows that the supervisor has a good relationship with the subordinate and spends a lot of time with him or her. In some countries, people are reluctant to pass on bad news, and it is impolite to say "no" while people in other countries frankly give their opinion to superiors.

Sufficient time should be allowed for building relationships and for context setting – translation and "cultural filtering." Questions should be open-ended supplemented by focused clarification questions and repetition of what is not understood. Another recommendation is to wait for the main point to emerge, to confirm it, and summarize. It is important to learn the body language of a given culture.

An example of a good mindset and attitude for cross-cultural communication is the Native American's talking stick.[1] It is a way of ensuring that people with different opinions understand one another and solve their problems. The procedure allows only the person holding the stick to voice his or her opinion. The rest are only allowed to communicate how they have understood the holder of the stick. This goes on until the person with the stick feels that the message has been understood by everybody. Then he or she has to pass the stick to the next person. Understanding is not the same as agreeing, though.

A lot of credit is given to those who try to understand the remote site - and this helps them when they make a mistake, which is bound to happen at some point in time. A smile is the shortest distance between humans.

Conclusion

Offshore outsourcing is a rapidly growing business in many markets. Given the shortage of key resources in many areas, the growth is likely to continue.

The news and commercials offer many numbers on the savings associated with offshore outsourcing – but costly elements are often left out. In an internal evaluation, 1 to 1½ years after setting up an Indian entity, Danish salaries were set to index 100 and Indian salaries to 20 to 25. On top of the Indian salaries, the following costs should be added: a multi-site overhead around at index 15, communication (data link, travels, and phone calls) at 7, higher Indian attrition rate at index 5, plus an extra load of management resources at 3. Housing and IT-equipment were excluded.

The important point is the often forgotten big multi-site overhead, such as expensive Danes supporting Indian developers in understanding requirements, development environment, and framework issues, design for maintainability, troubleshooting, and access to test equipment. The size of this overhead was valid at a certain stage and decreased over

time – but the size also depends on domain, technology, and many other factors. A way of minimizing this overhead without compromising the quality is to focus on the soft issues addressed in this article.

Typically, the multi-site overhead is even bigger during the initial phase as it takes time to train the remote team, prepare processes, and set up the IT infrastructure. Offshore outsourcing is an investment with a payback time.

Some of the risks associated with offshore outsourcing are certainly going to emerge from time to time, but the benefits might make it worth while. Those who are able to manage the risks and benefit from the advantages of globalization have a big upside. The standard perception is that opportunities are associated with risks. Many companies will simply have to accept these risks of offshore outsourcing as it might be their only access to additional resources, or because they need some specific competencies which are only available offshore.

References

1. Covey, S., The 8th Habit: From Effectiveness to Greatness.
2. Jain, N., Offshore Agile Maintenance, Agile 2006, p. 327-336.
3. *GAMP® 4, Good Automated Manufacturing Practice (GAMP®) Guide for Validation of Automated Systems*, International Society for Pharmaceutical Engineering (ISPE), Fourth Edition, December 2001, p. 46-47.
4. Foote, L., Quality Systems in the Pharmaceutical Industry, *Pharmaceutical Engineering*, March/April 2003.
5. Outsourcing Journal, July 2006 Issue: New Study Details What Makes Outsourcing Relationships Work, Ingredients for a Successful Relationship.

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PHARMACEUTICAL ENGINEERING Interviews

Dr. Thomas Zimmer, Senior Vice President of the Corporate Division Safety, Quality, and Environmental Protection, Boehringer Ingelheim

by Gloria Hall, Editor, *Pharmaceutical Engineering*

The Chair of ISPE's International Leadership Forum discusses the need for more innovative thinking, the importance of adopting a science- and risk-based approach early in the product life cycle, and the increasing impact of global harmonization.

Since 1981, **Dr. Thomas Zimmer** has been with Boehringer Ingelheim, where he's held several positions in pharmaceutical development and pharmaceutical manufacturing in addition to the Area Management Operations (Americas, Europe). He was also Head of the Project Production Alliance Europe (PAE) and later Head of Pharma Operations at Boehringer Ingelheim France. Since 2000, Dr. Zimmer has been the Senior Vice President of the Corporate Division Safety, Quality, and Environmental Protection for Boehringer Ingelheim. He is also the Chairman of the Anti-Counterfeiting Ad Hoc Group and member of the Manufacturing GMP ad hoc group at the EFPIA. He is Chair of the Industry Advisory Board for the Institute for Packaging of the University of Applied Sciences in Berlin. He is also member of ISPE's International Leadership Forum and of the Pharmaceutical Security Institute (PSI). He studied pharmacy at the Johann Wolfgang Goethe University in Frankfurt/Main and made his Doctoral Thesis in Pharmaceutical Technology.

Q What are you responsible for in your current role at Boehringer Ingelheim?

A I am responsible for global quality assurance, safety (other than drug safety), environmental protection, and occupational hygiene.

Q What led you into a career of safety, quality, and environmental protection?

A I am a pharmacist and gained broad experience in all sections of drug development and technical operations in my career. As quality and compliance are "cross-functional tasks," it is essential to also have a background in operations.

Q How is quality related to safety and environmental protection?

A Basically, either discipline is dealing with managing risks for the corporation. Quality assurance and Health, Safety, and Environmental (HSE) issues are both based on the same needs for quality systems such as Corrective and Preventive Actions (CAPA), change management, auditing, continuous improvement, etc. Many companies have recognized that and combined quality and HSE topics under the same umbrella.

Q What are some of the major barriers to environmental/occupational compliance you and other pharmaceutical manufacturers face?

A There should be more innovation, such as science- and risk-based approaches, quality by design, continuous improvement, and global harmonization of principles in drug development and drug life cycle management – rather than thinking in paradigms. Also, the impact coming from starting materials, APIs, and risks from sourcing of materials from animal origin should be considered.

Q What sets Boehringer Ingelheim (BI) apart from other pharmaceutical companies?

A Formally, the biggest difference is that BI is a family-owned company in the fourth generation. That means independence from stock market rules offers more flexibility for mid- and long-term decisions and strategies. Our strategic objective is to grow not by mergers and acquisitions, but by our own inherent power.

Q Do you see Environmental Health and Safety impacting product design and quality?

A Certainly yes, environmental risk assessments became part of the registration requirements for drug products. Also, part of the life cycle management idea includes the fate of drugs after the human metabolism and its impact on the environment. Developing application forms causing only limited API exposure during manufacturing are also challenges we have to face in the future.

Q What are some of the concerns and risks for environmental protection, safety, and quality?

A Today, the change management of products is too focused on formal compliance instead of risk- and science-based approaches; this drives cost of compliance and eats up resources needed for science-based work. Another issue is the complexity of registration procedures where the national rules differ from each other.

Q What are some of the key metrics used in your organization to gauge compliance or business performance or success?

A In addition to the classic Key Performance Indicators (KPIs) of quality measurement, which are mostly reactive such as complaints, recalls, out of spec results, etc., there are more prospective ones such as trend analysis, process capability, FMEA indices, readiness indices for product launches, or Chemistry, Manufacturing, and Controls (CMC) documentation.

Q What effect does the political environment have on your operations?

A Counterfeits challenge the confidence of the patient regarding the industrial drug distribution system. Parallel trade with lower quality standards endanger the whole quality level as patients cannot distinguish the different quality safety levels respectively.

Q Does BI have a global or a regional safety and environmental protection program?

A BI has a broad set of specific KPI monitoring and programs for energy and waste reduction, reduction of emission, etc. This is also an integral part of our investment procedure prior to the approval of projects. Furthermore, we established expert teams to investigate and implement measures to enhance energy efficiency and guarantee sustainability in engineering. Responsible care initiatives are driven by the different operating units as they are specific to the respective local situation.

Q Are you taking steps to globalize your processes?

A As drug development and technical operations are managed as a global resource for mainly globally marketed products, there are no differences in quality and compliance principles; however, if special local requirements require special profiles, it will be fulfilled.

Q Are there areas of the world BI has chosen not to manufacture because of environmental/occupational protection regulations?

A No, the landscape of production sites has historically grown and BI is represented in every continent with productions sites or third party manufacturing of BI products. The consolidation of the production landscape is driven by economic needs and investments focused on technologies needed by the new blockbusters.

Q What do you see as the challenges or barriers to achieving your goals?

A Some challenges are: further increase of formal requirements for drug registration and change management, slowly growing alignment for the insight into new principles for drug development, testing, and manufacturing, such as quality by design, specification setting, and change management.

Q Is there a collaborative process between environmental protection, safety, quality, and manufacturing?

A There are cross functional product life cycle teams installed which follow targets given by the different needs coming from technical operations, quality, marketing, and drug safety.

Q Is Boehringer Ingelheim enforcing standards for environmental/occupational protection, quality and safety?

A BI is very active in industry associations working on new standards for quality, GMP, environment, health, and safety; BI participates and contributes actively in meetings with public stakeholders such as health agencies, WHO, European Commission, etc. Internally we have set standards described in guidance documents and enforced by corporate audits.

Q What common concerns do regulatory agencies worldwide share when it comes to facilities?

A One of the most addressed issues is the follow up of critical findings, sustainable approaches, system-based approaches instead of fire-fight-

ing actions; this is an ideal area for Business Process Excellence initiatives such as Six Sigma, Crosby, and others.

Q What are the safety issues regarding containment? How do you view the regulatory trend in Germany?

A The challenge here is to align GMP and industrial hygiene requirements and to combine them with a well elaborated scientific rationale regarding the categorization of high potent drugs; this is a "multi-qualifier" driven approach and therefore complex. There is no special trend in Germany as we work closely together on a European level.

Q What technologies do you need to be developed to help you?

A Technology development should be driven by the intended use for manufacturing of drug products, i.e. cleaning validation, avoidance of cross contamination, workers' safety, and easy access for workers, but also sensor technology to measure critical to quality parameters (PAT scope). A joint effort between suppliers and the industry is needed to design equipment with intrinsic safety in terms of employees' protection thus still guaranteeing smart operability.

Q How do you work with the enforcement policies and other global regulatory agencies?

A The main platform in Europe is the European Federation of Pharmaceutical Industries and Associations (EFPIA) located in Brussels. Given the fact that the ad hoc groups or working teams are comprised of members from global pharmaceutical companies, the alignment within the companies on both sides of the Atlantic is therefore immanent. However, there are also contacts between EFPIA and PhRMA, where both parties include industry associations and regulators, in addition to issues being driven on the ICH level, where we have the US, Europe, and Japan working together. Apart from this, there are now more opportunities to exchange views between industry and regulators on issues other than ICH. ISPE is one of these platforms.

Q The EMEA is currently updating their regulations with regard to dedicated facilities. Some in industry are advocating for a risk-based approach; do you think this is achievable?

A It must be achievable as this approach is the only rational approach. However, it is complex as there are many qualifiers in the game, such as safety, GMP, toxicology, Cytotoxic, Mutagen, Reprotoxic (CMR) matters, handling attitudes, and technical boundaries. Very often during New Chemical Entity (NCE) development it's not fully understood at the beginning how a new API affects the human body, especially what adverse effects are connected to the new drug. That's why different safety factors have to be applied in development and later on in manufacturing. Our philosophy is to have a double layer of safety, first of all ensured by engineering controls and personal protection equipment as a second barrier where needed.

Q Are you aware of ISPE's Risk-Based Manufacture of Active Pharmaceutical Products (Risk-MaPP) Baseline Guide currently in development that will provide guidance on setting acceptable limits for cross contamination?

A ISPE is the world's number one platform for technical expertise in pharmaceutical engineering and the word of ISPE always influences or gives direction for the industry. I was impressed to hear what the experts here presented at the 2006 ISPE Annual Meeting in Orlando, Florida, USA, and how the present regulators took up the messages and discussed them with the industry.

We know that ISPE is developing guidance on 'dedicated facilities' and 'highly potent drug manufacturing.' We have been working on the same issue with the EFPIA.

Q Do you think additional government regulatory oversight is required for environment and safety quality?

A This is a difficult question. The answer is yes and no; yes in order to set a requirement for some principles and what to do and what to avoid, but no in regard to setting too detailed rules or even formalized classifications.

Q Can a liaison between fellow regulators around the world be achieved?

A It can be achieved and ICH and ISPE are ideal platforms for this. Maybe PIC/S can play a bigger role in the future too.

Q What technological and operational breakthroughs do you anticipate within the next five years in the pharmaceutical industry?

A We hope for progress on the ICH topics on drug development (Q8) and Quality Systems (Q10).

Q What do you think the major challenges will be for this industry in the future?

A To build a better bridge from clinical results to the design space of drug products, to gain regulatory flexibility in the formal procedures of change management, and to changes earlier in the pharmaceutical product life cycle. In addition to the regulations and guidance needed, pharmaceuticals and drug manufacturing must remain affordable for both people and the industry.

Q What would you like to see the ISPE International Leadership Forum (ILF) accomplish in the next year?

A Develop ISPE to a global platform of discussion for technical operations issues such as technical standards relevant for quality, process, and HSE. The ILF members contribute with their cross functional and managerial experience to this development.

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Risk-Based Equipment Qualification: A User/Supplier Cooperative Approach

Sandro De Caris, Marco Bellentani, Beny Fricano, Carlo Bestetti, Marco Silvestri, and Barbara Testoni

This article presents an efficient cooperative approach to Commissioning and Qualification (C&Q) for manufacturing equipment and covers the entire life cycle for the specification, design, manufacture, installation, commissioning, qualification, operation, and maintenance of the equipment in a risk-based approach. This article is based on work in progress by the GAMP Italia Equipment Validation Workgroup. The main topics covered in the article are:

- **holistic risk-based approach covering business, safety, and quality risks**
- **involvement of the supplier in the risk management process and risk analysis**
- **support from the supplier in the C&Q activities (risk-based)**
- **team building**
- **time savings**
- **trends**
- **good engineering practice**

Background

Most equipment currently available on the market is the result of a very long and uninterrupted improvement process that started many years ago and brought to the current design.

There is a significant difference between the purchase of a standard system, as opposed to the development of a bespoke or custom made equipment. Pharmaceutical users in most cases are just buying and installing standard pieces of equipment. The design of new parts or new functionality is often negligible, or limited to a small part of the process. Nonetheless, users are currently spending significant human efforts and financial resources in commissioning and qualification activities that are sometimes excessive and redundant, quite often including a mere repetition of verifications already performed by the manufacturer.

Inefficiencies also arise from the variable formulation of different requirements (from different users) for the manufacture of the same standard equipment (from the same supplier). This may easily lead to different validation approaches and sometimes to a very different set of documents on behalf of the supplier. A more uniform approach and a risk-based definition of the requirements can result in a significant savings in time and effort spent for both parties.

Risk-based qualification can improve quality and reduce validation efforts. ISPE is actively suggesting this approach, which is now being used more and more extensively.[7,8]

Risk management can be significantly enhanced with the supplier support, because they have a deep knowledge of the systems they produce. This approach can ensure faster, cheaper, more complete, and reliable results.

Indeed, C&Q activities can be significantly abbreviated when the supplier is involved since the early stages of the process and the efforts done during the product development and subsequent manufacturing are taken into account. This article suggests a more profitable role for the supplier during the entire equipment life cycle from specification and purchase, through manufacture and delivery,

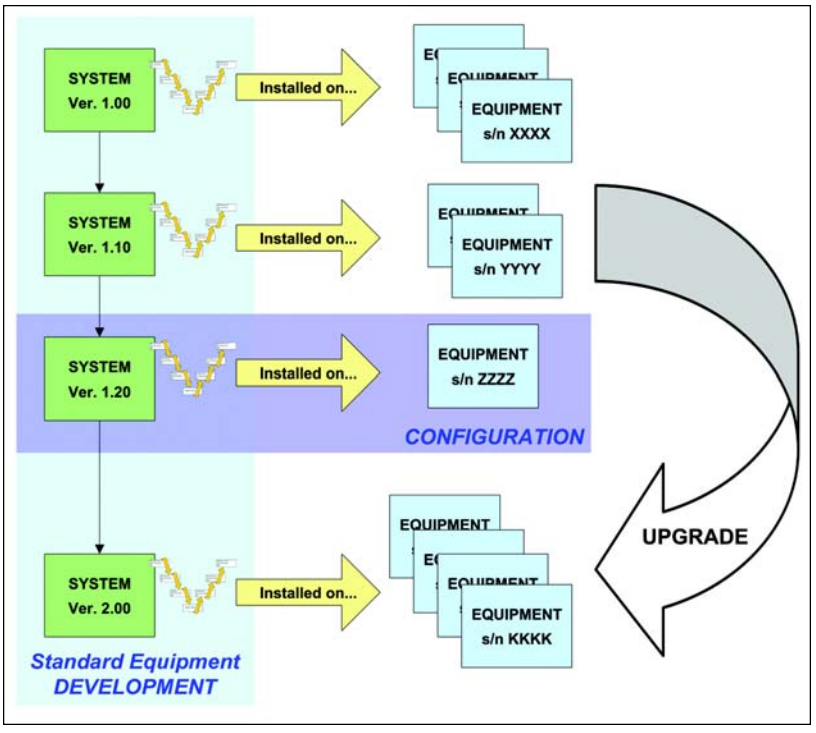

Figure 1. Standard equipment development life cycle.

commissioning and qualification, use, maintenance, and even retirement. This article addresses the basic concepts of a risk-based approach, the application of good practice, and the roles of the user and the supplier. A second article, currently under development, will give detailed recommendations on the whole life-cycle of a generic piece of equipment.

Considering the current high level of automation in the industry, it is important to look at computerized systems and process control software, either embedded or stand-alone related with the equipment. The importance of computer control systems is emphasized because in some cases, the equipment is completely dependent on the proper behavior of the software. Computer systems may include PLC or microcontrollers and Human-Machine Interface (HMI), supervisory PC (e.g., SCADA systems, statistical process control), as well as interfaces with other remote systems like Manufacturing Execution System (MES).

Therefore, the discussion includes both computer validation and equipment qualification in an integrated approach.

More complex and potentially GxP critical scenarios are on the horizon due to the emerging Process Analytical Technology (PAT) applications that may bring new computer systems operating in strict connection with the equipment to ensure product quality. The proper identification and management of Critical to Quality Attributes and the relevant Critical Process Parameters may significantly help develop a PAT-ready equipment and extend the ICH Q8 Design Space concept into the equipment process variables.[9]

Basic Concepts

Good practices help ensure high quality products. Properly designed and manufactured products are safe, robust, reliable, and well documented; therefore, they should be easy to qualify and/or validate. This is true for both pharmaceutical products and the equipment used to manufacture the products.

Commissioning, qualification, and validation activities are only the final stage of a long process, and can be more easily and successfully performed if the entire development life cycle of the equipment is considered, supporting best practice and the concept of "Quality by Design" (QbD) when these are pursued by the manufacturer of the equipment. This approach closely relates to good engineering practice, as described in the ISPE Baseline® Guide on Commissioning and Qualification.[7]

There is a similarity between GEP and GMP: in both cases, quality should be achieved by design, and not just tested at the end of the process. Embedding quality into an equipment design is mostly a supplier's responsibility in a cooperative and trustworthy relationship with the user.

A risk-based approach requires the identification of critical items, distinguishing them from "ordinary" items, and dealing with them in a differentiated manner. Criticality may refer to different aspects of the product or process: quality, safety, and business being the most common areas of interest.

Critical items and key documents should be identified from the beginning of the project (i.e., explicitly documented in the User Requirements Specification), properly traced to standard offerings of the supplier and managed during the design and manufacture of the equipment, and then carefully verified during C&Q in a conscious and efficient manner. C&Q should concentrate on critical items, according to a sound risk evaluation methodology, and following a structured risk management process.

