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PAT and QbD – Effects on 21st Century Laboratories in Development and Manufacturing

by Dr. Alex Brindle and Dr. Line Lundsberg-Nielsen

This article discusses the influence of PAT and QbD on Quality Control Laboratories and provides examples relating to changes occurring within laboratories connected to manufacturing and development.

There is little doubt that Process Analytical Technology (PAT)[1] and Quality by Design (QbD)[2] are starting to effect the way that the life science industry operates.[3] PAT and QbD will significantly influence the development process, submissions, manufacturing, and quality systems if implemented to their full capability.

Indicating that 'PAT and QbD will significantly affect the life science industry' is very broad and, indeed, vague at best. This article will attempt to clarify how it will effect ways of working in the laboratories and how this impacts what people do, what skills are needed, what technology will arrive, and ultimately what sort of team and facility laboratory staff will work in.

The laboratories most affected by PAT and QbD will be those used for product and process development, those supporting manufacturing, and those releasing products (QC laboratories). This is not to say that other laboratories will not take advantage of the useful tools found within PAT and QbD; it is simply that PAT and QbD is a framework designed to improve the life science industries ability to develop and manufacture drugs.

Therefore, this article shall specifically explore and provide examples relating to the changes occurring within laboratories connected to manufacturing (namely the QC laboratory and process support laboratory) and development (chemical, formulation, analytical, and process development).

Manufacturing Based on PAT and QbD – Impact on Related Laboratories

In order to understand how manufacturing support laboratories will be affected by PAT and QbD, it is best to first comprehend what PAT and QbD will entail for manufacturing.

The philosophy of PAT and QbD starts with putting the patient first. Working backward from this we determine how drugs should be manufactured and the process controlled to guarantee this - Figure 1. This has been formalized into parameters that are critical to the patient (Critical Quality Attributes or CQA). The CQAs arise from manufacturing processes or steps that can be described as Critical Process Parameters (CPP) and many of these CPPs are highly dependant on one another or correlated. In simpler terms, the CQAs describe what a manufacturing operation needs to do in order produce the drug with the right level of quality to meet the patient's needs, and the CPPs describe which parameters the manufacturing operation need to control to ensure this final quality.

Although this may sound like common sense, the role of PAT and QbD is to ensure that processes and products are understood in a scientific and engineering sense. This will create a closer match between what is required by the patient (and how QC guarantees this) and what is actually manufactured. Currently, this is not the situation in the life science industry. This discrepancy between the quality of manu-

Figure 1. The patient's needs should dictate to manufacturing and development what is required.

Figure 2. Sample preparation.

facturing output and what the patient receives is best demonstrated by using sigma levels, which is a statistical measure of how much the quality of the process varies from faultlessness.

Most life science manufacturing facilities have a manufacturing output of between two and three sigma[4] (errors of between 66,800 and 308,000 per million, i.e., an error level of 0.7% to 31%). Imagine if that has been the case in other industries such as aviation, automotive or even food. However, there is little doubt that the regulators are extremely good in ensuring that the industry implements a system (traditional end product testing by quality control) that is efficient in ensuring that high quality medicines reach the patient (6 sigma). This is achieved by scrapping or reworking intermediate or final product at great expense. One can summarize the life science industry as one that has poor manufacturing output allied to extremely efficient QC. The result being safe medicines, lots of waste, high cost of quality, and thus, higher cost of medicines.

It would be a logical step to either build in the quality from the start of the product lifecycle or to improve the quality of product (increase it to above 3 sigma). Moving away from end product testing to control strategies that adjust the manufacturing processes in real-time to assure the CPP is kept within the Design Space (Figure 7) would result in avoiding scrap, waste, and re-work. Thus, one of the major goals of QbD supported by PAT is to achieve the same quality of manufacturing (visionary goal of 6 sigma) the patient requires; this will avoid huge waste and make manufacturing more efficient.