Standard, non-critical parts (e.g., non contact parts, functionality with no or little impact on product quality) can be implicitly qualified during manufacturing if the supplier is

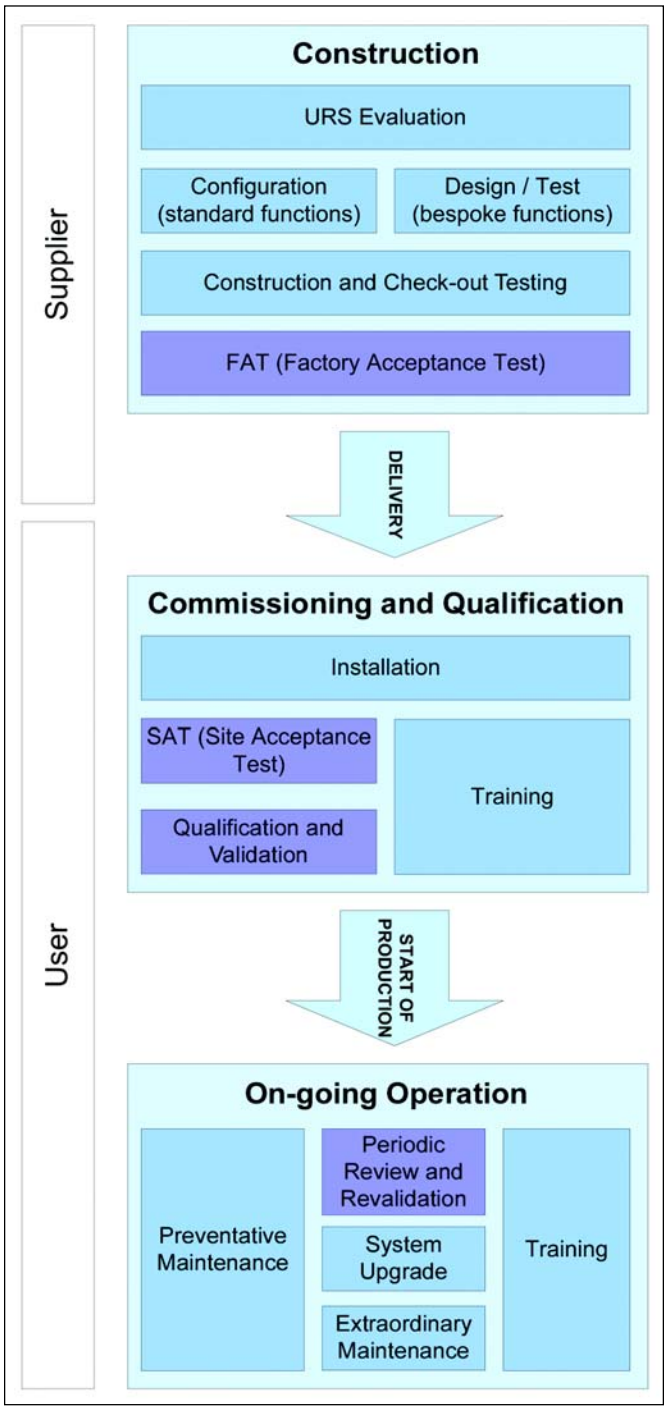

Figure 2. Delivery life cycle for a specific user.

capable of demonstrating suitable maturity in the design and manufacturing. Verifications performed during FAT and SAT can be used as a proof of the good design and good manufacture, without the need of repeating the same tests over and over.

The expertise and knowledge of the supplier and the activities performed during manufacturing should be used to avoid redundancy.

Development Life Cycle

A practical risk-based approach should consider the "real" life cycle of the product development (as opposed to the life cycle in the delivery of a single instance of the standard equipment). Most manufacturers today have very standard equipment, designed for a large market and highly modular. This is quite common for instance with automatic machines like capsule fillers and tablet presses, and packaging lines, etc. The "design" of the equipment for a single customer is largely a matter of choosing the right model and assembling together the appropriate optional parts. Practicing good engineering practice is largely sufficient to qualify many elements of standard equipment.

Equipment Categories

To simplify the management of equipment qualification/validation, it may be useful to distinguish the following main classes of equipment:

- standard equipment with no configurable parts or functions
- standard configurable equipment, having two possible levels of configuration:
  - definition of which standard parts are to be included
  - setting of parameters for the parts included
- custom or bespoke apparatus (prototypes of new equipment, custom built) specifically developed by the supplier to meet a set of specified user requirements

Standard configurable equipment may contain some custom parts that should be identified and treated as bespoke apparatus.

Development vs. Configuration

The development of new products (standard equipment) follows a complex life cycle, normally defined in the supplier's Quality Management System. A good reference is the V

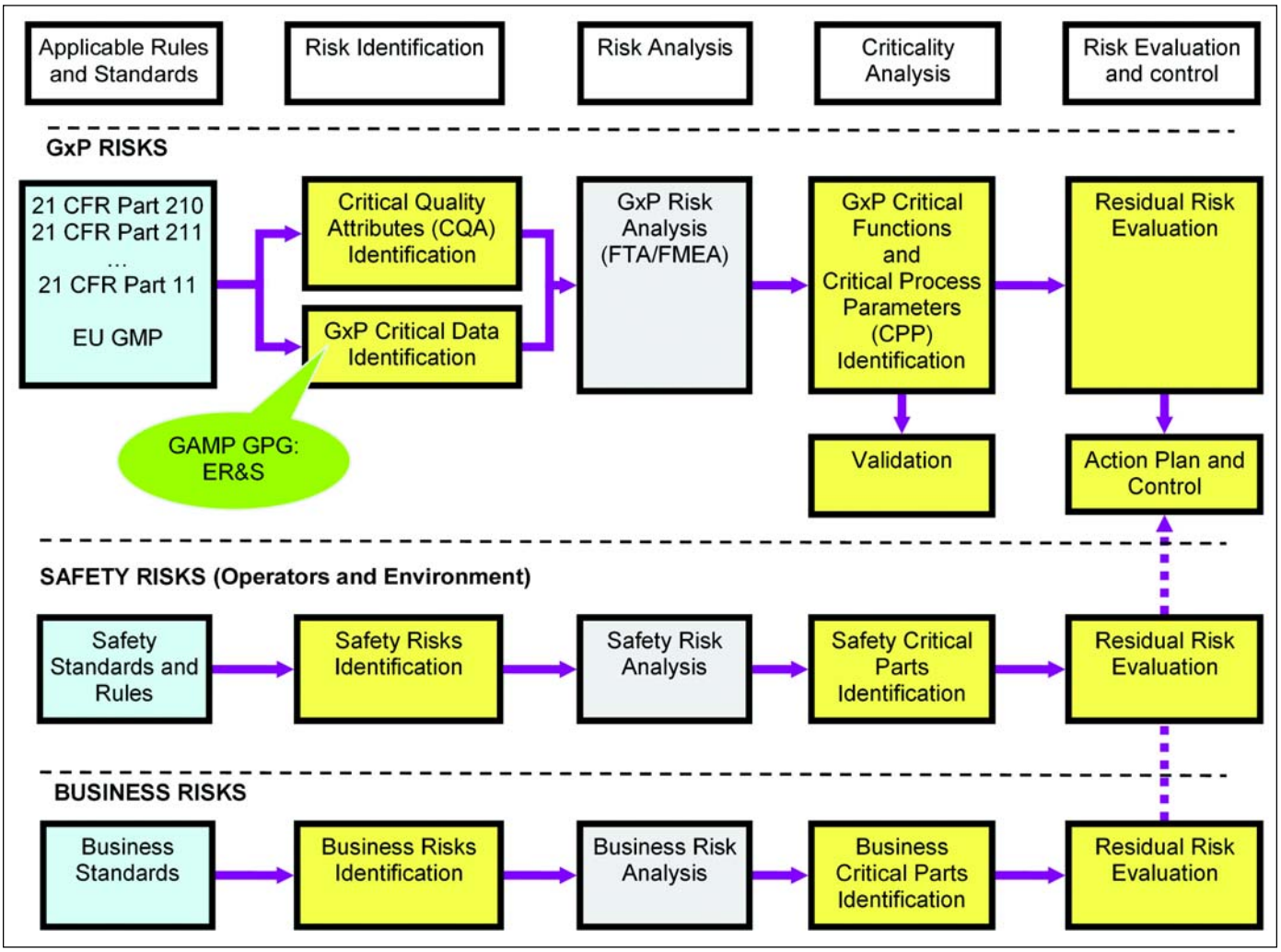

Figure 3. Overall risk management flow chart.

model included in GAMP Guide.[2]

The product is released on the market following an incremental life cycle with many different releases during the product life span. The entire process, limited to software portion for simplicity, may be summarized in Figure 1.

The large variety of customer requirements results in a very high level of modularity within the same equipment. Different models, different optional units, and a large amount of variable parameters are normally available in a standard equipment.

A new version of the equipment and/or its relevant control software is delivered to the customer only when the development process has been completed. This includes the management of functional and technical specifications, and the execution of all defined test cases. New custom (bespoke) functions may become part of the evolving standard.

Therefore, the standard product development line is orthogonal to the configuration process needed to tailor the general product to the customer specific requirements.

Software for a single piece of equipment is quite often upgraded during the operation period, even long after the start-up, for instance when new products are to be manufactured.

The life cycle for the delivery of a single system from a combined user and supplier viewpoint can be seen in Figure 2.

The knowledge of the actual product life cycle and the differentiation between the management of standard parts vs. bespoke parts is fundamental for an appropriate risk management.

A Holistic Risk Management Approach

Risks may arise in different areas:

- Quality
- Safety
- Business

Product Quality Aspects (GxP)

In this case, what matters in the pharmaceutical industry is the quality of the final product delivered to the patient. In this area, all GxP requirements are included. The quality hazard impact can be evaluated according to:

- damage to patient (illness, temporary or permanent side effects, death)
- compliance issues with the authorities

Typically, quality aspects are identified by Critical to Quality Attributes (CQAs) for the product.

Safety Aspects (Operator and Environment)

In this case, what matters is the evaluation of the potential damage to the personnel operating the equipment and/or the impact on the environment caused by system malfunctions. The safety hazard impact can be evaluated according to:

- damage to personnel (temporary or permanent injury, death)
- damage to the environment (damage to people who live outside the factory)

Business Aspects

In this case, what matters is the evaluation of the potential damage for the business caused by system malfunctions or lack of availability. The business hazard impact can be evaluated according to:

- cost of components to be replaced and workmanship (direct damage)
- production loss (indirect damage)

Business continuity, line efficiency, down time, size change over, and line set-up are important items in this perspective.

A description of an overall risk management process is shown in Figure 3.

Risk Analysis

The results of the analysis depend largely on the impact that the customer assigns to each identified source of risk. The same function could be potentially critical in a specific application and non-critical in a different one. Cooperation between customer and supplier is essential to properly manage risks.

User - Supplier Cooperation

The supplier can provide a large number of support activities and services during the life cycle of a product, under all the different perspectives, offering a significant contribution in the risk management process.

A general risk management flow can be adopted. ICH Q9 established a standard approach for "Quality Risk Management" that is quite general and can be easily adopted for all three areas.

Involvement of the supplier in the process can include a large part of the risk analysis, provided it is based on the information supplied by the user.

In more detail, the sequence of operations can be seen in Figure 4.

The flow of operation also illustrates the embedded Risk Communication process between user and supplier along the entire life cycle, and their different role and responsibility in the risk management process. The following three main phases can be distinguished:

1. **Specification Phase**. It's the responsibility of the user to communicate potential risks and the relevant impact to the supplier so that important items are properly managed during design and manufacturing of the equipment. The supplier should be made aware of unwanted issues impacting the quality of the product, the safety of the operators and the business, and the relevant impact level.

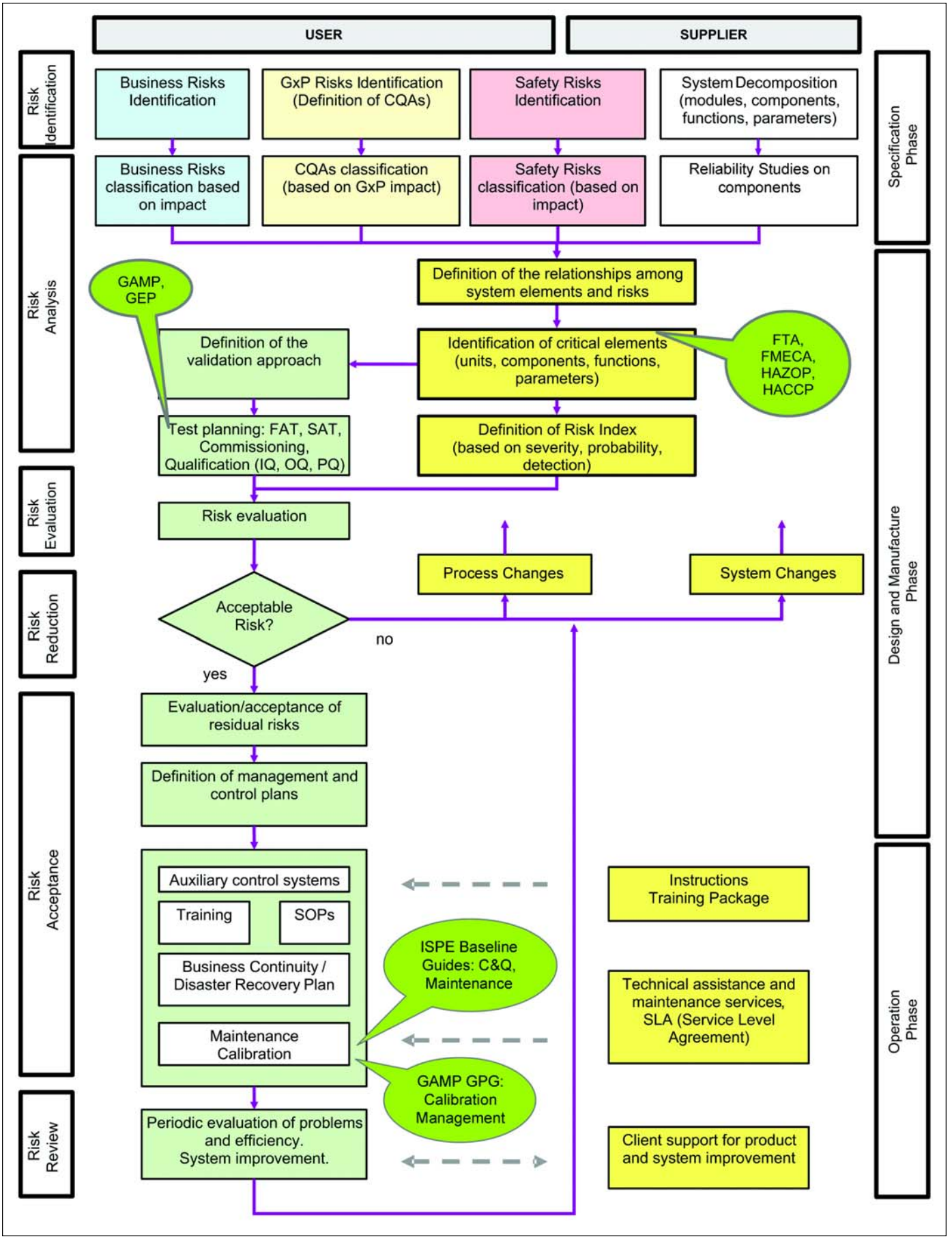

Figure 4. User-supplier cooperation scheme.

2. **Design and Manufacture Phase**. It's the responsibility of the supplier to identify critical parts (such as mechanical units, components, software functionality, or parameters) and communicate these to the user. The user can then wisely evaluate the risks and provide additional controls or countermeasures where necessary, and finally accept the system design when residual risks are below an acceptable threshold.

3. **Operation Phase**. The operation and maintenance of the equipment should be performed in cooperation with the supplier to maintain constant performances over time and/or improve the system when necessary.

It should be noted that while the technical part of the risk analysis can be performed by the supplier, it's a responsibility of the user to evaluate the risks, to provide any required additional controls, and finally to accept the residual risks. This possible separation of roles has been clarified in ICH Q9.[10]

It's important to distinguish between elements criticality and process (residual) risk: an element (system component or function) may be critical because it guarantees the product quality, nonetheless, the residual risk for the process can be low due to the high reliability of the element. However, irrespective of the residual risks, critical parts should be identified because they need qualification/validation.

Standard parts exhibit less risks than custom parts and functions. Under a risk perspective, the explanation is in their improved reliability and lower probability of failure (while the impact remains unchanged).

When the risk analysis is conducted purely for compliance purposes (e.g., to define qualification/validation activities), it can be performed at a high level, without entering into system details such as analysis at component level.

When the risk analysis is required to investigate on specific quality hazards or to cover safety and business risks (e.g., reliability of the equipment), additional difficulties arise on the user's side: the user doesn't have sufficient information and knowledge about the system and the analysis can be very labor intensive and time consuming. One of the difficult items to characterize the system is the probability of occurrence for adverse events since these are quite often related to system components reliability. The manufacturer on the other hand has the necessary knowledge, can guarantee an investigation with sufficient level of detail, and can afford an investment of time and resources on a product that is intended for a wide market and not only for a single user.

It's worth observing that risk analysis performed by the supplier should be somewhat "parametric." The results should in fact be tailored to the specific list of hazards and their impact level, as communicated by the user during the specification phase.

Conclusions

To save time and money in the commissioning and qualification activities still guaranteeing the final proper quality level of the equipment and the relevant production, it is basilar to use a risk-based approach that focuses on critical items of the equipment and critical activities of the life-cycle.

The knowledge of the actual manufacturing life cycle may aid in the identification of critical steps in the process, distinguishing the production and assembling of standard parts from the design of custom parts.

Supplier involvement from the early stages of the process can further improve savings. Building a trustworthy relationship between the user and supplier can reduce redundancies and provide significant advantages for both parties.

C&Q efforts can be significantly reduced using mature products and mature suppliers. Using best practices in the design and manufacturing bring the mature supplier closer to the sphere of Quality by Design, improving their products and services.

Glossary

C&Q	Commissioning and Qualification
CQA	Critical to Quality Attribute
FAT	Factory Acceptance Test
GAMP	Good Automated Manufacturing Practice
GEP	Good Engineering Practice
GMP	Good Manufacturing Practice
GPG	Good Practice Guide
HMI	Human Machine Interface
MES	Manufacturing Execution System
PAT	Process Analytical Technology
PLC	Programmable Logic Controller
QbD	Quality by Design
SAT	Site Acceptance Test
SCADA	Supervisory, Control, and Data Acquisition
URS	User Requirements Specification

References

1. *GAMP® 4* Good Automated Manufacturing Practice *(GAMP®) Guide for Validation of Automated Systems*, International Society for Pharmaceutical Engineering (ISPE), Fourth Edition, December 2001.
2. *GAMP® 4* Good Automated Manufacturing Practice *(GAMP®) Guide for Validation of Automated Systems*, International Society for Pharmaceutical Engineering (ISPE), Fourth Edition, December 2001, Chapter 6 "Validation Overview."
3. *GAMP® 4* Good Automated Manufacturing Practice *(GAMP®) Guide for Validation of Automated Systems*, International Society for Pharmaceutical Engineering (ISPE), Fourth Edition, December 2001, Appendix M2 "Guideline for Supplier Audit."
4. *GAMP® 4* Good Automated Manufacturing Practice *(GAMP®) Guide for Validation of Automated Systems*, International Society for Pharmaceutical Engineering (ISPE), Fourth Edition, December 2001, Appendix M5 "Guideline for Design Review and Requirements Traceability Matrix."
5. *GAMP® Good Practice Guide: A Risk Based Approach to Compliant Records and Signatures* International Society for Pharmaceutical Engineering (ISPE), First Edition, April 2005.

6. *GAMP® Good Practice Guide: Testing of GxP Systems*, International Society for Pharmaceutical Engineering (ISPE), First Edition, December 2005.
7. *ISPE Baseline® Pharmaceutical Engineering Guide,* Volume 5 - *Commissioning and Qualification*, International Society for Pharmaceutical Engineering (ISPE), First Edition, March 2001.
8. A White Paper on Risk-Based Qualification for the 21st Century, ISPE, 9 March 2005.
9. Branning, R., et al., "Quality by Design, Validation, and PAT: Operational, Statistical and Engineering Perspectives," *Pharmaceutical Engineering,* Vol. 26, No. 6, 2006, pp.
10. ICH Q9 - Quality Risk Management (step 4, approved Nov 2005).

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Risk Analysis of Transdermal Drug Delivery Systems

This article presents an application of risk analysis concepts to Transdermal Drug Delivery Systems.

by Maziar Kakhi, Suneela Prodduturi, Anna M. Wokovich, William H. Doub, Lucinda F. Buhse, and Nakissa Sadrieh

The objective of this article is to apply risk analysis concepts to Transdermal Drug Delivery Systems (TDDSs), often referred to as (transdermal) *patches*. The factors affecting TDDS performance are reviewed as part of a hazard analysis with a particular focus on 'what can go wrong?' with regard to the most important outcome, defined as 'desired therapeutic effect.' The results of this hazard analysis are summarized in the form of an influence diagram, which is instrumental in generating an event tree for the use of a TDDS to achieve a therapeutic effect. Adhesion, a system probability of the proposed event tree, is then further analyzed using a success tree in terms of peel and shear testing to evaluate the likelihood of adequate adhesion. Areas of future research beneficial to addressing the risk assessment of TDDSs are highlighted. Further development of this work, particularly in relation to product quality considerations, could be carried out on a specific example of a TDDS as a pilot project involving industry and the US Food and Drug Administration (FDA).

Introduction

TDDSs provide an attractive alternative to conventional dosage forms, primarily through the avoidance of first pass metabolism pathways, improved patient compliance, and their ability to provide constant drug delivery rates over periods ranging from 24 hours to a week. The objective of this study is to present a framework for the risk analysis of TDDSs. This is partly motivated by the diversity of sensitive technologies and multitude of exacting requirements needed to ensure that these dosage forms work safely and efficaciously. The added complexity of penetration enhancement techniques, which confer increasing importance to this class of products, further underpins the rationale for using risk analysis to facilitate informed decision-making among the stakeholders, such as patients, medical practitioners, healthcare providers, industry, lawmakers, and regulatory agencies.