Having a vision such as this is great and sounds like common sense, but it is hard to comprehend how an analyst working in QC or a process scientist can support this during their normal work. Therefore, this article will use concise examples to demonstrate in detail how using PAT and QbD tools can really help contribute to the overall goal and have a positive impact on the bottom line finances of the business.

The first of these is the humble identity test. It is a requirement from the regulatory authorities that raw materials be tested before manufacturing to ensure that the correct material is being used. Until recently, this identity test has been predominantly performed using either Ultra-Violet (UV) or Infra-Red (IR) spectroscopy. Such tests required the following steps: 1. bulk sample from manufacturing, 2. transport to laboratory, 3. sub-sample in laboratory, 4. sample preparation, and 5. analysis.

To scientists and engineers working in the life science industry where complex work flows are common place, this may not appear to have a lot of steps, but to anyone from other industries used to more rapid feedback of results, this would seem a torturous way to go about it. It also places the operator at increased risk because sampling can be a highly manual process and modern API is becoming increasingly toxic in nature.

A well-documented solution to this problem is the use of Near Infra-Red (NIR) spectroscopy. This technique first came to prominence in the food and allied industries as a practical way to identify solids such as grains and their quality. The key to NIR being so useful in this situation is the fact that it can be used in reflective mode to good accuracy. Therefore, it can identify solids without the need for sample preparation (Figure 2), unlike UV or IR, which require complex sample preparation. In fact, NIR being a spectroscopic technique

Sigma Level (1)	Yield 1 Step %	Yield 10 Step %	Yield 100 Step %	Yield 1000 Step %	C_p before Sorting	System Downtime per Year (days)	COPQ (2) % of Sales	COPQ (3) % of Sales	
1	30	0	0	0	0.33	255	> 40	> 70	Non-competitive
2	69	0.02	0	0	0.67	112	30-40	> 40	Non-competitive
3	93	50	0.1	0	1.00	24	20-30	25-40	Average Pharma (4) (Sigma = 5 after sorting)
4	99.4	94.0	54	0.20	1.33	2.27	15-20	15-25	Average Industry
5	99.98	99.8	97.7	79	1.67	0.085	10-15	5-15	
6	100	99.997	99.966	99.66	2.00	0.0012	< 10	< 1	World Class Pharma
7	100	100	100	99.998	2.33	0.000069	?	?	
8	100	100	100	100	2.67	0	?	?	World Class Industry

Table A. Sigma levels and associated Cost Of Poor Quality (COPQ).

means that if the container of the API can let the correct wavelength of light through it (such as a clear polyethylene bag), there is even no need to take the API out of the primary container. The identity test can be performed in-situ using a NIR 'gun' (Figure 3) with no sampling or sample preparation. Add to this the fact that a user interface can be built up allowing operators, such as warehouse operators not skilled in analytical science, to use it . This results in an extremely cost-effective, quick (analysis times reduced from hours to seconds), and reliable technique. There are many examples where thousands of man hours have been saved annually and lead time radically reduced from the introduction of just one NIR instrument. Other less quantifiable but significant benefits include greatly improved operator safety.

One can argue whether such a simple application is PAT or not since it is debatable that there is an increase in process understanding. However, what this analysis does is to assure the starting materials are correct. However, scientists are using NIR for much more than this and have created add-ons to the identity test which can collect important information on the raw material such as water content, particle size, and morphology, which when identified as raw material CQAs are deemed critical for the in-process material or the final product. This data can then predict how subsequent processing can take account of this information.

However, the effort and skill needed to build and maintain PAT tools should not be underestimated. New skills will need to be acquired and strengthened to ensure that PAT tools such as NIR are implemented and fully supported.

This example is interesting and perhaps shows that in the case of the identity test, testing will not be performed by analytical scientists, but by the plant operators themselves.

More fascinating perhaps is the question: What if this way of thinking is applied to everything related to how laboratories support manufacturing, quality assurance, and product release? The typical QC testing that needs to be performed would be significantly different if PAT tools were applied.