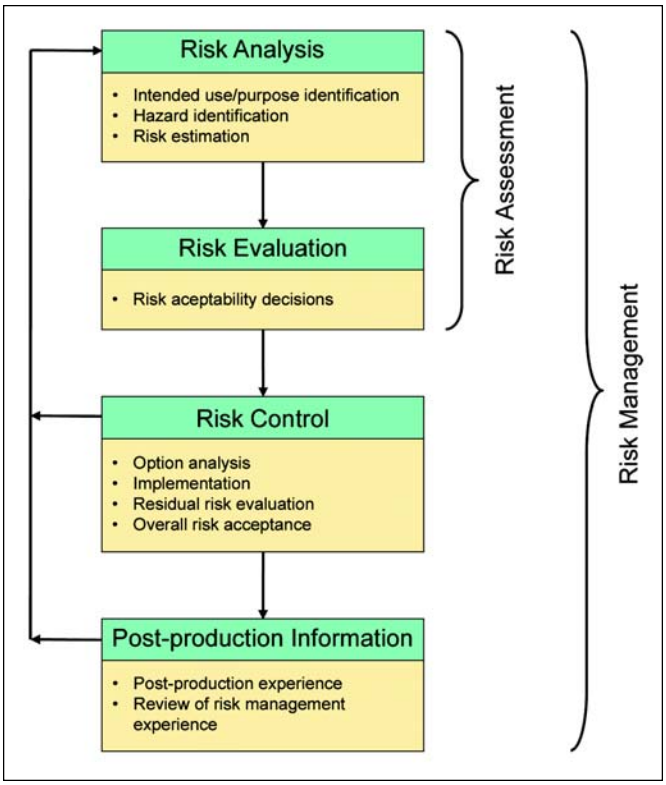

Figure 1. Flow chart summarizing principal stages in a risk management process.[5,9]

The drug review process within the Center for Drug Evaluation and Research (CDER) of the FDA is concerned with understanding and controlling risk. To this end, a multidisciplinary team of experts forms its assessment by reviewing a wide-ranging array of data relat-

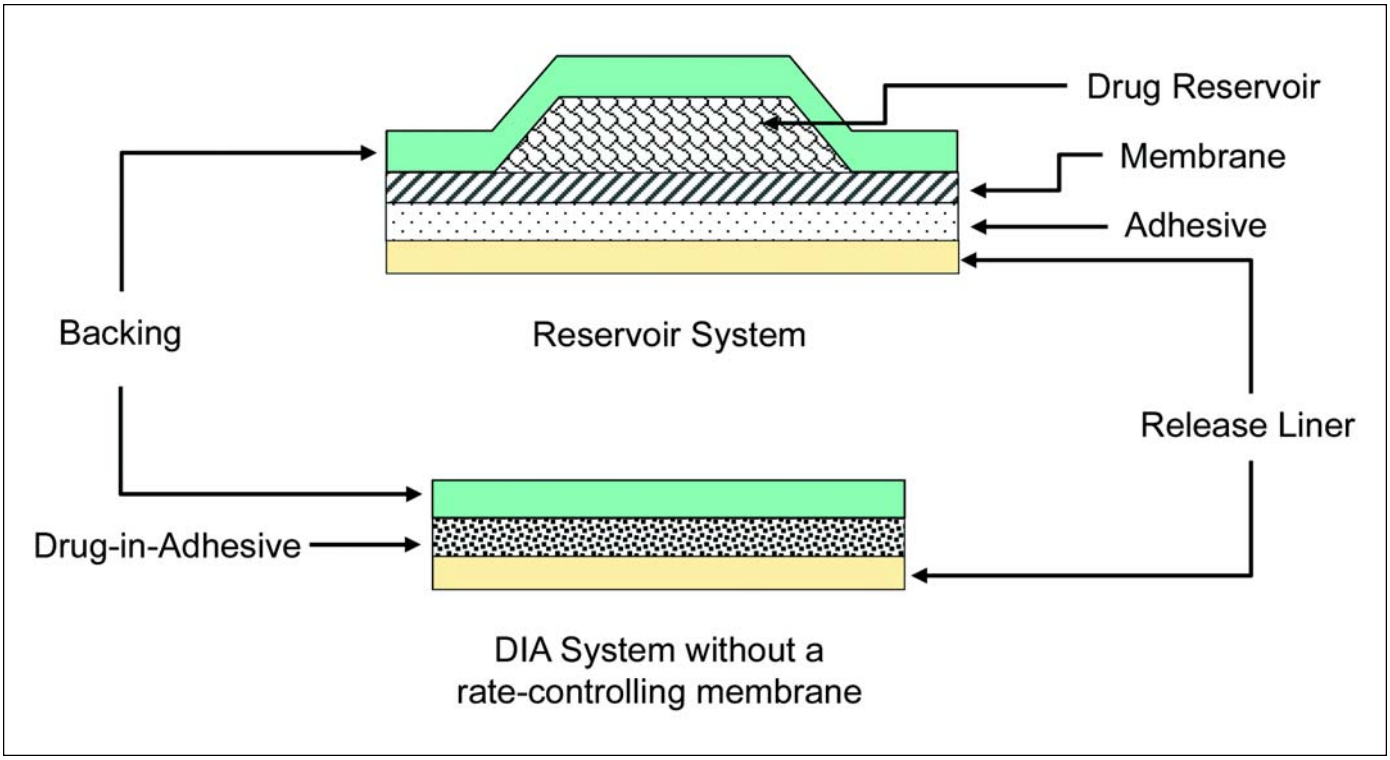

Figure 2. Schematic of the two basic types of TDDS design. Not to scale.

ing to the drug product. By complementing established review methods with structured risk management principles, the review process can be made more flexible both for sponsors and reviewers. This will ultimately benefit patients by reducing the time to market for drugs with even higher quality and safety attributes.

Risk analysis relies on a team of experts that understands the processes and challenges in the segment of the supply chain under consideration. Consistent with the "Quality by Design" approach in drug development, there is a need to identify, understand, and control critical product quality attributes and processing parameters. Very often, this poses fundamental scientific and engineering challenges. Risk analysis concepts can be used to facilitate the identification of key processing and product quality attributes. Ideally, these attributes can then be monitored and controlled using process analytical technology.

In this article, the risk analysis of transdermal dosage forms is presented with an emphasis on adequate adhesion (to skin). Adhesion is of primary importance for effective percutaneous absorption; involuntarily detached patches disrupt therapy, present a risk of exposure to third parties, and their frequent replacement poses a financial burden on patients.

The analysis proposed here is currently preliminary and qualitative in character. It is beyond the scope of the current working group's objectives to engage in a more systematic and exhaustive treatment of this subject. Nevertheless, this study can serve as a starting point for further in-depth work, ideally drawing on participants from industry and the FDA with a focus on a specific product.

Risk Management Process

Risk management practices are well-established in the aerospace, automotive, and nuclear industries. Many of the formative concepts stem from reliability and safety studies initiated in the military sector.[1] The importance of risk-based methodologies in the public health sector has been highlighted in several official documents.[2,3,4,5] Examples of applications include the Healthcare Failure Mode and Effect Analysis (HFMEA™)[6] for evaluating healthcare processes, Hazard Analysis and Critical Control Point (HACCP) for ensuring food safety,[7] and the FDA's risk-ranking procedure used in prioritizing site inspections of drug establishments.[8] Furthermore, international standards exist to guide risk management techniques in the medical devices and diagnostics industry,[9] where it is reported that roughly 80% of manufacturers use some form of Failure Mode and Effects Analysis (FMEA).[10]

Figure 1 illustrates the key elements of a risk management project. Given its cross-cutting and resource-intensive nature, very often a careful consideration of the problem definition and formulation of the risk assessment questions by upper management is essential to ensure a tangible return on the investment of man-hours. An interdisciplinary team is charged with addressing the risk assessment questions. This begins by analyzing product purpose and intent, and in relation to this, identifying hazard pathways throughout the processing stages and evaluating their consequences at every level. This can be performed systemically with the assistance of other risk analysis tools such as FMEA, Fault Tree Analysis (FTA), and Hazard and Operability (HAZOP) studies.[11,12,13] FMEA uses 'bottom-up' or forward logic, where the analyst

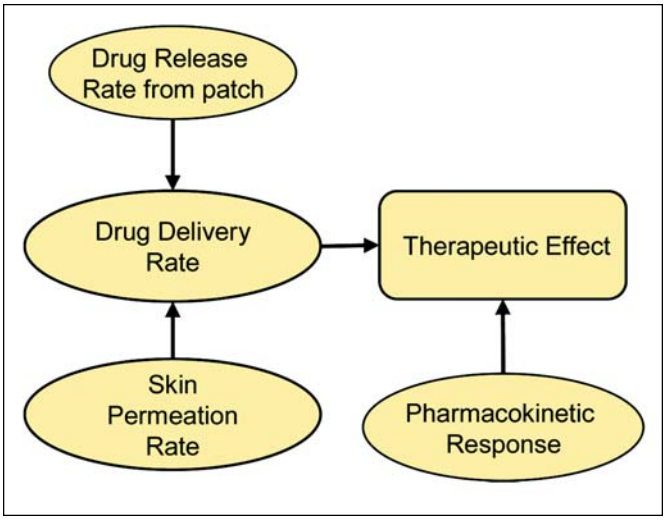

Figure 3. Top most interactions of influence diagram.

starts looking at the lowest level elements in the system and asks: "what happens when a given failure occurs?" The 'mode' of failure at one particular system level translates into an effect (or consequence) in the one higher up, and this cascade proceeds until the top most level or event (e.g., undesirable therapeutic effect) is reached. In contrast, FTA is characterized by deductive (top-down) logic where only those factors that contribute to the top event are relevant. In this work, a top-down approach has been adopted. Focusing the study on situations where lack of process control strongly influences product quality ensures that the risk assessment team's resources are optimally utilized to meet objectives in a timely manner.

Risk is commonly defined as the product of the probability (or likelihood) of harm and its severity, where the scale and units of the variables are usually tailored to the needs of the project. Risk estimation requires some method of quantifying the risk. For this purpose, post-marketing data or in-house measurements and/or modeling can be used. When this is not possible, expert elicitation using risk scores provides an alterative.[14]

After the risk estimation, the next crucial step is assessing whether the risks are acceptable. The criteria for this depend on socio-economic and legal constraints, and are very often laid out in the form of a risk management plan. If risk control measures are deemed necessary, various options are available, ranging from re-engineering the design to the inclusion of safety information – the choice is very often determined by the status of the development process. Even after risk control measures have been applied, residual risks remain, which still require consideration to ascertain whether further risk reduction is needed or even if new hazards have been introduced. If the residual risk is judged unacceptable, the medical benefits of the product need to be weighed against the risks to determine whether to proceed with the design. Since many individual risks are typically identified, it also is necessary to ensure that the *overall* level, or cumulative risk, is acceptable.[15] A periodic review of the criteria used to characterize risk acceptance and feedback from post-market data (such as recalls or incident reports) is essential for continuous updating of the original risk assessment.

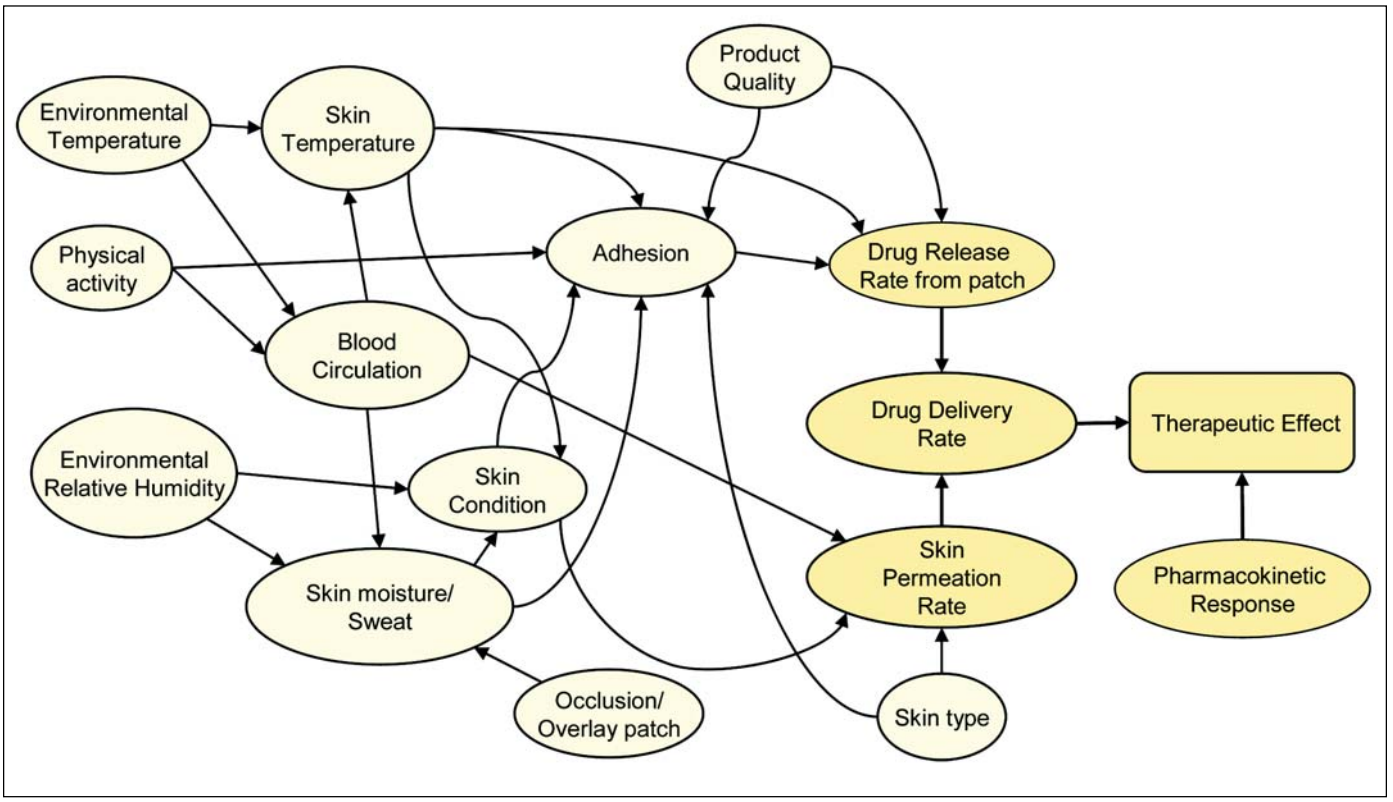

Figure 4. Influence diagram showing dependencies of variables.

Risk Analysis Framework of TDDSs

General Approach and TDDS Characteristics

The model proposed in this work prioritizes the patient's well-being and defines the therapeutic effect as the pivotal objective of the TDDS. If the TDDS delivers the labeled amount of drug at the indicated rate, provided the conditions for its intended use are observed, it is assumed that the desired therapeutic effect is achieved from a statistical perspective and any deviation from this elicits an undesirable systemic response.

The two basic types of TDDS designs currently in widespread use within the US market can be classified as *reservoir* and *Drug-In-Adhesive* (DIA), - *Figure 2*.

In the reservoir design, the drug is very often suspended in a partially solubilized state by means of a liquid excipient.[16] Ideally, the solid active particles in the reservoir will maintain a constant drug concentration in the reservoir solution phase to ensure zero order release kinetics (constant drug delivery rate). DIA patches, with or without a rate-limiting membrane, include drug and excipients in the adhesive polymer to provide maximum utilization of surface area for drug release. A rate limiting control membrane helps minimize intra- and interperson variability and/or can serve as physical support in multilaminated designs.[17]

Transdermal products generally treat systemic disorders in locations distant from the site of application. Hence, transdermal products, compared to topicals, require a high flux (typically expressed in $\mu g/cm^2/hr$) to allow for penetration of the outer skin layer, known as the *stratum corneum*.[18] The stratum corneum is generally considered to be the rate-controlling barrier for diffusion.[19] Both its lipid composition and its physical thickness affect the flux of drug. The permeant must diffuse from the skin surface across the stratum corneum through a tortuous path of hydrophilic and lipophilic domains. Eventually, the permeant encounters a capillary of the cutaneous microvasculature and gains access to the systemic circulation.

Influence Diagram

An influence diagram serves to illustrate succinctly the dependence relationships among the variables that contribute to the primary variable of interest, namely the therapeutic effect.[20] Much of the information expressed graphically in an influence diagram originates from a hazard analysis. The current model assumes that at the topmost level, the actual drug delivery rate through the skin and the patient's pharmacokinetic response most directly influence the therapeutic effect. The latter also can be extended to include potential drug-drug interactions. These dependencies are illustrated in an isolated portion of an influence diagram shown in Figure 3. The directed arrows indicate dependence of the target node (adjacent to arrow head) on the uncertainty or magnitude of a source node (adjacent to arrow tail).

Figure 3 expresses the fact that the actual rate of delivery depends on whether the skin (Skin Permeation Rate) or the TDDS (Drug Release Rate from Patch) is the rate limiting barrier to diffusion. Figure 4 depicts a more complete influence diagram and the arrow dependencies are further elucidated in the following text.

In Figure 4, skin type and skin condition are defined as composite qualifiers which group together various skin attributes and can impact both adhesion and skin permeation rate. Skin condition is assumed to incorporate aspects that are influenced by behavior and can be controlled or treated to a greater or lesser extent, for example, skin that is damaged, cracked, sunburnt or irritated, depilated/hairy, and skin treated with cosmetics, creams, and ointments. In contrast, skin type is defined by factors such as subcutaneous fat content (oiliness), age, race, sensitivity, and general health of the subject as manifested by skin diseases or skin responses of general diseases. Parameters such as skin pH and dryness can fall into both of the aforementioned categories.

Skin pH typically lies between four to five,[19] but this can be modified by sweating or the use of cleaning and cosmetic products. Equally, soaps and detergents can denature the proteins of the stratum corneum, thereby making the skin more permeable.[21] This is expressed graphically in Figure 4 by the dependency of skin permeation rate on skin condition. Prescribing information for patches warn against the use of such agents at the site of patch application.[22] The strength of adhesion is strongly dependent on the nature of the substrate (e.g., its surface roughness, porosity), and given the variability of skin, the influence of skin condition and type on adhesion is intuitively plausible. In the case of damaged or compromised skin (treated as skin condition), the skin permeation rate can be substantially increased, such that drug release from the patch becomes rate-limiting.

The influence of race on skin properties has been reported.[23,24] The literature highlights the difficulty in interpretation of results created by bias associated with socioeconomic, environmental, regional, and hereditary factors. Comparisons of the stratum corneum in black and white skin groups indicate similar average thicknesses. With respect to the effect of age, skin samples from aged (70 to 80 years) and young adults (20 to 30 years) indicate a comparable stratum corneum thickness.[25] However, *in vivo*, young subjects demonstrate higher absorption rates of permeant due to an increased rate of clearance of the permeant from the dermis into the circulatory system. Full term infants (37 to 40 weeks gestation, one to three days postnatal) have a stratum corneum comparable to that of adults, whereas premature infants (26 to 30 weeks gestation, one to three days postnatal) have little if any.[26,27] However, a child has less body volume per unit area of skin than an adult; therefore, the effect of a permeant will have a greater systemic effect, or even serious adverse effects associated with accidental transfer of the patch from adult to infant.

Thermal imaging at ambient conditions shows skin temperature variations ranging from 24°C to 36°C.[28] More extreme environmental conditions can bring about greater temperature variations; this is particularly relevant for patches worn behind the ear. Studies of regional absorption rates of various chemicals indicate that the arm, chest, and back, where the majority of patches are placed, appear to have

Hazard	Effect	Action Required
Inadequate drug/excipient purity and stability.	Variable dosing and adhesion.	Assay of raw materials, intermediates and stability characteristics.[38]
Formulation-materials interaction.	Degradation of active/excipients. Change of rheological properties.	Verification of interactions and re-evaluation of materials selection.[38]
Phase incompatibility of formulation components.	Phase migration of excipients. Weakening of adhesive bond.[37]	Re-formulate for phase balance or miscibility of excipients.
Inadequate backing seal.	Leaking matrix solution. Inadequate dosing.	Re-assessment of backing material and heat-sealing parameters.[38]
Excessive occlusion.	Adhesion decay, changes in release rate, microorganism growth.	Use of porous adhesives and facestock with consistent pore size distribution.[39]
Membrane variability: composition, thickness, pore size distribution.[16]	Batch-to-batch inconsistency in drug delivery rates.	Tighter control of specifications or change supplier.
Permeable packing film.	Transmission of vapors.[16]	Re-evaluation of materials selection for packing film.
Stock solution preparation, mixing of ingredients.[40]	Content uniformity and viscosity out of specification.	Monitoring of mixing speed; analysis of solution viscosity, and drug content uniformity.[16]
Poor coating uniformity of solution/ suspension.	Target release rate profile not achieved.	Calibration of coating apparatus. Thickness control: ± 1 g/m^2.[40]
High levels of residual monomers/ solvents after drying.	Skin irritation, systemic toxicity. Modified properties of matrix solution.	Re-examination of oven temperature, air circulation and line speed in drying chamber.
Cosmetic defects: Pin-holes, creases, bubbles, entrapped dirt.[30]	Compromised TDDS integrity, release rate and adhesion.	In-line monitoring to identify and mark defect. Harmonization of web tension and roll speeds.
Lamination pressure.	*Excessive*: Irreversible damage. *Insufficient*: Lack of patch cohesiveness.[40]	Inspection of product after lamination. Peel adhesion testing for adhesive mode of failure.
Storage.	Supersaturation of active from loss of volatile, release rate –.[41] Crystallization at adhesive/liner interface in DIA –tack –.[19,37]	Stability studies to determine conservative expiry dates. Clear labeling thereof on package.

Table A. Preliminary Hazard Analysis in relation to the manufacturing of TDDSs.

comparable absorption levels within an order of magnitude.[21,29] An increase in environmental temperature affects adhesion through greater molecular mobility of the polymer resulting in increased tack, but reduced shear resistance.[30] Skin temperature adjusts according to external temperature as part of the homeostatic control of body temperature. The role of blood circulation here is essential. A change in temperature modifies the viscosity of the lipid phases (a skin condition), and this in turn affects the skin permeation rate - *Figure 4*.

The effects of physical exercise, and in particular, heat have been shown to have a dramatic effect on percutaneous absorption.[31,32] This is attributed to vasodilation and increased blood circulation drawing on a drug depot in the skin. Reduced skin perfusion, as a result of vasoconstriction, can in contrast reduce the overall drug uptake.[33] In addition, heat application or elevated temperatures increase the solubility of the active in the TDDS, which in turn raises the drug concentration gradient across the stratum corneum and results in a higher flux from the patch.[34]

The stratum corneum becomes dry and relatively inelastic at very low humidity, whereas high ambient humidity softens it.[21] With severely dry conditions, the skin surface can develop fissures and show signs of inflammation which facilitate diffusion. In contrast, hydration of the stratum corneum, brought about by an increase in external relative humidity or sweating, increases the diffusion coefficient, and in turn the skin permeation rate of the drug.[34,35] The water content of the stratum corneum, normally 5% to 15%, can (under occlusive conditions) increase up to 50% with corresponding increases in skin temperature and pH.[36] More specifically, under an occlusive transdermal patch or the application of an overlay tape, trapped moisture can be taken up into the hydrophilic adhesives, which in turn can modify the adhesives' ability to hold the active ingredient in solution. Very often this leads to a higher concentration of drug in solution which induces a larger drug flux.[19] Moisture build up, resulting from occlusion or sweating, also can lead to a weakening of the patch to skin adhesion.[37]

Misuse and abuse of TDDSs are difficult to control and monitor. Some of the aforementioned dependencies, such as application of heat (e.g., heating pads, saunas) and ointments/ creams implicitly cover aspects of misuse. For this reason, it has not been included explicitly in Figure 4. Efficiency of drug delivery from the patch, defined as the quantity of drug delivered within the application period divided by the total drug content in the patch, can range from 9% to 72%.[16] Given the low toxicity threshold of a number of transdermally delivered drugs and the fact that they permeate through the skin rapidly, the low efficiencies pose a definite source of harm to a third party if the patch is not disposed of appropriately. Other dosage forms also can be misused or abused. However, an important distinction with TDDSs relates to their ease of use, to the extent that the patient may be unaware, regardless of the conditions of use, that he/she is continually receiving

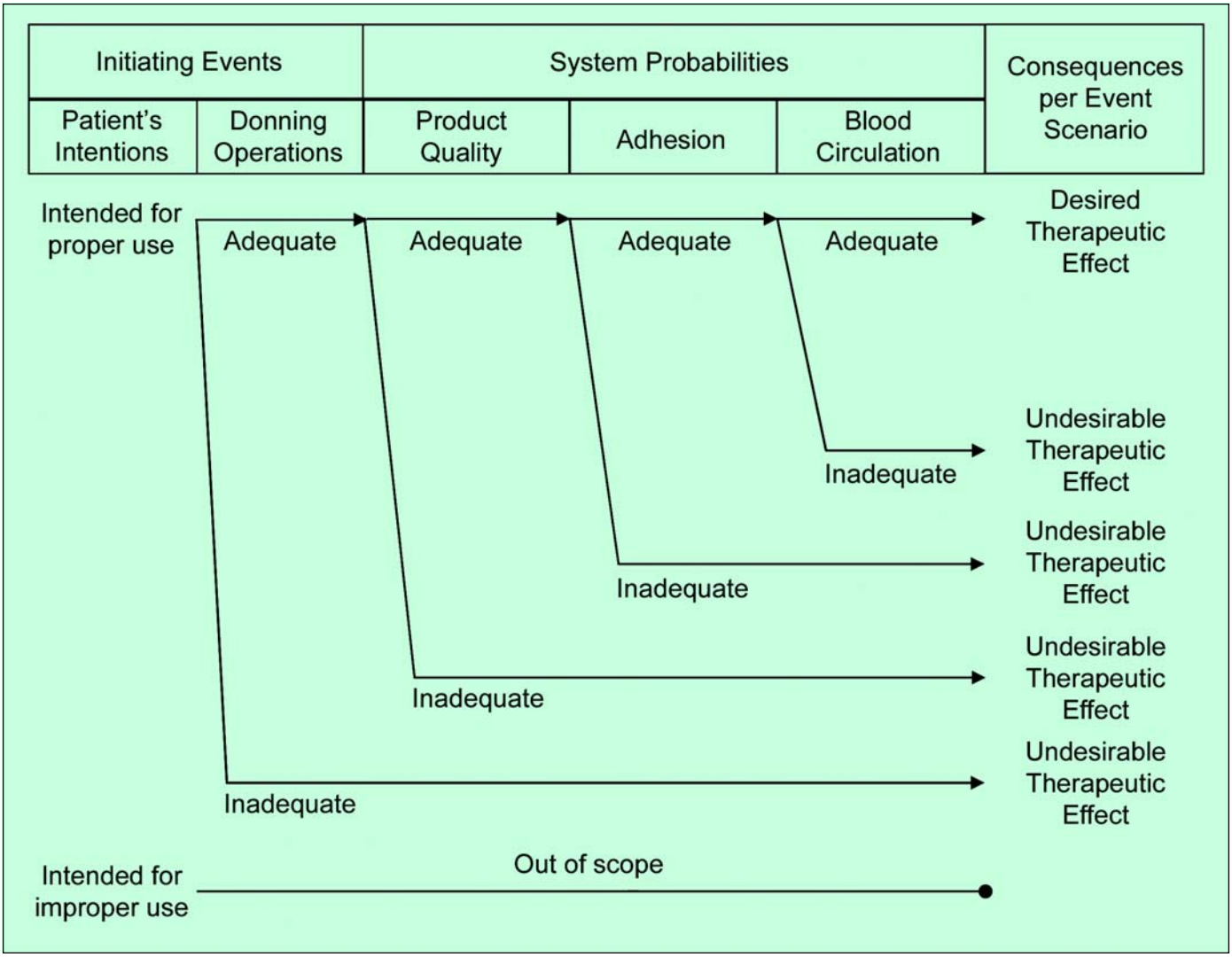

Figure 5. Simplified event tree for the risk assessment of TDDSs.

medication until the adverse reaction manifests itself. In such instances, continual patient education and monitoring by healthcare providers are the most effective risk reduction tools.

Figure 4 lists product quality as one of the contributing factors affecting therapeutic effect. Clearly, this is a gross generalization of a vastly multivariate problem. Of all the factors influencing the performance of TDDSs, product quality is one which is amenable to a state of control. From the manufacturer's point of view, this is where efforts relating to risk management must be devoted. Table A shows a preliminary selection of hazards, their influence on product quality, and possible mitigating actions associated with the various processing stages of a TDDS.

The hazards analysis in Table A could be incorporated into Figure 4, targeting product quality to expand the existing influence diagram.

Event Tree Analysis

Event tree analysis is a tool for systematically identifying accident scenarios and quantifying risk in situations involving a consecutive group of events.[20] The event tree starts with an initiating event followed by binary branching to illustrate how the system evolves depending on success or failure.[1] At each event category associated with the operation of the system, the aforementioned branching logic results in a tree structure tracing out scenarios with varying levels of probability. Figure 5 illustrates an event tree which models the sequence of events leading to two classes of therapeutic effect (desired/undesirable). The current model does not accommodate redundancy since failure at any stage of the process is assumed to elicit overall failure ('undesirable therapeutic effect').

Human-related risks are a significant contributing factor to overall risk. In this instance the patient's intentions and donning operations are considered to be the initiating events. Donning operations involve removal of patch from the packaging and application to the skin. A misinformed patient applying a patch to a location of damaged skin constitutes a failure of the donning operation. Data are rarely available to ascertain which mechanism is the root cause of failure. For example, physical rupture of a rate controlling membrane

upon removal of a liner could be attributed to product quality failure or improper donning by the user.[16] Consequently, the current event tree is a conceptual aid to identify where to focus efforts for a meaningful and manageable risk analysis.

The event tree model in Figure 5 indicates that 'successful' drug delivery is achieved when the events associated with product quality, adhesion, and uptake into the capillaries all succeed. The patient's pharmacokinetic response is presently ignored for simplicity. The occurrence probability of the top branch scenario leading to the desired therapeutic effect is the product of the probabilities of the aforementioned constitutive events. The occurrence probability for successful donning operations and blood circulation are difficult to define, let alone quantify. In the case of blood circulation, this is very much affected by environmental conditions and the patient's activity and health. Adhesion and product quality, in contrast, can be tested and controlled systematically. Figure 4 illustrates the central role of adhesion. Indeed, adhesion can be viewed as a product quality attribute in view of the reported failures associated with TDDSs.[42] However, Table A indicates several parameters which do not primarily influence adhesion, but nevertheless affect the therapeutic effect. The intrinsic drug release rate from the patch is one such example. This parameter is commonly evaluated by *in vitro* testing in various USP dissolution vessels and Franz diffusion cells.[16] These methods are useful as quality assurance tools because they can pin-point batches which perform out of specification. However, an effect which cannot be captured *in vitro* is that of drug clearance from the innermost skin layers via the blood circulation. Consequently, a validated *in vitro* / *in vivo* correlation is necessary in order to assess the harmful impact of a dosage form performing outside its specification window. Addressing product quality using more detailed event modeling techniques is beyond the scope of this work and will necessarily require the participation of industry experts involved in design, development, and manufacturing of TDDSs. The subsequent section describes how the risk analysis framework can be further developed to quantify the probability of adequate adhesion through mechanical testing.

Success Tree for Adhesion

Adequate adhesion of a TDDS implies intimate skin contact throughout the application period, but also sufficient cohe-

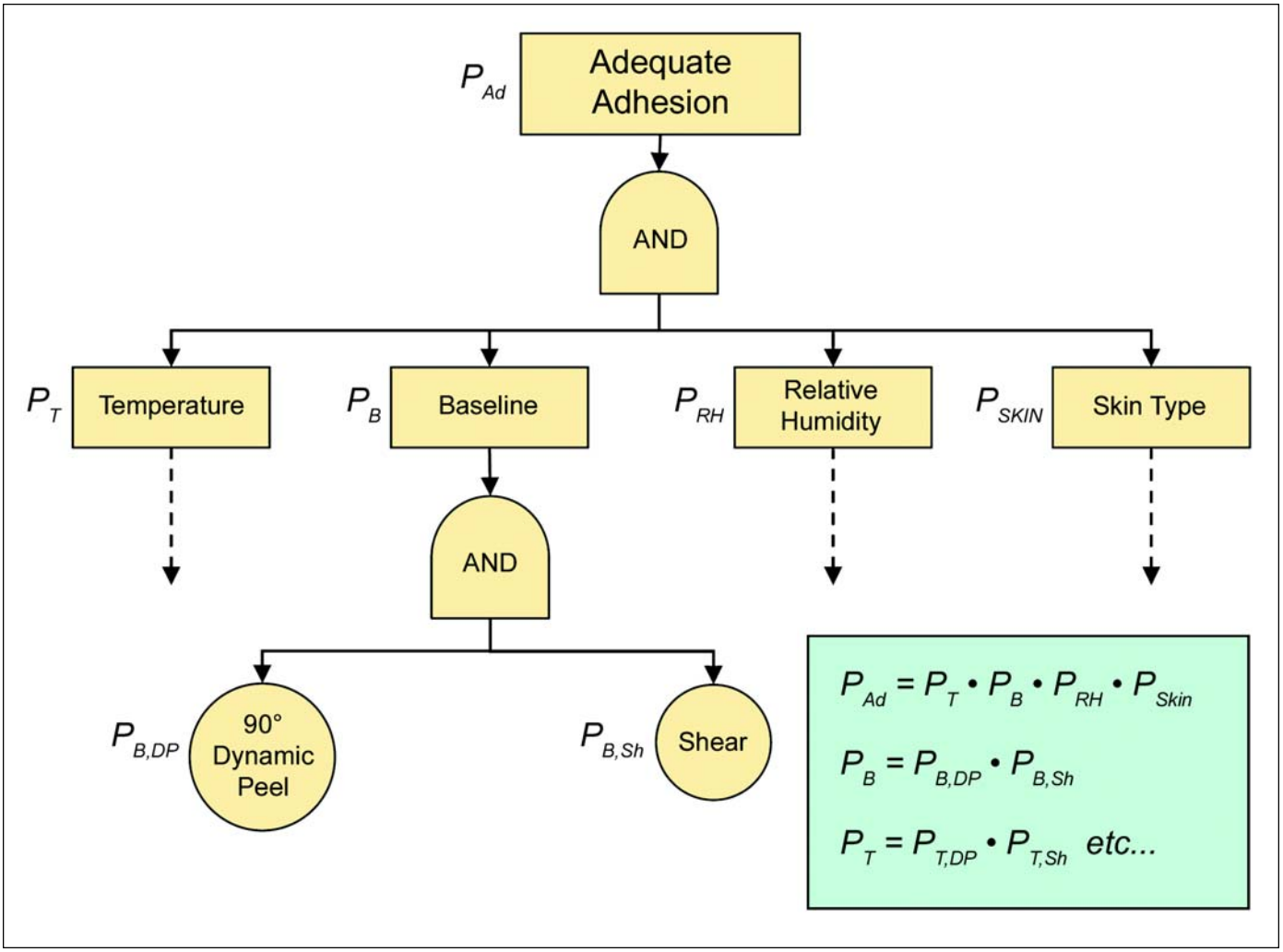

Figure 6. Success tree for adhesion. Dotted arrows indicate similar structures to the arm which is already fully expanded under "Baseline." Each event has a probability of success, and the box in the lower right hand corner shows how they are evaluated in terms of the basic event probabilities.

siveness to allow for convenient, voluntary removal causing minimal skin trauma (such as irritation or adhesive residue).[37] Ideally, the viscoelastic polymer properties should strike a correct balance between rapid short term (surface wetting) and limited long term ("cold") flow characteristics. This ensures quick initial adhesion (with minimal application of pressure) that lasts during the prescribed use period.[43]

Success trees are the complement of fault trees, which were outlined above (in the section entitled 'Risk Management Process'). Very often, these tools are used in conjunction with event tree analysis to elucidate system complexities.[20] The success tree, shown in Figure 6, traces pathways from a predetermined top event (adequate adhesion) to the basic events (90° dynamic peel and shear tests).

Basic events are the lowest-level events for which success probabilities must be obtained from measurements and/or modeling. With respect to the (90° dynamic) peel test, 'success' is interpreted as the value of peel adhesion falling within a predetermined range so that the requirement of adequate adhesion (described in the first paragraph of this section) is satisfied. A similar definition follows for the shear test. The probability of success is defined as the number of successes per number of attempts, and these are denoted as $P_{B,DP}$ and $P_{B,Sh}$ for the peel and shear tests respectively. The Boolean 'AND' logic gates imply that success of all lower-level events is required in order to propagate success further up the tree. In the present model, provided the results of the peel and shear tests are statistically independent, the probability of adequate 'baseline' adhesion, P_B, is the product of the individual basic event probabilities.[1] The 'baseline' refers to a standardized set of conditions for the peel and shear tests. This means a set of conditions where the temperature, relative humidity, and skin type are controlled. Results from the peel and shear tests under varying conditions of temperature, relative humidity, and skin types would yield the event probabilities P_T, P_{RH}, and P_{Skin} (respectively), which can then be combined as shown in Figure 6 to evaluate the overall probability of adequate adhesion.

Several organizations provide official standards for peel and shear tests of pressure sensitive adhesives (PSAs).[44,45,46] It is important to note that these tests were developed with industrial tapes and adhesives in mind rather than TDDSs. The official standards involve fixed ambient conditions and surrogate substrates such as stainless steel. These conditions are quite remote from the actual conditions of use of a TDDS and can lead to conflicting trends. This has been observed in comparisons of human skin and stainless steel[47] as potential substrates. The success tree calls for a baseline characterization of skin, which is difficult and subjective, but potentially feasible based on a statistically adequate sample size of appropriate volunteers. However, the practicality of using live human skin for routine quality control testing implies that the use of artificial surrogates is inevitable. In addition, it has been shown that adhesive bonds when subjected to a cyclic stress can fail at loads well below their first yield as determined in dynamic peel tests.[48,49] Under normal wear, shear stresses occurring at a relatively low frequency are expected to be the primary source of loading on the TDDS.

While tack, as measured in the quick stick and Polyken probe tests,[30] is a quintessential feature of any PSA, it has not been included in the success tree model due to its strong correlation with peel tests, suggesting its redundancy.[50] Similarly, in view of the shear test specified in the success tree, the 90° peel configuration is specified rather than 180°, since the former is reported to involve only tensile stresses whereas, the latter is a combination of tensile and shear.[51] Occlusion is not explicitly included partly because the effect of moisture build up is accounted for by variations in temperature and relative humidity.

Conclusions

This study was motivated by the need to develop better tools to predict product quality and performance of transdermal dosage forms and to understand how they are influenced by diverse factors, such as environmental, physiological, design, and manufacturing considerations.

A hazard analysis, summarized graphically using an influence diagram, shows the interdependency of factors that ultimately influence the therapeutic effect of the TDDS. This diagram highlights the pivotal role of adhesion. Building on the information from the influence diagram, an event tree is constructed showing the key events involved in the application of a TDDS. One of these key events is adhesion for which a success tree is used to evaluate the probability of adequate adhesion in terms of standard peel and shear tests for PSAs. Shortcomings are identified in regard to the suitability of these tests to address the effect of cyclic loads on TDDSs, which typically occur during actual wear.

Product quality and adhesion are identified as events where a quantitative risk-based approach deserves further merit. It is suggested that this is best accomplished in collaboration with industry partners.