It is apparent from Table B that much of the testing can be moved out of the laboratory and into the production environment. Additionally, these technologies can be implemented for more than end product testing; they also can provide relevant

Specification	Traditional Test	21st Century Testing
Dissolution	Dissolution Test	NIR
Disintegration	Physical Test	NIR
Assay	HPLC	NIR/other
Hardness	Physical Test	NIR
Content Uniformity	HPLC	NIR
Impurity	HPLC	On-line HPLC/HPLC
Stability	Testing Program	NIR/Accelerated Testing Program
Appearance	Appearance	Colorimetry/NIR
Identification	IR/UV	NIR
Water	Karl-Fischer	NIR/NMR/Others

Table B. Traditional vs. 21st century testing.

Figure 3. NIR analysis for identity.

in-process testing with the main purpose of controlling the process, i.e., measuring and adjusting the relevant process parameters as well as releasing a specification at the same time. There are huge benefits associated with using PAT technology and associated ways of working, including: rapid feedback for process control, reduced analytical lead times, less effort, more quality information which ultimately leads to reduced scrap, reduced production lead time, appropriate quality, increased process understanding, and cost savings.

In secondary manufacturing for example, assay is an important CQA and the assay testing can be performed by using NIR (rather than time consuming laboratory High Performance Liquid Chromatography or HPLC). The analysis can be performed after tablet compression to avoid coating bad tablets as well as to make a real-time release possible - *Figure 4*.

If all of this currently available knowledge and technology is applied, will it mean the end of the QC laboratory? Probably not, but it will radically change it. Most QC tests can be moved to the production area by using the alternative technologies such as those suggested in Table B. These tests could be in-line instruments supported by specialists or indeed flexible and mobile at-line units which could be moved around the factory floor. There might be certain laboratory techniques which may not be cost-effective to move to the plant floor, such as impurity testing, until sensitive non-destructive on-line technologies have been developed that can really compete with the conventional laboratory-based technologies.

Figure 4. Tablet assay by NIR.

Development Based on PAT and QbD – Impact on Related Laboratories

If the impact of PAT and QbD on laboratories supporting manufacturing is significant, the effect on development laboratories is potentially huge. Not only will this affect what the development laboratories do and how they are designed, the development laboratory will have a large influence on manufacturing, quality systems established, and how medicines are submitted to the authorities and later released.

Developing a drug in the life science industry is a complex business. A typical, successful pharmaceutical company would need several laboratory functions to ensure that a drug reaches the market, including:

- Chemical Development
- Formulation Development
- Process Development
- Analytical Development
- Specialist Support (NMR, XRD, etc.)

The challenge for these laboratories will be to implement new technologies, acquire new professional skills, change ways of working for both how a process and a product in the future is developed, as well as who will do it.

Changing working practices does require the industry to overcome a significant hurdle. Whether this is overcome quickly or over a long period of time depends on the frankness, readiness, and how risk-driven the management is to make and implement changes to get high quality products faster to the market and at a lower cost. As this change management process will affect many parts of the company, the management needs to agree on a corporate strategy defining the level of QbD and PAT that will be implemented. A new set of strategies and working structures for the laboratories, plant operations, quality, and regulatory affairs have to be established considering how API, formulations, and processes are designed within this new framework. This should include how CQAs are identified (close cooperation with clinical development groups; yet another new working partner), their related CPPs identified, the design space established, and finally, how the CPPs are controlled and maintained within the Design Space (control strategy). Raw material needs, their characterization, and their CQAs should be identified to assure the right quality of final product. Similarly, in-process material CQAs need to be identified and a control strategy established. Process scale-up and process outsourcing are other activities that need to be redefined. Finally, how the API or the drug product will be submitted (submission strategy) and later released (release strategy) has to be decided.