References

1. Clemens, P.L. and Simmons, R.J., System Safety and Risk Management – A Guide for Engineering Educators, NIOSH Instructional Module, March 1998. Available at: http://www.cdc.gov/niosh/topics/SHAPE/pdfs/safriskengineer.pdf (last accessed 12/06).
2. U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Initiation and Conduct of All 'Major' Risk Assessments within a Risk Analysis Framework. A Report by the CFSAN Risk Analysis Working Group, March 2002. Available at: http://www.cfsan.fda.gov/~dms/rafw-toc.html (last accessed 12/06).
3. U.S. Food and Drug Administration, Center for Drug Evaluation and Research, ONDC's New Risk-Based Pharmaceutical Quality Assessment System, September 2004. Available at: http://www.fda.gov/cder/gmp/gmp2004/ondc_reorg.htm (last accessed 12/06).
4. Department of Health and Human Services, U.S. Food and Drug Administration, Pharmaceutical cGMPs for the 21st Century. A Risk-Based Approach. Final Report, September 2004. Available at: www.fda.gov/cder/gmp/

gmp2004/GMP_finalreport2004.htm#Toc84065734 (last accessed 12/06).
5. International Conference on Harmonization Q9, Guidance for Industry: Q9 Quality Risk Management, June 2006. Available at: http://www.fda.gov/CDER/guidance/7153fnl.htm (last accessed 12/06).
6. DeRosier, J., Stalhandske, E., Bagian, J.P., and Nudell, T., Using Healthcare Failure Mode and Effect Analysis™: The VA National Center for Patient Safety's Prospective Risk Analysis System, The Joint Commission Journal on Quality Improvement, 28 (5): 248-267, May 2002.
7. National Advisory Committee on Microbiological Criteria for Foods, Hazard Analysis and Critical Control Point Principles and Application Guidelines, August 1997. Available at: http://www.cfsan.fda.gov/~comm/nacmcfp.html (last accessed 12/06).
8. U.S. Food and Drug Administration - Center for Drug Evaluation and Research, Risk-Based Method for Prioritizing cGMP Inspections of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model, September 2004. Available at: http://www.fda.gov/cder/gmp/gmp2004/risk_based_method.htm (last accessed 12/06).
9. Medical Devices - Application of Risk Management to Medical Devices. British Standard, BS EN ISO 14971, 2001
10. Schmidt, M.W., The Use and Misuse of FMEA in Risk Analysis. Medical Device and Diagnostic Industry, March 2004. Available at: http://www.devicelink.com/mddi/archive/04/03/001.html (last accessed 12/06).
11. Analysis Techniques for System Reliability – Procedure for Failure Mode and Effects Analysis (FMEA), International Standard IEC/CEI 60812, 2006.
12. Fault Tree Analysis, International Standard CEI/IEC 1025, 1990.
13. Hazard Operability studies (HAZOP studies) – Application Guide International Standard CEI/IEC 61882, 2001.
14. Tran, N.L., Hasselbalch, B., Morgan, K., and Claycamp, G., Elicitation of Expert Knowledge about Risks Associated with Pharmaceutical Manufacturing Processes, Pharmaceutical Engineering, 25 (4): 24-38, 2005.
15. Schmidt, M.W., Establishing Overall Risk for Medical Devices, Medical Device and Diagnostic Industry, February 2003. Available at: http://www.devicelink.com/mddi/archive/03/02/005.html (last accessed 12/06).
16. Peterson, T.A., Wick, S.M., and Ko, C., Design, Development, Manufacturing, and Testing of Transdermal Drug Delivery Systems, in Transdermal and Topical Drug Delivery Systems, Ghosh, T.K., Pfister, W.R., Yum, S.I., Eds., Interpharm Press, Inc.: 249-297, 1997.
17. Dohner, J.W., Development of Processes and Equipment for Rate-Controlled Transdermal Therapeutic Systems, in Transdermal Controlled Systemic Medications, Chien, Y.W., Ed., Marcel Dekker, Inc.: 349-364, 1987.
18. Shah, V.P., Peck, C.C., and Williams, R.L., Skin Penetration Enhancement - Clinical Pharmacological and Regulatory Considerations, in Pharmaceutical Skin Penetration Enhancement, Walter, K.A., Hadgraft, J., Eds., Marcel Dekker: 417-427, 1993.
19. Hadgraft, J. and Guy, R.H., Feasibility Assessment in Topical and Transdermal Delivery: Mathematical Models and In Vitro Studies, in Transdermal Drug Delivery, Second Edition, Guy, R.H., Hadgraft, J., Eds., Marcel Dekker, Inc.:1-23, 2003.
20. Ayyub, B.M., Risk Analysis in Engineering and Economics, Chapman & Hall/CRC, 2003.
21. Flynn, G.L., Linn, E.E., Kurihara-Bergstrom, T., Govil, S.K., and Hou, S.Y.E. Parameters of Skin Condition and Function, in Transdermal Delivery of Drugs, Volume II, Kydonieus, A.F. and Berner, B., Eds., CRC Press, Inc., Boca Raton, FL: 3-17, 1987.
22. Duragesic® (Fentanyl Transdermal System) – Full Prescribing Information. Available at: http://www.duragesic.com/html/dur/potential_prescribing.jsp;jsessionid=K35MPMZEOWBWMCQPCCEDC0YKB2... (last accessed Dec 2006).
23. Andersen, K.E. and Maibach, H.I., Black and white human skin differences, Journal of the American Academy of Dermatology, 1 (3): 276-282, 1979.
24. Gupta, S.K., Sathyan, G., and Hwang, S.S., Clinical Assessment of Transdermal Drug Delivery Systems, in Transdermal and Topical Drug Delivery Systems, Ghosh, T.K., Pfister, W.R., Yum, S.I., Eds., Interpharm Press, Inc.: 215-248, 1997.
25. Christophers, E. and Kligman, A.M., Percutaneous Absorption in Aged Skin, in Advances in Biology of the Skin, Montagna, W. (Ed.), Pergamon Press, Oxford: 163-175, 1965.
26. Fisher, L.B., Studies on the Permeability of Infant Skin, in Percutaneous Absorption: Mechanisms-Methodology-Drug Delivery, Second Edition, Bronaugh, R.L. and Maibach. H.I., Eds., Marcel Dekker: 135-143, 1989.
27. Behl, C.R., Bellantone, N.H., and Flynn, G.L., Influence of Age on Percutaneous Absorption of Drug Substances, in Transdermal Delivery of Drugs, Volume II, Kydonieus, A.F. and Berner, B., Eds., CRC Press, Inc., Boca Raton, FL: 109-132, 1987.
28. Ring, E.F.J., Thermal Imaging of Skin Temperature, in Handbook of Noninvasive Methods and the Skin, Serup, J. and Jemec, G.B.E., Eds., CRC Press, Boca Raton: 457-471 1995.
29. Wester, R.C. and Maibach, H.I., Regional Variation in Percutaneous Absorption, in Percutaneous Absorption: Mechanisms-Methodology-Drug Delivery, Second Edition, Bronaugh, R.L. and Maibach. H.I., Eds., Marcel Dekker: 111-117, 1989.
30. Benedek, I., Test Methods, in Pressure Sensitive Adhesives and Applications, 2nd Edition, CRC Press: 629-713, 2004.
31. Barkve, T.F., Langseth-Manrique, K., Bredesen, J.E., and Gjesdal, K., Increased Uptake of Transdermal Glyceryl Trinitrate During Physical Exercise and During High Ambient Temperature, American Heart Journal, 112 (3): 537-541, 1986.
32. Klemsdal, T.O., Gjesdal, K., and Zahlsen, K., Physical

Exercise Increases Plasma Concentrations of Nicotine During Treatment with a Nicotine Patch, British Journal of Clinical Pharmacology, 39: 677-679, 1995.
33. Ademola, J., Maibach, H.I., Safety Assessment of Transdermal and Topical Dermatological Products, in Transdermal and Topical Drug Delivery Systems, Ghosh, T.K., Pfister, W.R., Yum, S.I., Eds., Interpharm Press, Inc.: 191-214, 1997.
34. Sun, J., Skin Absorption Enhancement by Physical Means: Heat, Ultrasound, and Electricity, in Transdermal and Topical Drug Delivery Systems, Ghosh, T.K., Pfister, W.R., Yum, S.I., Eds., Interpharm Press, Inc.: 327-355, 1997.
35. Blank, I.H., Moloney, III,J., Esmilie, A.G., Simon, I., and Apt, C., The Diffusion of Water Across the Stratum Corneum as a Function of its Water Content, J. Investigative Dermatology, 82 (2): 188-194, 1984.
36. Bucks, D.A.W., Maibach, H.I., and Guy, R.H., Occlusion Does Not Uniformly Enhance Penetration in Vivo, in Percutaneous Absorption: Mechanisms-Methodology-Drug Delivery, Second Edition, Bronaugh, R.L. and Maibach. H.I., Eds., Marcel Dekker: 77-91, 1989.
37. Marecki, N.M., Design Considerations in Transdermal Drug Delivery Systems, Pharm. Tech. Conf. Proc.: 311-318, Sept 22-24, 1987, in East Rutherford, NJ.
38. Bova, D.J., Ahmuty, V.N., Cirrito, R.L., Holmes, K.O., Kasper, K., LaPrade, C., LaPrade, R., Maag, G.A., Mantelle, J.A., McCarty, J.A., Miranda, J., Morton, F.A., and Sablotsky, S., Product Development and Technology Transfer for Transdermal Therapeutic Systems, in Transdermal Controlled Systemic Medications, Chien, Y.W., Ed., Marcel Dekker, Inc.:379-396, 1987.
39. Krug, K. and Marecki, N.M., Porous and Other Medical Pressure Sensitive Adhesives, Adhesives Age, 11 (11): 19-23, 1983.
40. Wolff, H.S., Hoffmann, H.R., and Cordes, G., Development of Processes and Technology for Adhesive-Type Transdermal Therapeutic Systems, in Transdermal Controlled Systemic Medications, Chien, Y.W., Ed., Marcel Dekker, Inc.: 365-377, 1987.
41. Brain, K.R., Hadgraft, J., James, V.J., Shah, V.P., Walters, K.A., and Watkinson, A.C., In Vitro Assessment of Skin Permeation from a Transdermal System for the Delivery of Oestradiol, International Journal of Pharmaceutics, 89: R13-R16, 1993.
42. Wokovich, A.M., Prodduturi, S., Doub, W.H., Hussain, A.S., and Buhse, L.F., Transdermal Drug Delivery System (TDDS) Adhesion as a Critical Safety, Efficacy and Quality Attribute, Eur. J. Pharm. Biopharm., 64: 1-8, 2006.
43. Lucast, D.H. and Taylor, C.W., Crosslinked acrylate adhesives for use on skin, Polymers, Laminations and Coatings Conf., TAPPI Proc.: 721-725, 1989.
44. Muny, R.P., Testing Pressure Sensitive Adhesives, in Handbook of Pressure Sensitive Adhesive Technology, 3rd Edition,. Satas (ed.), Satas and Associates, Warwick Rhode Island: 139-152, 1999.
45. Musolf, M.C., Pressure Sensitive Adhesives: Science and Engineering, in Transdermal Controlled Systemic Medications, Chien, Y.W., Ed., Marcel Dekker, Inc.: 93-112, 1987.
46. Satas, D., Peel, in Handbook of Pressure Sensitive Adhesive Technology, 3rd Edition,. Satas (ed.), Satas and Associates, Warwick Rhode Island: 62-85, 1999.
47. Ko, C.U., Factors Influencing Adhesive Selection for Transdermal Systems, Prediction of Percutaneous Penetration, 4B: 7-13, 1996.
48. Conti, J.C., Jones, E., Strope, E., Rohde, D., Dynamic Peel Analysis Demonstrates Package Seal Failure not Predicted by Standard Peel Test, in Proc. 21st Annual Meeting of the Adhesion Society: 418, 1998.
49. Conti, J.C., Strope, E.R., Gregory, R.D., and Mills, P.A., Cyclic Peel Evaluation of Sterilized Medical Packaging, in Proc. 22nd Annual Meeting of the Adhesion Society: 116, 1999.
50. Satas, D., Tack, in Handbook of Pressure Sensitive Adhesive Technology, 3rd Edition,. Satas (ed.), Satas and Associates, Warwick Rhode Island: 36-61, 1999.
51. Johnston, J., Alternate Methods for the Basic Physical Testing of Pressure Sensitive Adhesive Tapes and Proposals for the Future, Proc. 22nd Annual Meeting of the Adhesion Society, Panama City Beach, FL: 327-329, Feb. 21 1999.
52. Johnston, J., Peel Adhesion Testing of Pressure Sensitive Adhesive Tapes, Adhesives Age, 11 (4): 20-26, 1968.
53. Johnston, J., Alternate Testing Methods for Pressure Sensitive Products, Polymers, Lamination & Coatings Conference, TAPPI Proceedings: 55-62 1990.

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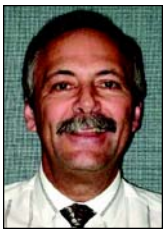

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This article presents the changing manufacturing environment and how companies can develop an infrastructure to continue to meet their strategic objectives.

Pharmaceutical Manufacturing: Linking Vision and Decision-Making to Achieve a Roadmap Toward cGMPs for the 21st Century

by Beatrijs Van Liedekerke and Ingrid Maes

Introduction

Despite the innovatory and advanced science nature of many of its products, the pharmaceutical industry has been more used to incremental change in manufacturing rather than quantum leap advances. Now, however, there is the prospect of more rapid change in the industry. Changes in the regulatory stance and compelling business reasons are prompting companies to consider 'big leap' rather than 'small step' changes. But many companies remain wary of drastic change. How can companies judge how best to prepare for the future manufacturing strategy and infrastructure? How fast and how far should they move? Many companies are seeking to implement manufacturing change, but are doing so in sub-optimal ways that do not maximize benefit for the company. This is because, often, changes in manufacturing practice and infrastructure are not being informed by a clear manufacturing vision. Such a vision must address the regulatory, market, scientific, and technological forces that will shape pharmaceutical manufacturing in the future. Changes in regulation and technology are already influencing how existing products are tested. Looking ahead, regulatory, scientific, and technological developments have the potential to produce significant change in the interaction of manufacturing and the market. This article considers this changing context and looks at how companies can develop a manufacturing vision. It outlines four possible manufacturing scenarios that companies may find themselves considering. The IT/manufacturing infrastructure that will be important for each scenario is presented.

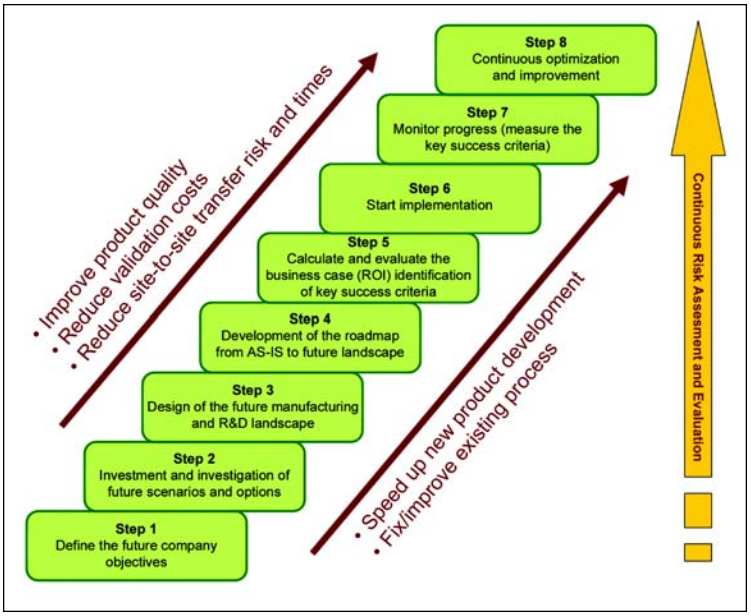

Figure 1. Moving toward the manufacturing vision.

The Changing Manufacturing Context

The pharmaceutical manufacturing sector has been inherently conservative in its approach to manufacturing change. Regulation is a key driver for change. Historically, though, the regulatory framework, with its reliance on batch inspection, has de-

terred manufacturing innovation. Regulation has driven change, but in an 'after the event' fashion with compliance reliant on enforcement and inspection. Now, recent initiatives of the US Food and Drug Administration (FDA) herald an era where regulation can act as a more dynamic driver of change with both quality and regulatory compliance 'designed in' to the manufacturing process. The FDA's PAT framework and its cGMPs for the 21st Century initiative provide significant opportunities for improvement and innovation in pharmaceutical manufacturing. The FDA talks about a 'desired state' of manufacturing with:

- product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- an ability to affect continuous improvement and continuous "real time" assurance of quality[1]

The final report of the FDA's cGMPs for the 21st Century Initiative[2] highlights the choices that pharmaceutical companies face:

> "At the end of the cGMP initiative, the pharmaceutical community has arrived at a cross-road; one path goes toward the desired state and the other maintains the current state. The path toward the desired state is unfamiliar to many, while the current state provides the comfort of predictability. The Agency hopes the pharmaceutical community will choose to move toward the desired state."

This new regulatory approach presents companies with the possibility of new manufacturing visions. It also comes at a time when the risk reward context for pharmaceutical manufacturing is changing. Companies are becoming more exposed to powerful wider market forces. The pharmaceutical industry is at a key turning point in many respects. Historical ways of delivering value will not be sustainable on their own in the future. All the key planks of value are in transformation – drug development pipelines are drying out, pricing is under pressure, and generic competition is more intense. Cost containment is the name of the game both for the government customer bodies that play a lead role in the pharmaceutical market around the world and the private insurance customers in mar-

Case Study 1: Manufacturing Vision Development

Background

A pharmaceutical company has a product that will soon run out of patent and generic manufacturers are becoming strong competitors. Reducing manufacturing costs has been defined by this pharmaceutical company as a key business objective.

A Typical Response

The company decides to appoint a team of experts whose task is to review manufacturing and propose optimization proposals. After a couple of months, this team presents the cost reduction initiatives to their management. A list of suggestions have been made, such as better planning to remove Work In Progress (WIP) and to lower inventory; optimization of manufacturing yields and costs by enlarging the batch size (higher filling levels in manufacturing equipment); in-line inspection instead of manual inspection; and installation of process analyzers to detect batch end-points, for example for drying and blending. The team shows that these measures will deliver a reduction in manufacturing costs.

A 'Manufacturing Vision' Response

Another company takes a different approach. Instead of appointing a team to look for optimizations and improvements, it first organizes a high level meeting with representatives from a range of departments - R&D, manufacturing, sales and marketing, regulatory affairs. The aim of the meeting is to investigate what will be needed in five to 10 years time, taking account of business challenges, technological options, and regulatory opportunities.

The group has already looked at their current product portfolio and future portfolio, based on their pipeline. It has investigated the consequences of this new portfolio on the current manufacturing infrastructure. It has considered what the future manufacturing landscape will look like to be able to cope, not just with the new product portfolio, but also with the future market and environmental requirements, business model requirements, regulatory changes, etc. A scenario planning exercise has supported the exploration of possibilities and future scenarios. This study results in the identification of a manufacturing vision, which describes the future required manufacturing landscape that will best fit with the most likely scenarios.

This vision makes it easier to identify the gaps between the current "as is" manufacturing situation and the future "to be" one. It also helps to indicate the improvements and changes that the company can already start to implement. A roadmap linking the "as is" and the future "to be" situation enables the company to focus on the improvement and optimization projects that help it move to the future situation. The company can avoid investments which, taken in isolation, might have a sufficient Return On Investment (ROI) to implement, but when looked at in a fuller context, would not achieve a more sustainable advancement for the company. This broader perspective enables the company to move forward in the knowledge that it is not just investing in little islands of optimizations, but is linking them to a wider and bigger quantum leap forward.

kets such as the US. Double-digit sales and income growth has come to an end under pressure from patent expirations, generic competition, and Over The Counter (OTC) switches.

Alongside these trends, we are not so far from a future where it will be possible to develop drugs that are tailored to the individual genetic and proteomic profile of the patient, making the therapy more effective and having less side-effects by optimizing dosage and drug composition for each patient. An investigation by the national academy of science of the UK concluded: "personalized medicines; tailoring drug treatments to a person's genetic profile, also known as pharmacogenetics, have a promising future,"[3] predicting that "over the next 10 to 20 years, we expect to see several pharmacogenetic products enter mainstream healthcare."[4] The report pointed out that "industry will continue to favor drug candidates that avoid the effect of genetic variation, but where that is not possible, the development of drugs with an associated diagnostic test is expected to become routine in the next 10 to 20 years."[5] In part, mainstream pharmaceutical M&A companies have reflected this future with repeated acquisitions of biotechnology companies. These moves have been designed to boost drug pipeline portfolios in the short to medium term and build capacity for a more genetically-driven industry of the future in the medium to long term.

Such a future is very relevant to a company's manufacturing vision. As a consequence, drugs will need to be manufactured or produced in smaller batches that are formulated on request to match the profile of certain segments of patients or even a single patient. There will be fewer big blockbuster drugs and more personalized medicines. To accommodate these changing production needs, new flexible regulatory approaches and batch control strategies have to be developed. Moreover, since the treatment is formulated on request and is intended for a patient who may urgently need the medication, product development and manufacturing lead time and release times will have to be drastically reduced.

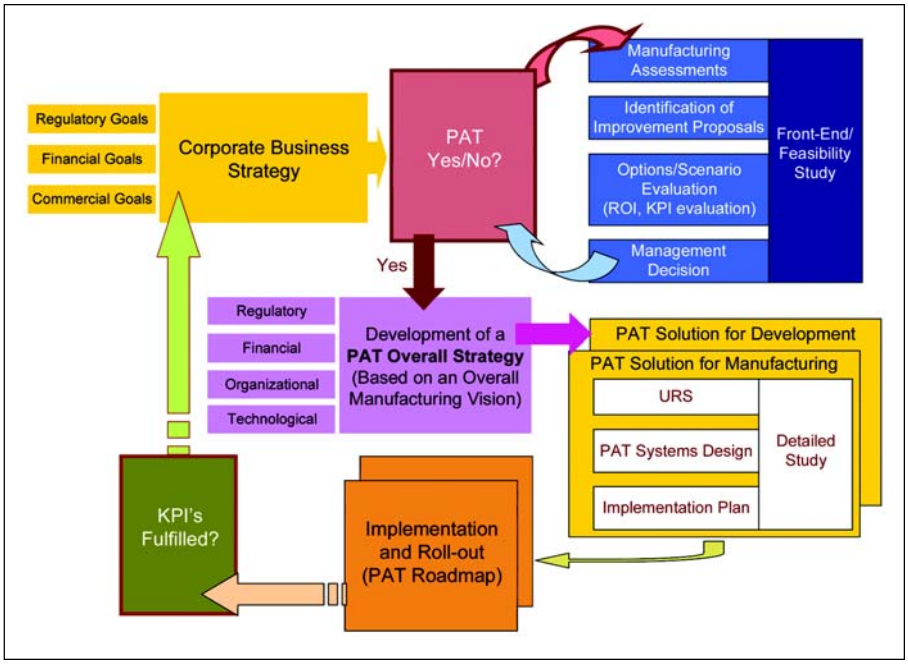

Figure 2. The pharmaceutical manufacturing change context.

Developing a Manufacturing Vision

Therefore, pharmaceutical manufacturers face a complex and in some respects, contradictory set of demands. On the one hand, they have the opportunity to make significant investments in automation and process technology, but on the other hand, they face cost pressures, meaning that such investments must deliver the maximum benefit. They face a future drug market that may be more personalized, posing key dilemmas for whether the manufacturing plant development should be large scale or small scale.

Mergers and acquisition activity have made it easier for some companies to close or modify existing outdated plants. In our practical experience, we see companies starting a lot of investment projects both as part of post acquisition activity and elsewhere. They are called various names, such as improvement projects or cost containment projects, but they have in common the aim of manufacturing modernization. However, they are rarely informed by a real look at the bigger picture of where the company wants its manufacturing to be in five to 10 years time (see Case Study 1). Classically, when companies consider investment in Process Analytical Technology (PAT) for example, they often see it as replacing one form of testing with another form of testing without considering its full potential. No wonder Dr. Ajaz S. Hussain, who at the time of being quoted was Deputy Director at the Office of Pharmaceutical Science CDER at the FDA, was prompted to remind companies: "you've got to remember that PAT is not about just throwing in-line sensors at a production line. It is more about understanding the sources of product variability during production and controlling your processes in a flexible way to allow you always to produce a quality product."[6]

Investment tends to be on a limited scale and fragmented, focusing perhaps on one production unit or process, but not making connections across the manufacturing software and infrastructure which, often, remains standing alone or only present on isolated production units. This often results in sub-optimizations instead of an overall optimization. In the future, the requirement will be for all the supporting software and different applications to be interconnected. As Graham Cooke, Director Technology and External Supply EMEA of Wyeth, has emphasized, companies need to avoid developing isolated islands of innovation: "'Islands' of PAT (need) to be tied together as part of an overall strategy. Feed back and feed forward controls. (Companies need to) develop the 'integrated plan'

Case Study 2: Status Quo vs. Automation vs. Full PAT Implementation in a Vaccine Plant

Background

A vaccine plant was seeking to achieve cost savings through modernization of manufacturing infrastructure. Interviews with different stakeholders and analysis of manufacturing data led to:

- the identification of areas for cost savings through the assessment of possible improvement scenarios
- an outline of operational and financial benefits for these various scenarios
- assessment of the impact of different scenarios on the following KPIs:
  - labor (people)
  - manufacturing throughput time
  - quality
  - waste
  - inventory levels

Improvement Scenarios

Three improvement scenarios were identified. Each of these scenarios describe the various steps toward optimal PAT-enabled manufacturing, delivering the maximum benefits in terms of cost savings.

The scenarios are built up in such a way that maximum benefits are realized with minimal investments. They start with the quick wins followed by a sequence of medium to longer term improvement investments. Each improvement investment goes hand in hand with benefits which are displayed as an effect on the Key Performance Indicators (KPIs).

- Some of the scenarios can be executed in parallel; however, when activities are carried out in parallel, the necessary skilled resources need to be available in order to deal with the complexity and the project management.
- A timeline was developed illustrating how much time it takes to implement the improvements as well as the resources and skill set needed for each of the improvement projects. The time to get regulatory approval should be superimposed on the outlined project execution time lines.
- In parallel with the timeline, the sequence of investments needed to realize improvements was established.

Results

The result was a calculation of the optimal scenario (in this case, scenario 3) and its impact on the KPIs:

- Labor: 1/4 of operations people could be re-allocated and 1/3 of the QA/QC people could be freed up for other work.
- Manufacturing throughput time: throughput time decreased with 1/3 freeing up capacity and allowing extra production with the same headcount.
- Quality: 13% of the cost of QA and QC are eliminated because of improvement in right first time.
- Waste reduction: 3.5%
- Inventory: inventory could be reduced by 1/3 (representing about US $14.3 million in this case).

Observations

In terms of PAT implementation, maximum benefits were achieved with a broad PAT definition. This means looking at the full opportunities offered by PAT, as outlined in the FDA PAT Guidance (e.g., real-time product release, manufacturing performance improvement, quality consistency improvement, and regulatory flexibility). This was preferable to a "limited PAT" approach based only on the implementation of an on-line sensor. We found that the feasibility of a broad PAT enabled manufacturing process could be demonstrated with much more certainty.

first and then create focus and dive deep into individual unit operations before extending to other unit operations."[7] In addition, whether it is PAT or other innovation, the infrastructure will need to be of high quality and reliability because the recourse to running the production manually will not be an option.

How can companies judge how best to reshape their manufacturing strategy and infrastructure? In the context of PAT, Cooke emphasises the need for 'wider company' multi-disciplinary thinking: "…a number of success factors have been identified for implementation of PAT. These include the need for multi-disciplinary project teams, a clearly defined implementation process, and a strong business rationale."[8] Companies need to address the culture change implications of investments such as PAT which include breaking down silos within organizations and also rethinking job roles. Far-sighted companies seeking to capture the full competitive advantage potential of PAT will, for instance, be looking at the links outside of manufacturing into the consumer-facing functions of product development and marketing. Skill-set requirements will change significantly. Enterprise-wide data management, retrieval, and querying will be vital. Pharmaceutical scientific skills will need to extend into understanding the supportive database structure and be capable of managing knowledge retrieval systems in an efficient, usable, and timely manner.

In our view, the starting point has to be the manufacturing vision and all parts of the business need to be involved in looking ahead on a 10 to 15 year time frame. The following case illustration highlights the importance of framing decisions in such a context and contrasts that with the typical approaches that we, as authors, see many pharmaceutical companies taking.

The approach outlined in Case Study 1 allows companies to prioritize specific problems within the context of long-term change. The range of specific concerns could include a need to fix or improve existing processes, speed up new product development, reduce site to site transfer risk and times, reduce validation costs, or improve quality

reliability. Most companies are likely to want to realize a blend of these benefits. Their immediate priorities will be determined by the current state of play of their manufacturing and its fit with their regulatory compliance, market and business goals. Most importantly, though, they need to combine this review of current wider concerns with the type of longer-term wider scenario planning outlined in the case illustration above. Figure 1 outlines the steps companies might take to put this process into practice.

Figure 2 provides an overview of the type of overall decision-making process that a company needs to undertake. The current manufacturing infrastructure has to be assessed in the light of the future manufacturing vision (in line with the global company's objectives). What are the current bottlenecks and what are the improvement possibilities? The resulting list of improvement proposals have to be evaluated to judge just what they bring to the company and whether they help achieve the manufacturing vision and its objectives. Depending on which market the company is in, the regulatory constraints need to be superimposed in order to make sure no surprises are encountered. Even for those countries that are actively driving changes (such as the FDA in the US), it is important to involve the regulators early on in the process.

Four Change Scenarios

The outcome of this type of process will be a view about what type of manufacturing strategy and plant the company needs in a more medium to long term timeframe, say five to 10 years time. The answer may be different from plant to plant and many companies are likely to need to plan for a mix of scenarios. For example, a company may choose to implement relatively modest improvement investment in a plant that is manufacturing a product that is nearing the end of its patent period (scenario one in Figure 3). Elsewhere it may choose to plan for a rapid and full scale move to PAT enabling full realization of the FDA's vision of real time product control and release, based on continuous manufacturing operations

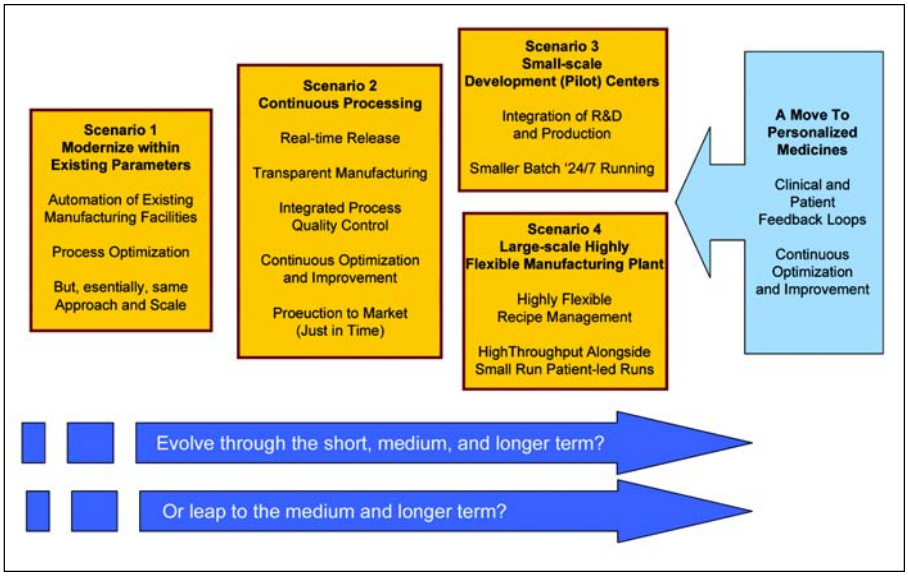

Figure 3. Four change scenarios.

(scenario 2 in Figure 3).

Companies also will be mindful that a possible trend toward more personalized medicines will increase manufacturing complexity, and in turn, pose challenges for Manufacturing Execution Systems (MES) and quality systems. A larger variety of products and variation of the same products will require greater flexibility of production as well as closer integration along the whole pharmaceutical chain - R&D, manufacturing, sales, and the end customer.

Scenarios three and four in Figure 3 highlight how companies will face a choice between big plants with flexible recipe production versus small-scale development (pilot) plants which also will be production facilities with dedicated lines. For both models of production, industrial IT systems will play a strategic role, requiring tremendous flexibility, in the first model, to support the flexibility of production that will be necessary, and in the second smaller scale model, to link production with continuous development and learning from clinical trials. The regulatory stance will be a key factor in this mix and at present, regulators are investigating how to support this evolution with the appropriate regulations

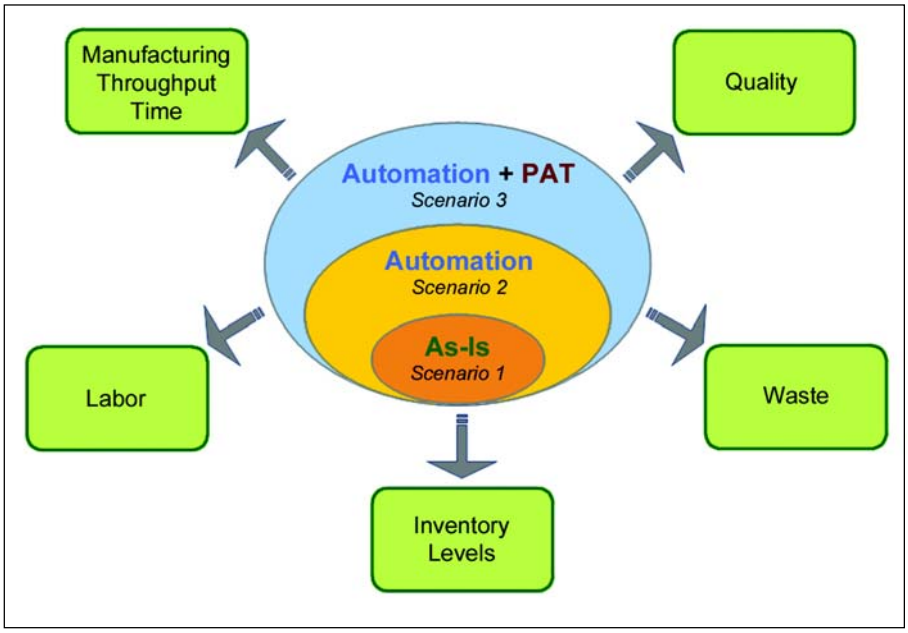

Figure 4. Impact of scenario implementation on various KPIs.

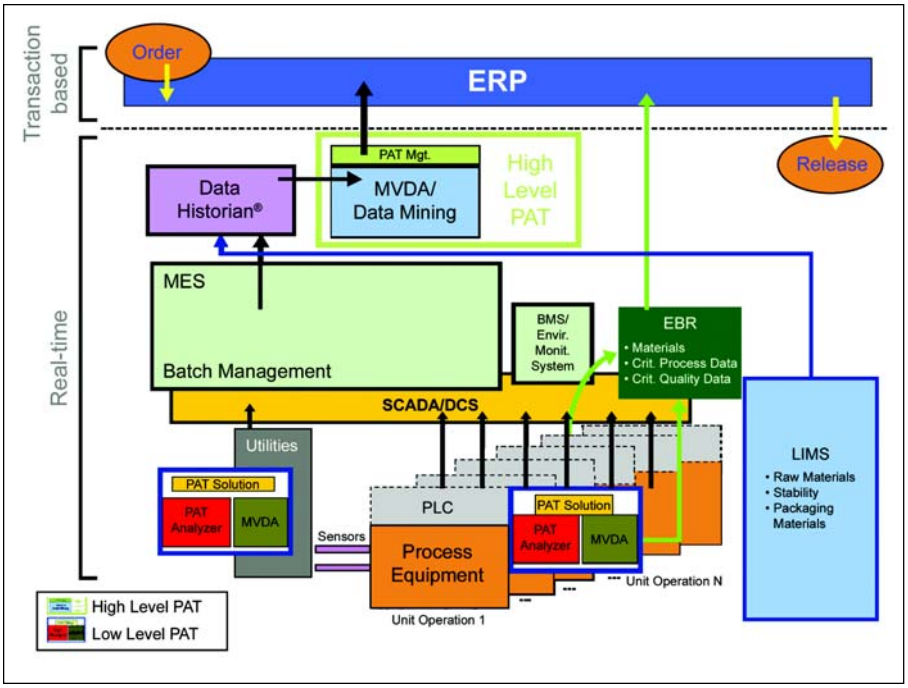

Figure 5. Manufacturing infrastructure scheme.

and guidelines.[9]

A key influence will be the demand side and we are likely to see a mix of large scale, very high throughput facilities handling generic production, and micro-process centers concentrating on higher end personalized medicines. Therefore, pharmaceutical companies need to investigate the investment in planning for a potentially very different manufacturing future as well as responding to pressures on their current manufacturing set-up.

Choosing Between Scenarios – Evolution or Drastic Change?

A critical issue for companies contemplating scenarios such as outlined in Figure 3 will, of course, be how to make choices between them. The identification of the right evaluation criteria (Key Performance Indicators (KPIs) for improvement) is crucial for evaluating the options and for monitoring progress and achievement of the objectives. Each company's situation will be different and judgements on the focus and pace of change will vary according to the ROI analysis of the different options open to them. For example, some companies may consider that certain plants or processes do not merit investment, others will only need minor investments and others require drastic change.

Even in the case of drastic change, it is the authors' experience in many real-life cases that a change, which at first sight may appear quite drastic and associated with big investments, can be shaped into smaller pieces, solving at the same time some technical issues. This allows a step-by-step investment and implementation with each step having a ROI case, providing justification of the investment. The company, although taking small steps, is doing so in the context of a journey toward a manufacturing infrastructure which meets the future business challenges. This will enable companies to be ready for the possible future business scenarios and to take advantage of adopting new technologies early. The critical elements are the selection of the improvement options, the identification of the right KPIs, the size and sequence of the steps, and last but not least, the fit of the future manufacturing vision with the possible future business landscape. Case Study 2 illustrates how this might work in action in a vaccine plant.

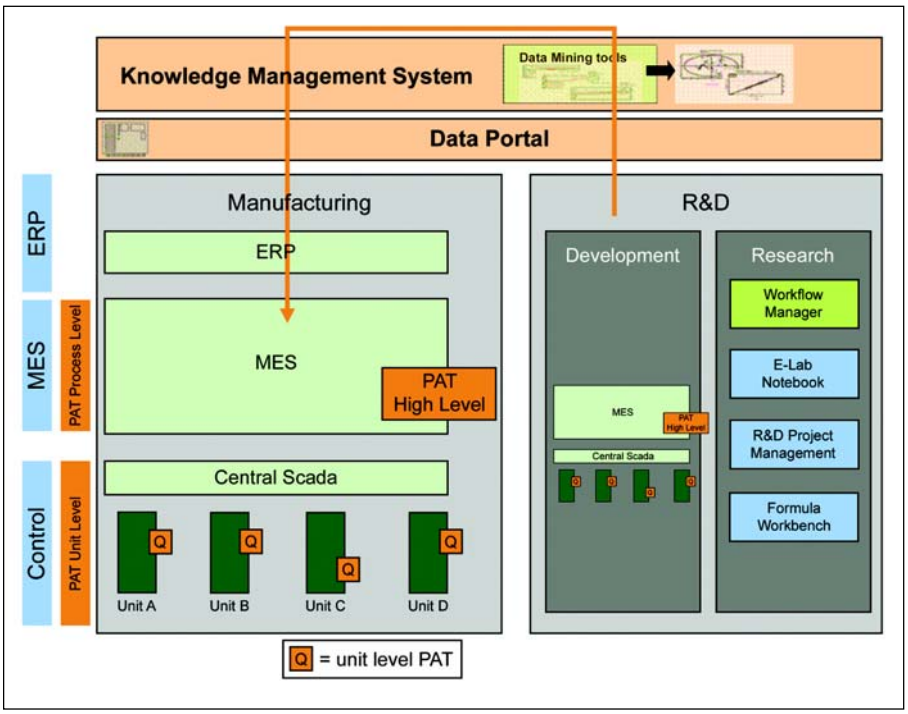

Figure 6. Tighter integration of development, manufacturing and knowledge to achieve continuous improvement.

Manufacturing Infrastructure

Once they have chosen between different possible manufacturing visions and completed some scenario planning, companies will, of course, need to decide on the manufacturing and IT infrastructure that will be required for the chosen scenario. Decisions about the future architecture will differ between the various scenarios, and crucially between those with smaller size process equipment and larger scale

manufacturing. As an example, Figure 5 outlines a manufacturing infrastructure scheme corresponding to scenario 2 of Figure 3. The PAT solution has interfaces to the process equipment, the process automation, and will take care of data collection from the process, eventually from extra real-time measurements (PAT Analyzer) as well as data storage and retrieval. It consists also of an MVDA engine able to interpret quality data and translate this into control and correction actions. The high level PAT solution will combine various unit operations and will take care of the overall product release of the final product.

In general, the role of the quality management system will shift to the manufacturing floor and will be of more strategic importance, as it is essential for real-time product release. Greater integration of multi-disciplinary teams will be an important factor alongside the hardware and software. The quality management system will consist of a LIMS system and PAT systems (on unit and on line level). It will allow Production Performance Analysis (PPA). In turn, for faster time-to-market, a closer link between development and manufacturing is required that allows for continuous improvement. Figure 6 outlines the wider architecture that is needed. A central role will be occupied by knowledge management systems and data portals, but also by advanced data mining techniques. The role of knowledge management systems and data portals will be essential for this change.

Conclusion

A combination of regulatory, market, scientific, and technological forces is likely to mean that pharmaceutical manufacturing will undergo rapid change in the next five to 10 years. Many companies are already investing in change projects, but they are often piecemeal and not accompanied by a clear manufacturing vision. The absence of such a vision also means that companies sometimes feel caught between 'big leap' and more incremental changes. In fact, incremental change is vital to achieve a longer term 'big leap.' But, in the absence of a manufacturing vision, companies find themselves with no roadmap. The consequence is that changes are made in relative isolation without maximizing their potential incremental contribution to longer term improvement or, worse, moving the company further away from the manufacturing it will need in the future.

We have shown how companies can use a range of tools – scenario planning, ROI analysis, KPIs – to construct such a roadmap to ensure changes are linked together, thereby avoiding piecemeal and sub-optimal change. There is a need for companies to more consistently align investment in IT and manufacturing with their vision of the manufacturing that will be needed in the future. In doing so, companies will be able to ensure that investments don't just deliver specific gains, but also help accelerate the company's progress toward longer term goals.

References

1. Innovation and Continuous Improvement in Pharmaceutical Manufacturing: The PAT Team and Manufacturing Science Working Group Report: A Summary of Learning, Contributions, and Proposed Next Steps for Moving Toward the "Desired State" of Pharmaceutical Manufacturing in the 21st Century. http://www.fda.gov/cder/gmp/gmp2004/manufSciWP.pdf.
2. Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach Final Report. Department of Health and Human Services, US Food and Drug Administration, September 2004. http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm#_Toc84065738.
3. The Royal Society, Personalised Medicines: Hopes and Realities, press release, 21 September 2005, ref 18/05.
4. The Royal Society, Personalised Medicines: Hopes and Realities, September 2005, p 2.
5. ibid. p 1.
6. Quality Manufacturing: A Blockbuster Opportunity for Pharmaceuticals, Economist Intelligence Unit, 2005.
7. PAT Strategy: Islands of PAT to be Tied Together, Graham Cooke, European Pharmaceutical Review, issue 5, 2006.
8. Ibid.
9. Innovation Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products, US Department of Health and Human Services, Food and Drug Administration, March 2004.

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ProPharma Group and Computer Compliance Announce Merger

ProPharma Group and Computer Compliance announced the merger of their companies. The merger will provide their clients with expanded, streamlined access to a broad array of validation services. The management team will remain the same.

ProPharma Group Inc., www.propharmagroup.com. Computer Compliance Inc., www. ccionline.com.

Pharmadule to Deliver Modular Facility to Excelvision AG

Pharmadule, a division of Pharmadule Emtunga AB, has signed a contract with Excelvision AG for the delivery of a modular facility for the manufacturing of ophthalmic products. The project is an extension of an existing plant in Hettlingen, Switzerland and will include both new construction and upgrading of the existing facility. Pharmadule's scope comprises design, fabrication, and validation of the two-story facility extension with a total size of approximately 720 sqm.

Pharmadule, www.pharmadule.com. Excelvision AG, www.fareva.com.

Air Enterprises Purchases Thermotech Enterprises

Bill Weber and Mal Mixon, owners of Akron, Ohio-based Air Enterprises, purchased Thermotech Enterprises, an energy recovery wheels manufacturer located in Oldsmar, Florida. Weber stated, "The built to last products of these two companies lower operating expenses and prevent replacement of costly integrated HVAC systems." Thermotech will remain and operate as an independent company and continue to be directed and managed by founder and CEO, Krister Eriksson, PE.

Air Enterprises, www.airenterprises.com. Thermotech Enterprises Inc., www.thermotech-usa.com.

Amgen to Acquire Alantos

Amgen has agreed to acquire Alantos Pharmaceuticals, a privately held company in Cambridge, Massachusetts, developing drugs for the treatment of diabetes and inflammatory diseases. Alantos' lead drug candidate, ALS 2-0426, is a DPP-IV inhibitor in clinical development (Phase 2a) for the treatment of type II diabetes. Under terms of the agreement, Amgen will pay $300 million in cash to acquire Alantos, which will become a wholly-owned subsidiary of Amgen.

Amgen, www.amgen.com. Alantos Pharmaceuticals, www. alantos.com.

Avesthagen and Manipal AcuNova Announce Collaboration

Avesthagen signed a memorandum of understanding with Manipal AcuNova Ltd to collaborate on providing their competencies in discovery, pre-clinical, clinical research including regulatory matters. This partnership will enable them to jointly provide a fully integrated platform from early discovery to filing approvals for new products. Avesthagen and Manipal AcuNova will also collaborate in validation of molecular diagnostics kits and product co-development.

Avesthagen, www.avesthagen.com. Manipal AcuNova Ltd, www.acunovalife.com.

Pall Opens New Center of Excellence in India

Pall Corp. inaugurated its newest Life Sciences Center of Excellence in Bangalore, India. The Center will drive process optimization innovations for the global life sciences market to meet the evolving opportunities and challenges of this fast-growing industry throughout Asia. The new Center includes a state-of-the-art proteomics laboratory to help customers speed the drug discovery process, a validation laboratory, and a training facility with specialty experts to support Indian and regional customers.

Pall Corp., www.pall.com.

Human Papillomavirus Vaccine Granted Reimbursement Status in Sweden

The Pharmaceutical Benefits Board in Sweden has included the Human Papillomavirus vaccine Gardasil® in the national Pharmaceutical Benefits Scheme, marking the first time that the Board has granted a vaccine reimbursement status. The reimbursement applies to girls ages 13-17 years. Gardasil®, Human Papillomavirus Vaccine [types 6,11,16,18], is the only licensed vaccine for the prevention of cervical cancer and other Human Papillomavirus diseases that occur before cervical cancer and beyond the cervix.

Sanofi Pasteur MSD, www.spmsd.com.

PharmaServ Partners with CompuCal Software Solutions

PharmaServ announced a new partnership with CompuCal Software Solutions (CSS). CSS is an Irish software solutions company specializing in the development of compliant web-based maintenance and calibration management solutions.

PharmaServ, www.pharmaservpr.com. CompuCal Software Solutions, www.compucalsolutions.com. PE

*To submit material for publication in **Pharmaceutical Engineering**'s Industry and People department, e-mail press releases with photos to **pharmeng@ispe.org** for consideration.*

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Vial Filling System

Bosch Pharmaceutical USA, a Bosch Packaging Technology company, augments its portfolio of vial filling solutions with the FLT1020, a new system designed for increased efficiency in clinical trials. The new filler is a downsized alternative to larger vial filling systems, specifically designed for the clinical/trials phase. Based on production technology, the FLT1020 minimizes packaging and processing variables when shifting into the full scale production stage.

Bosch Pharmaceutical USA, www.bosch.com.

Multi-Bag Filter

The MAXILINE™ MBF HE Multi-Bag Filter from Eaton, with up to 24 individual filter bags, has been designed to handle system flow rates up to 4500 gallons per minute. The filter works with Eaton Size 02 Filter bags, rated from 1 micron all the way up to 800 microns, as well as most standard, 7" x 32" size 02 bags.

Eaton Filtration LLC, www.filtration.eaton.com.

Heel Removal Technology

Total heel removal from a Nutsche filter-dryer can be achieved with Comber's "Heel Break-Up System" and "Whirl Snake®" high efficiency turbines. The combined effect of "Heel Break-up System" (counterblow from below the base) and "Whirl Snake®" (counterblow with nitrogen from the top) guarantees the total powder removal not only on the filtering base, but also on the agitator and all vessel internal surfaces.

Comber, www.comber.it.

Real-Time Locator System

Honeywell has introduced its Honeywell Instant Location System (HILS), a real-time location solution that industrial manufacturers can use to ensure safety, improve security, and manage people and valuable assets within their facilities. HILS integrates the latest identification and location technologies available today, such as Ultra-Wideband, Global Positioning Systems (GPS), Wi-Fi, and active radio-frequency identification, with Honeywell's process automation system, Experion® Process Knowledge System (PKS). Installed at locations throughout a facility, receivers can pinpoint the location of an employee or piece of equipment and send the information to the HILS server, which directly feeds the information to the operator's workstation.

Honeywell International, www.honeywell.com.

Steam and Distillation Unit

The combined pure steam and distillation unit Combitron from Christ simplifies the provision of ultra-pure media: instead of using two units, pure steam and Water for Injection (WFI) can be generated in a single unit. This is made possible by the use of a first column with a larger diameter and of the natural circulation principle. The media can be produced simultaneously or separately in all columns and with an output of about 1,000 kg of pure steam and up to 4,000 liters of WFI per hour.

Christ Water Technology Group, www.christwater.com.

Clamps

Now available from plastic tubing and hose manufacturer NewAge Industries are clamps for fitting attachment in three different styles. Consisting of ear

type, worm gear, and double bond, the clamps are used in all sorts of industries, including OEM, chemical, aerospace and aviation, food and beverage, laboratory, medical and pharmaceutical, pool and spa, robotics, appliance, automotive, MRO, recreational vehicles, marine, and many others.

NewAge Industries, www.newage industries.com.

Peristaltic Pumps

Watson-Marlow Bredel, a leading manufacturer of peristaltic pumps, announces the 720 Series peristaltic pump. The newest addition to the Watson-Marlow Bredel family, the 720 Series peristaltic pump allows for increased capacity and tighter flow control. The 720 Series is designed for accurate metering and dosing of corrosive, abrasive and sensitive fluids, and is ideal for the contamination-free transfer of acids, paints, oils, inks, dyes or waste slurries found in industrial, chemical, pulp and paper, printing, and food processing markets.

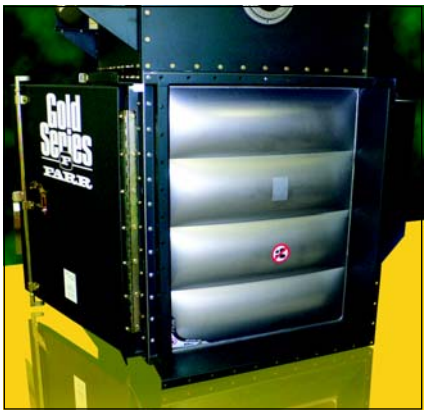
Watson-Marlow Bredel, www.watson-marlow.com.

Mixing System

ATMI LifeSciences, world leader in scalable disposable mixing and storage technologies, announces the upcoming launch of their ground-breaking Newmix™ Jet-Drive™ technology. ATMI's proprietary Jet-Drive and A-Mix™ bag system uses an integrated turbine for fast, homogeneous mixing of fluids with different densities. Their innovative multipoint horizontal mixing jet is specifically designed to eliminate the dead zones found in most 3-D disposable mixing systems.

ATMI LifeSciences, www.atmilifesciences.com.

Dust Collector



Farr Air Pollution Control is now offering its popular "GOLD SERIES®" dust collector with a new high performance explosion vent for applications involving the capture of explosive dusts. The new "X-vent" is NFPA approved and CE and ATEX certified for European use. The multi-ribbed vent delivers a very high negative static operating pressure rating of -80" WC for enhanced performance, and is designed to open up at +1 psi (30" WC).

Farr Air Pollution Control, www.farrapc.com.

Sensor

A new permanently installed sensor, designed to provide convenient and accurate temperature measurement of liquid hydrocarbons in tanks or other large storage vessels, has been introduced by Weed Instrument of Round Rock, Texas. The ACCU-TEMP Type M Tank Measurement Sensor determines either average or multiple spot temperature. Lightweight and coiled for ease of installation, the sensor is built of flexible, corrosion-resistant stainless steel or Monel annular-ring hose and can be used in tanks as high as 200 ft (61m).

Weed Instrument, www.weed instrument.com.

Contained Filtration

The PSL simplefilter by Powder Systems Ltd is an economic and versatile contained filtration solution, ideal for many applications in the pharmaceutical and fine chemical industry. Eliminating the requirement for Personal Protective Equipment (PPE), the PSL simplefilter can be utilized in many processes that currently necessitate the use of extensive PPE. As an ideal choice for pilot plant use, typical applications include chemical development and API production, carbon filtration, hydrogenation, catalyst recovery, and pre filtering for micro-filtration.

Powder Systems Ltd, www.powdersystems.com.

Cartridge Filters

Millipore Corp. announces the availability of its new Fortis SL cartridge filters. With broad chemical and caustic compatibility of polytetrafluoroethylene, these filters are ideal for use in the manufacture of active pharmaceutical ingredients containing methylene chloride, acetone, isopropyl alcohol, ethyl acetate, and other organic solvents. Fortis SL cartridge filters are available in 10-, 20-, and 30-inch sizes and can be autoclaved or steamed in place up to 135°C.

Millipore Corp., www.millipore.com. PE

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Mark Your Calendar with these ISPE Events

August 2007

8 14th SAM and GMP Meeting (Regulatory COP), Japan
9 Puerto Rico Chapter, Packaging Program, Puerto Rico, USA
9 San Diego Chapter, Vendor Night, Theme: Football Tailgate Party, Hilton La Jolla Torrey Pines, La Jolla, California, USA
10 San Diego Chapter, Annual Golf Tournament, Twin Oaks Golf Course, San Marcos, California, USA
21 San Francisco/Bay Area Chapter, Commuter Conference: Maintenance Panel - Predictive vs. Preventative, Best Practices, Nektar, San Carlos, California, USA
23 Puerto Rico Chapter, BioPharm/Medical Device/Tech Convention, Puerto Rico, USA
29 Nordic Affiliate, Science Based Manufacturing - Packaging, Stockholm, Sweden
30 Puerto Rico Chapter, Member's Night, Puerto Rico, USA

September 2007

2 - 4 ISPE Australasia Conference, Plenary Session, Seminars, Table Top Exhibits, Sofitel Gold Coast, Queensland, Australia
6 San Diego Chapter, Dinner Meeting - Outsource Services Panel: Component and Media Prep, PK Toxicology, Preclinical, API and Finish Fill, and Analytical Testing, with Workshops on: Security Policies and Building Automation Systems, San Diego, California, USA
10 - 13 2007 ISPE Boston Training Courses, Skills and practical knowledge for biotechnology, regulatory, HVAC, and GAMP professionals, Hyatt Regency Cambridge, Cambridge, Massachusetts, USA
11 Delaware Valley Chapter, Program Meeting, Delaware Biotech Park, Pennsylvania, USA
12 GAMP Americas Forum, Offers the latest on GAMP and current activities of the GAMP Americas special interest groups, Hyatt Regency Cambridge, Cambridge, Massachusetts, USA
12 Nordic Affiliate, Lab Design and LEED, Stockholm, Sweden
17 - 20 2007 ISPE Berlin Conference, Covering trends and best practices for GAMP, biotechnology, commissioning and qualification, and more, Hilton Berlin, Berlin, Germany
18 Boston Area Chapter, Isolation Technology Seminar, Massachusetts, USA
18 Chesapeake Bay Area, Annual Golf Tournament, Whiskey Creek Golf Club, Ijamsville, Maryland, USA
20 Greater Los Angeles Area Chapter, Technical Training at Amgen, Thousand Oaks, California, USA
20 Ireland Affiliate, Full-Day Seminar on Risk Based Validation, Dublin, Ireland
25 San Francisco/Bay Area Chapter, Commuter Conference: Innovation in Cell Culture-Disposables, Feed Strategies, Baxter, Hayward, California, USA
27 Central Canada Chapter, Annual General Meeting, Mississauga, Ontario, Canada
27 Spain Affiliate, Evening Technical Session followed by an Informal Dinner, Hotel Hesperia Mar., Barcelona, Spain
27 Puerto Rico Chapter, Technology Showcase and GAMP PR Forum, Puerto Rico, USA

October 2007

2 San Diego Chapter, New Member Breakfast, San Diego, California, USA
3 Nordic Affiliate Event, GAMP Event, Stockholm, Sweden
4 San Diego Chapter, Full-Day Extended Education Course - HVAC Systems, California, USA
8 - 11 2007 ISPE Dublin Training Courses, Skills and practical knowledge for biotechnology, project management, water, validation, and commissioning professionals, Dublin, Ireland
9 Delaware Valley Chapter, Program Meeting, Pennsylvania, USA
9 San Diego Chapter, New Member Breakfast, San Diego, California, USA
10 United Kingdom Affiliate - North West Region, Joint Day Seminar with the IChemE at the Museum of Science and Industry, Manchester, UK
11 Greater Los Angeles Area Chapter, Membership Drive at Gilead, San Dimas, California, USA
11 Italy Affiliate, Risk Management and Business Continuity in Life Science Manufacturing, Hotel Baglioni, Florence, Italy
12 Puerto Rico Chapter, Training, Santo Domingo, Dominican Republic
16 GAMP Forum, Manchester, United Kingdom
17 Boston Area Chapter, 16th Annual Product Show, Gillette Stadium Clubhouse, Foxboro, Massachusetts, USA
18 Chesapeake Bay Area Chapter, Bio-Showcase, Gaithersburg, Maryland, USA
18 Delaware Valley Chapter, Fall Education Course, Pennsylvania, USA
18 Puerto Rico Chapter, Update on FDA Guidelines Track, Puerto Rico, USA
18 San Diego Chapter, Oktoberfest, La Jolla, California, USA
23 Italy Affiliate, MC International Conference and Fair of Industrial Maintenance: OEE Lines Performance Indicators, Why, What, and How?, Verona, Italy
23 Nordic Affiliate, Science Based Manufacturing - Powder/Tablets, Copenhagen, Denmark
23 Spain Affiliate, 2nd Annual Congress, Auditorium Hotel, Madrid, Spain

Dates and Topics are subject to change

PQLI

What is it?
Product Quality Lifecycle Implementation

What does it mean?
To implement the new Q8 and Q9 Quality guidelines developed by the International Conference on Harmonisation (ICH), ISPE has launched a brand new concept, "Product Quality Lifecycle Implementation" (PQLI), which focuses on the 21st century perspective on the product quality lifecycle. The goal of PQLI is to garner input from industry to help develop a pragmatic approach to implementing Q8, Q9, and ultimately, Q10. Output from PQLI will include guidances produced by ISPE for the industry.

How does it affect me?
These ongoing sessions provide the opportunity for professionals to discuss and in some cases, give input and suggestions to how these guidelines will be written. It is a direct opportunity to create change in your own future.

What is the basis of the initiative?
The ICH Quality guidelines on Q8 (Pharmaceutical Development) and Q9 (Quality Risk Management) are internationally harmonized guidelines within the three ICH Regions: U.S., Europe, and Japan. Q8 and Q9 seek to integrate quality systems and risk management approaches into the existing program and encourages adoption of modern and innovative manufacturing technology. The new guidelines help industry professionals and regulators improve efficiency and flexibility, while maintaining high quality standards.

The Q8 guideline describes the suggested contents for the 3.2.P.2 Pharmaceutical Development section of a regulatory submission in the ICH M4 Common Technical Document (CTD) format. Its implementation delivers product quality and performance achieved through the design of effective and efficient manufacturing processes as well as product specifications. These specifications are based on a mechanistic understanding of how formulation and process factors impact product performance.

The Q9 guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labelling materials in drug products, biological and biotechnological products).

PQLI Session Locations and Dates to Remember:
Berlin, Germany; 19 September 2007
Las Vegas, Nevada, USA; 5-6 November 2007
Copenhagen, Denmark; 9-11 April 2008

PQLI Approach to Quality by Design

More than 200 industry professionals and regulators gathered for ISPE's inaugural session of Product Quality Lifecycle Implementation (PQLI) to help craft a pragmatic approach to implementing Q8 and Q9 for the industry.

This two-day session held at the ISPE Washington Conference in June offered an exclusive opportunity for ISPE delegates to be seen and heard by industry regulators, and to discuss real world solutions with industry experts. Participants exhibited an intense level of interest, energy and excitement, engaging in the interactive sessions.


George Millili and Russ Somma of the PQLI Steering Committee.

Leaders from science, manufacturing, quality, and engineering engaged with the US Food and Drug Administration (FDA) to begin the process of turning Q8 and Q9 into a cross-functional and practical reality, helping to shape the future thinking of our industry on a global level. During the Washington sessions, Moheb Nasr, PhD, Director, ONDQA, CDER, US FDA; Joseph C. Famulare, Deputy Director of

Continued on page 3.

PQLI

Continued.

PQLI Steering Committee (SC) and Subject Matter Experts (SME):
Robert Baum, PhD, Executive Director, Pfizer, Inc. (PhRMA Advisor, SC)
John Berridge, PhD, Senior Regulatory Consultant, Pfizer, Inc. (EFPIA Advisor, SC)
Bruce Davis, Global Capital Director, AstraZeneca (Technical Team Leader, SME)
Paul D'Eramo, Executive Director Johnson & Johnson (SC)
Charles P. Hoiberg, PhD, Executive Director, Pfizer, Inc. (SC)
George Millili, PhD, Senior Director of Tech Development, Ortho McNeil GPSG (Project Team Co-Chairman, SME)
Joseph X. Phillips, International Regulatory Affairs Advisor, ISPE (SC)
Thomas W. Schultz, PhD, Director, Global Regulatory Affairs, Johnson & Johnson (Technical Team Leader, SME)
Russ Somma, PhD, SommaTech, LLC (Project Team Chairman, SC)
James Spavins, Vice President Regulatory CMC/QA, Pfizer, Inc. (Technical Team Leader, SME)

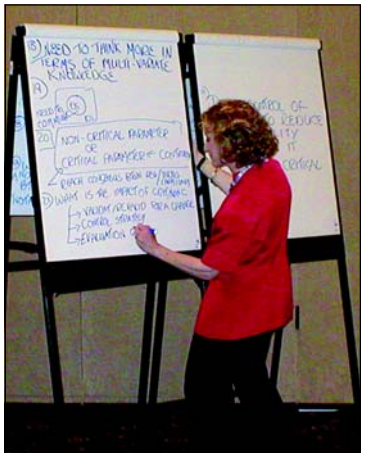
ISPE ENGINEERING PHARMACEUTICAL INNOVATION

PQLI Approach to Quality by Design

Continued from page 2.

Office of Compliance, CDER, US FDA; and Yatindra Joshi, PhD, Vice President of Technical Research and Development at Novartis, gave keynote sessions that addressed the 21st century perspective on the product quality lifecycle.

Workshops examined Q8 and Q9, and identified the subjects/terms that need to be further elaborated, as well as explained why there is a need for a clarification. These six highly interactive workshops focused on NCEs (vs. biotech drugs) and covered API Design Space, DP Design Space, API Critical vs. Non-Critical, DP Critical vs. Non-Critical, API Control Strategy Traditional vs. Quality by Design (QbD), and DP Control Strategy Traditional vs. QbD.



A working group will continue to monitor progress, collect information, and develop session output into white papers, guidances, and technical documents between sessions. The team will gather various views from within the industry to get understanding of the challenges and opportunities.

"ISPE has set up task teams with subject matter experts to identify the knowledge gaps between what the ICH guidelines are and what firms need to embrace," explains ISPE's President and CEO, Robert P. Best. "These teams will develop implementation documents. This will be an ongoing initiative with a horizon of three-plus years. Obviously, filling the knowledge gap would be of great benefit to the industry and the regulators."

Berlin: The Next Step in PQLI

On 19 September, the next phase of PQLI sessions will take place in Berlin, Germany, continuing ISPE's unique leadership in the facilitation of practical solutions for a globally-based industry. This will be an industry initiative, offering an update to attendees, and will build on the work begun by the PQLI initiative in Washington.

Professionals from within the pharmaceutical manufacturing industry will have the opportunity in Europe to continue to define practical solutions to implementing Q8 and Q9 at the PQLI session held in conjunction with ISPE's Berlin Conference, 17-20 September. Regulators will also be present to listen to audience views and to provide their perspective.

"ISPE's PQLI provides the linkage between the high level ICH guidelines and the needs of those wanting to implement them: this seminar is a critically important opportunity to understand the latest developments from those directly involved in ICH and to contribute to clarifying the issues and opportunities of implementation."

John Berridge, Pfizer Ltd., UK, and
EFPIA Advisor to the PQLI Steering Committee

"ISPE's PQLI provides the linkage between the high level ICH guidelines and the needs of those wanting to implement them: this seminar is a critically important opportunity to understand the latest developments from those directly involved in ICH and to contribute to clarifying the issues and opportunities of implementation," according to John Berridge, Pfizer Ltd., UK, and EFPIA Advisor to the PQLI Steering Committee.

The goal of this program is to update the attendees on the progress to date of the PQLI initiative and to discuss future plans to present and progress PQLI, and particularly to assist with design of the ISPE PQLI meeting in Copenhagen, Denmark, 9-11 April 2008.

Berlin Seminar Leaders will be **John Berridge,** Pfizer, UK, and **Bruce Davis,** AstraZeneca, UK. Other speakers include:

Susanne Keitel, BfArM, Germany
Gert Moelgaard, NNE PharmaPlan, Denmark
Jacques Morenas, French Health Products Safety Agency, France
Chris Potter, AstraZeneca, UK
Tom Schultz, Johnson & Johnson, USA
Jim Spavins, Pfizer, USA

Attendees will be able to listen to and share with colleagues practical solutions on how QbD affects your job today. They will gain insight and discuss critical components of the ICH guidelines to help shape implementation, documents, and positions which will transform the industry. They also will gain understanding from previous sessions and raise questions as to how quality systems can be used as an enabler for implementation of QbD.

Concludes on page 5.

ISPE-PCC Offers New Credential; First Exam Available in July

Enhanced credibility, peer respect and recognition, greater opportunities for professional advancement, and a competitive edge when job seeking, are some of the benefits that pharmaceutical manufacturing professionals can gain with certification as a Certified Pharmaceutical Industry Professional℠ (CPIP℠) made available through the ISPE Professional Certification Commission (ISPE-PCC).

This new credentialing program offers the first competency-based international certification for pharmaceutical professionals and covers a range of competencies from drug product development through manufacturing. Candidates are assessed through demonstrated education, experience, and a rigorous examination.

The CPIP program is hailed by many in the industry as beneficial to team leaders, allowing the ability to impact greater quality and efficiency in their specific roles.

"Our industry benefits from employees certified in diverse knowledge, and with the ability to apply this knowledge across all segments of our industry," said Ali Afnan, PhD, of the United States Food and Drug Administration.

According to Donovan Wearne, CEO of SeerPharma Pty Ltd.: "SeerPharma provides expert QA and GxP consulting services to the pharmaceutical, biotechnology, and medical devices industries. In our business, our reputation and success absolutely depends on the technical knowledge, innovation, and responsiveness to change of our consulting team," said Wearne.

"The CPIP credential is therefore a perfect fit with our corporate vision and aspirations for our consultants and business," Wearne said. "We intend to strategically use the CPIP credential now and in the future to qualify our team and support their ongoing professional development."

The 2007 exams for the new certification for pharmaceutical manufacturing professionals will be available to the industry:

- 9 July - 4 August
- 5 November - 8 December

According to Jerry Roth, P.E., Director of Professional Certification, likely candidates for this credential are those who work in drug product development, drug product manufacturing operations, facilities/process engineering, facility and process equipment manufacturing and supply, project management, regulatory compliance/ QA/validation, and technical support.

FOYA Category Award Winners at INTERPHEX*2007*

Attendees to INTERPHEX2007, held 24-26 April at the Jacob Javits Convention Center in New York city, had the opportunity to meet personally with representatives of the Facility of the Year Award category winners to discuss the success stories associated with these pharmaceutical manufacturing facilities.

Category winners included:

- Cook Pharmica, selected as winner of the Facility of the Year Award for Facility Integration.
- Genentech, selected as winner of the Facility of the Year Award for Project Execution.
- Shanghai Roche Pharmaceuticals, selected as winner of the Facility of the Year Award for Project Execution Regional Excellence.
- Taiyo Pharmaceutical Industry, selected as winner of the Facility of the Year Award for Equipment Innovation.
- Vetter Pharma-Fertigung, selected as winner of the Facility of the Year Award for Process Innovation.

ISPE-PCC Offers New Credential...

Continued.

Eligibility applications should be submitted at least 60 days prior to exam dates. Those CPIP candidates deemed eligible by the PCC will be authorized to register for and take the exam.

The examination will be available in Thomson Prometric Professional Testing Centers located in major cities around the world. Eligible candidates will be able to make a reservation on-line at a local testing center close to work or home. To obtain a CPIP eligibility application (free download) or to purchase the CPIP Study Guide, visit www.ispe-pcc.org.

PQLI Approach to Quality by Design

Continued from page 3.

In addition, attendees can drill into areas of Design Space, Control Strategies and Critical versus Non-Critical and help develop the understanding of these issues; and relate these issues to the Q9 Quality Risk Management Lifecycle concepts of State of Control, Knowledge Management, and Quality Management being proposed in Q10.

Annual Meeting: Las Vegas, Nevada, November 2007

The next phase will continue at the 2007 ISPE Annual Meeting in Las Vegas, Nevada, USA where team representatives will convene on 5-6 November for the Design Qualification and Design Review to present PQLI updates and identify next steps.

The goal of these particular sessions is to further define areas where industry will be able to provide the technical framework for the implementation of QbD in regulatory submissions. Regulators from around the world view this critical "next phase" PQLI event as imperative to the success of the industry.

Copenhagen – April 2008

The next session will be held during the ISPE Conference on Innovation, 9-11 April 2008, in Copenhagen, Denmark. Subsequent sessions will follow as concepts are developed and input received worldwide, the conclusions from which will result in technical implementation documents produced by ISPE for industry's use in the worldwide market place.

ISPE encourages you to get involved and be a part of these critical meetings.

2007 ISPE Australasia Conference, 2-4 September

ISPE's Australasia Affiliate welcomes local, international, and TGA experts and professionals to join this September at the Sofitel Gold Coast, Queensland, for discussion on building a sustainable future for the pharmaceutical manufacturing industry. Conference highlights will include distinctive one and a half day streams covering facility lifecycle, manufacturing excellence and compliance, networking events, sponsorship opportunities, and table top exhibits.

For more information and to register, contact Bruce Moon at tel: +61-2-9987-4486, e-mail brmoon@tpg.com.au, or visit www.ispe.org/goldcoastconference2007.

PIC/S and ISPE Join for Workshop for First Time

ISPE and PIC/S will present an Interactive Workshop: "Systems Approach to Quality Risk Management" on 22-23 November 2007 at the Grand Copthorne Waterfront Hotel, Singapore. ISPE and the Pharmaceutical Inspection Cooperation Scheme (PIC/S) will co-host this interactive workshop opportunity for industry and regulatory leaders from up to 40 nations.

This is the first time that PIC/S has joined with another organization to co-host a training event and the first time that PIC/S inspectors and regulators will participate in training alongside industry personnel. We welcome you to join us for this foundational event.

Quality Risk Management has always been required, but now you can not only understand the latest developments, but also help to influence their actual implementation in your work place.

"Systems Approach to Quality Risk Management" will examine the ICH (International Conference on Harmonization) Quality Vision, provide updates on Q8, Q9, and Q10, and identify the opportunities and greater affects for industry as they are implemented synergistically.

This two-day, hands-on workshop is a unique opportunity to make a true difference by working side-by-side with regulators from around the world with the goal of creating a better working relationship between regulators and industry.

Through this interactive workshop, you will gain a deeper understanding of Quality by Design (along with each separate guidance; Q8, Q9, Q10), plus build on that knowledge through dialogues and concept sharing with PIC/S regulators for a better understanding of the opportunities associated with Quality by Design.

Speakers, Leaders and Presenters

Nils Eric Anderson, AstraZeneca
John Berridge, Senior Regulatory Consultant, Pfizer, Inc.
Sharon Bleach, Vice President Quality Strategy Development, GlaxoSmithKline
Ron Branning, Principal Consultant, Commissioning Agents
Bruce Davis, Global Capital Director, AstraZeneca; ISPE Chairman
Frans Dubois, VP Worldwide Quality, Global Biologics Supply Chain, LLC, a Johnson & Johnson company
Gordon Farquharson, Principal Consultant, Bovis Lend Lease Technology Division
Jacques Morenas, Assistant Director, AFSSAPS; PIC/S Chairman
Miguel Sanchez, Head of Inspection Department, Pharmaceutical Products and Cosmetics, French Health Products Safety Agency
Sion Wyn, Director, Conformity Ltd.
Other speakers TBA

"Delivering Today, Transforming Tomorrow"

If you have a choice to travel to just one place this year, make sure it's to ISPE's premier occasion – the 2007 ISPE Annual Meeting which will be held at Caesars Palace in Las Vegas, Nevada, USA, from 4-7 November. Ask anyone who's been in the past, and they will tell you how much they gained from attending the informative sessions taught by industry leaders.

This year, ISPE will deliver the knowledge and case studies you need to help you do your job better by offering more than 30 educational sessions at its 2007 Annual Meeting.

The theme this year, "Delivering Today, Transforming Tomorrow," will feature sessions focusing on delivering the latest in what's new, current, and relevant to pharmaceutical manufacturing industry professionals and will focus on fundamentals, best practices, transformation, and innovation. In addition, this meeting will allow professionals to interact with visionaries from the industry and be an active participant in shaping the future not only of your company, but the industry.

This year, the keynote speakers will raise the bar by providing highly informative topics on several timely and compelling topics, including the cost of quality, a perspective from the automotive industry, and an insider's view of a generic facility. Speakers include:

- Louis Schmukler, Senior Vice President, Pharmaceutical Operating Unit at Wyeth, will discuss the cost of quality considering the cost of proactive investments in technology in processes in order to maintain quality and prevent negative regulatory impact.

- Gary Convis, Chairman of Toyota Motor Manufacturing Kentucky and Executive Vice President of Toyota Motor Engineering and Manufacturing North America, will discuss the role of management in lean manufacturing, along with its commitment to a "customer first" philosophy.

- Uri Boneh, Director of Global Engineering for Teva Global Generic Resources, will speak about Teva's Jerusalem oral solid dosage plant recently completed and approved by the US Food and Drug Administration.

New to the ISPE Annual Meeting, will now be the choice of seven different tracks to help attendees choose the events that best meet their needs, or allow them to cross-train or gain insight in an area of interest outside their fields. These tracks include:

Have You Seen the New COP Web Portal?

Signing in and chatting with colleagues is easier than ever thanks to ISPE's new Web site portal for its Communities of Practice.

Whether your interest lies in packaging, investigational products, biotechnology, project management, or one of 10 other areas, ISPE's Communities of Practice are the place where you can interact with others in your same area of expertise.

By signing on to www.ISPE.org/COPs, just log in and sign up for the Community of Practice that interests you, and you can join in discussions, chats, polls, see news, events, biographies of fellow Members, and more.

"Delivering Today, Transforming Tomorrow"

Continued.

1. Regulatory/Compliance
2. Facilities and Engineering
3. Guides and Guidance Documents
4. Manufacturing
5. Innovation
6. Investigational Products
7. Project Management

At least 32 sessions will be offered, including regulatory workshops that provide ongoing interaction about Product Quality Lifecycle Implementation (PQLI), Risk MaPP, personalized medicine, nanotechnology, real world project management, disposables, containment, and three newly-released ISPE technical documents including Active Pharmaceutical Ingredients.

For a full list of speakers, please visit www.ISPE.org/AnnualMeeting Speakers.

Other Highlights

Facility of the Year Award: In addition to the educational offerings, the overall 2007 Facility of the Year Award winner will be announced for the first time in a ceremony. Category winners for 2007 were Cook Pharmica of Bloomington, Indiana; Genentech of Ocean City, California; Shanghai Roche Pharmaceuticals, Ltd., of Shanghai, China; Taiyo Pharmaceutical Industry Co., Ltd., of Takayama City, Japan; and Vetter Pharma-Fertigung GmbH & Co. KG, of Ravensburg, Germany.

Representatives from those companies will be on hand, and one will be named overall FOYA winner and awarded a stunning crystal trophy. For more information, visit www.facilityoftheyear.org.

The **ISPE Membership and Awards Ceremony** will be held 6 November, and reveal the winners of the ISPE Member of the Year, Company of the Year, Chapter or Affiliate of the Year, PE Article of the Year, International Student Poster Competition winner, among many others.

Workshops for the new **Certified Pharmaceutical Industry Professional (CPIP)** will be held 5-7 November. For more information, please visit www.ISPE.org/CPIP.

The **Communities of Practice** will feature roundtable events on 4 November. For more information on COPs, please visit www.ISPE.org/cops.

A **table top exhibition** will be held 4-6 November to showcase products and services from the industry. For information, contact Dave Hall at +1-813-960-2105 or dhall@ispe.org or visit www.ISPE.org/AnnualMeeting/exhibits.

For more information or to register for this premier meeting, please call + 1-813-960-2105 or visit www.ISPE.org/AnnualMeeting.

On-Line Exclusive Article
PHARMACEUTICAL ENGINEERING®
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International

The **Global Harmonization Task Force (GHTF)**[1] has issued guidance on the content of the Summary Technical Documentation (STED) for demonstrating conformity with the Essential Principles of Safety and Performance of Medical Devices. The STED is derived from the technical documentation held by the manufacturer and allows the manufacturer to demonstrate to Regulatory Authorities that the medical device complies with SG1/N041:2005 *Essential Principles of Safety and Performance of Medical Devices*.

The **PIC/S**[2] GMP Guide has been revised in order to comply with the format adopted by the European Union. The Guide has been divided into two parts, covering GMP principles for the manufacture of medicinal products and APIs used as starting materials, respectively. Annexes have been incorporated into a separate document and include the newly adopted Annex 19 on Reference and Retention Samples. The revised PIC/S GMP Guide entered into force on 5 April 2007.

Australia/New Zealand

No information of significance was added to the **Therapeutic Goods Administration (TGA)** Web site[3] in April/May 2007:

In May 2007, the **Australia New Zealand Therapeutic Goods Authority (ANZTPA)**[4] released on its Web site two documents for public consultation:

- In-Vitro Diagnostic Devices (IVD) Revision Draft of the proposed Australia New Zealand Therapeutic Products Regulatory Scheme (Medical Devices) Rule 2007.

As *In vitro* diagnostic medical devices (IVDs) fall with the definition of a medical device, it is proposed that they will be regulated as a subset of medical devices by ANZTPA. The regulatory framework will be in line with the principles of the Global Harmonization Task Force (GHTF) model.

- Consultation Paper: The Regulation of Human Cellular and Tissue Therapies (HCTs).

The purpose of this document is to provide an explanation of the proposed means by which human cell and tissue therapies (HCTs) will be regulated by the new Authority. It is intended that the matters detailed in this document will be included in Rules relating to "Biologicals" of which HCTs will be a part.

The closing date for submissions on the IVD Revision Draft of the Medical Devices Rule and the Consultation Paper on HCTs was 13 June 2007.

In May, the availability of the first Australia New Zealand Therapeutic Products Authority Project Newsletter was also announced. It is available on their Web site[5] and contains a comprehensive list of current documents from the consultation program on the proposed regulatory framework (of ANZTPA).

Brazil

Brazil's Regulatory Authority, **Anvisa**[6], has implemented a new procedure for drug product variations to manufacturing sites, including site of primary and secondary packaging with the intention of reducing regulatory delays in implementing the change. Subject to conditions that there is no change to formulation, process or primary packaging, a change to a manufacturing site or primary packaging site may be implemented after 45 days if no feedback from Anvisa is received. However, Anvisa may still request additional information after the 45-day period. A change to a secondary packaging site would not require any feedback before implementation.

Europe

Reported on the Web site for the **European Medicines Agency (EMEA)**[7] in April/May 2007 was the launch of a new database, called EudraGMP, designed to facilitate the exchange of information on good manufacturing practice (GMP) compliance within the EU medicines network. It contains information on all manufacturing and importation authorizations issued nationally within the network, i.e., the EU Member States and Iceland, Liechtenstein, and Norway. It will also contain information on GMP certificates, which the competent authorities issue following each GMP inspection conducted either within the network or in third world countries. EMEA expect that this database will enhance the ability of EU authorities to supervise the quality of medicines.

The **European Commission DG Enterprise**[8] announces that, in preparation for a Directive on GMP for certain excipients, excipient manufacturers and manufacturers/importers of medicinal products for human use are invited to contribute to an on-line consultation on the possible impact of different policy options. Excipient distributors may also participate. With the questionnaires for excipient manufacturers and excipient users, drafts for certain excipients are published. The excipient categories to be controlled include those prepared from TSE relevant species (excluding lactose), from human or animal material with viral contamination potential, those sold as sterile and used without further sterilization and those with significant endotoxin potential intended for parenteral use. Specifically glycerol and polyethylene glycol are also included. Comments are requested by 30 July 2007.

The **Committee for Medicinal Products for Human Use (CHMP)**[9] have published their monthly reports from the March and April Plenary meetings held 19-22 March and 23-26 April 2007, respectively. Two relevant guidelines have been prepared by the Quality Working Party:

- Corrected Guideline on stability testing: stability testing of existing active substances and related finished products (CHMP/CVMP/QWP/105431/2007).

- Questions and Answers on residual solvents (EMEA/140443/2007).

The **Committee on Herbal Medicinal Products (HMPC)** have published their monthly meeting report[10] for the

meeting held 7-8 March 2007.

In May 2007, the **(Committee for Veterinary Medicinal Products) CVMP)**[9] published the following:

- Guideline on Environmental Impact Assessment for Veterinary Medicinal Products (EMEA/CVMP/ERA/418282/2005). This guideline is provided in support of VICH Guidelines GL6 and GL38 and will come into effect in November 2007. An overview of the comments received on the draft guideline is also available.

- A concept paper on the revision of the Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products (EMEA/CVMP/QWP/103377/2007) has been published. CVMP wish to address apparent inconsistencies with VICH Stability Guideline GL3 such as in storage conditions and selection of batches for study, which are not scientifically justified. Deadline for any comments is July 2007.

The **European Directorate for the Quality of Medicines and Healthcare (EDQM)**[11] have announced the availability of a new set of procedures and guidelines for the batch release (OCABR or OBPR) of immunological veterinary medicinal products (IVMPs) on their Web site. All current procedures and guidelines for OCABR/OBPR can be downloaded directly from this site.

The **Heads of Agencies**[12] Web site has been updated with reports from the CMD(h) meetings held 19-21 February and 19-21 March 2007.

Ireland

The **Irish Medicines Board (IMB)**[13] has advised on their Web site that national laws implementing the European Directive 2004/24/EC: Traditional Herbal Medicinal Products should come into force in June 2007. The regulations provide exemptions for traditional herbal medicinal products that were on the Irish market on the coming into force of the regulations. In order to ensure that relevant products hold either a marketing authorization or a certificate of traditional-use registration by the required date in 2011, IMB advise that the new regulations include a provision to establish dates by which applications for traditional-use registration must be submitted.

Malta

The Maltese Health Division[14] has announced the successful end of the derogation period. All Marketing Authorizations (MA) for medicinal products with a Provisional Marketing Authorization (PMA) for which the applicant has submitted the requested documentation have been issued, or are in the final stages. Marketing authorization holders who had not replied to letters sent by the Medicines Authority by end of March 2007 are advised that their authorizations are now withdrawn.

United Kingdom

MHRA[15] have issued guidance on the Qualified Person (QP) declaration on the GMP status of the API Manufacturer. QP declarations concerning the GMP status of API and finished product manufacturers and batch release sites are required in accordance with EU directive 2004/27/EC. The guidance on content and presentation of the declaration may be found in *Frequently Asked Questions* in the Variations section of their Web site but can also be extended to requirements for new Marketing Authorizations, to variations to change other sites and to renewals.

Israel

The **Israeli Ministry of Health**[6] has issued a guideline for the child-resistant packaging of bulk oral tablets, powders and liquids marketed for human use in the community. The requirement does not apply to blister packaged tablets, individually wrapped powders, liquid drops or inhaler dosage forms, nor to packs intended for hospital or retirement home use. The requirements would appear to be broadly in line with those currently applied internationally and will come into effect on 1 July 2007 for new products with a 24 month grace period for those already on the Israeli market.

Korea

The **Korea Food and Drug Administration (KDFA)**[16] has announced that a further 22 APIs will be subject to Drug Masterfile (DMF) requirements from the beginning of 2008. API manufacturers are advised to submit DMFs in order to finalize the regulatory process in time for the change.

References

1. ICH - http://www.ich.org/
2. PIC/S - http://www.picscheme.org/index.php
3. TGA - http://www.tga.gov.au/media/index.htm
4. ANZTPA - http://www.anztpa.org/index.htm
5. ANZTPA - http://www.anztpa.org/newsletters/index.htm
6. RAJ Pharma, Vol. 18, No. 5, May 2007.
7. EMEA - http://www.emea.eu.int/pdfs/general/direct/pr/19364007en.pdf
8. EC - http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/new.htm
9. EMEA - http://www.emea.eu.int/PressOffice/presshome.htm
10. EMEA - http://www.emea.eu.int/pdfs/human/hmpc/13821707en.pdf
11. EDQM - http://www.pheur.org/
12. HOA - http://heads.medagencies.org/
13. IMB - http://www.imb.ie/
14. MA - http://www.medicinesauthority.gov.mt/news&events.htm
15. MHRA - http://www.mhra.gov.uk/home/
16. RAJ Pharma, Vol. 18, No. 4, April 2007.

This information was provided by Peter Hagger, Pharmaceutical Research Associates (UK).