Laboratories will have to take a leading role in this new way of working. PAT, QbD, and possibly also LEAN[5] and Six Sigma tools need to be available and maintained making the laboratories a resource for developing processes from API to final packaging. The new way of working and the new skills required will require the labs to cooperate in establishing this toolbox. A lot of the tools are process independent (chemometrics or NIR spectroscopy is the same discipline whether a chemical reaction or a tablet compression process is considered) and new organizations may well be introduced in the future.

Examples of the new set of tools that laboratories will have to implement are: risk assessment tools, knowledge management tools, statistics and chemometrics (e.g., process capability, DoE, multivariate methods), Six Sigma tools[4] (e.g., QFD, DMIAC, DMADV), LEAN tools (e.g., 5S, Value Stream Mapping (VSM), inventory and lead-time reduction), PAT instruments (univariate sensors (pH, temperature, etc.), and multivariate analyzers (NIR, Raman, FBRM, etc.)).

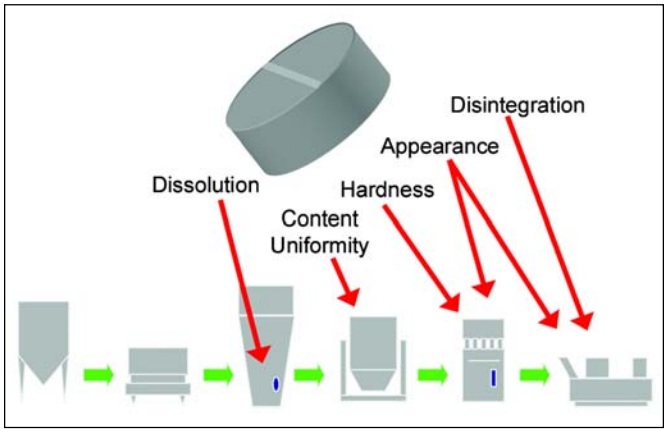

Figure 5. CQAs such as appearance, hardness, and content uniformity, and where CPP is critical in the process.

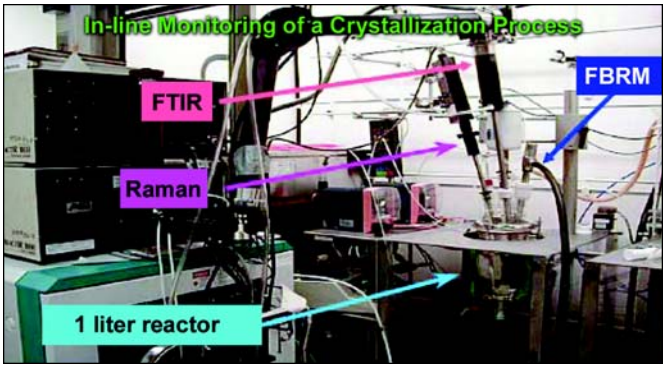

Figure 6. Raman, FBRM, and IR for following an API reaction in the laboratory.

Currently, development laboratories work in project teams, but are far from integrated. Analysts work in the analytical laboratory, while formulators work in the formulation laboratory. Teams are set up with classical hierarchy, the process development scientists report to their manager who reports to the overall project manager. Scientists and engineers sitting around a table discussing the best way to combine the science of formulation, analysis, and process development is not a common occurrence.

Working within a PAT and QbD framework will force a change in this status quo. The level of understanding needed to file a submission and full scale manufacturing based on a PAT and QbD control strategy is high. This makes it impossible to reach this level of understanding working in isolation.

In the new way of working, product or project specific cross organizational teams, including scientists and engineers from the different development laboratories, will be established. Processes can no longer be separated in primary and secondary processes, but a holistic approach has to be applied. The chemist working in primary development also will have to consider the CQAs of the final drug product and to understand how the variability in the primary processes impact the final product. Therefore, a close cooperation between the chemist and pharmacists from the labs are needed and they will have to learn from each other.

Taking a typical secondary manufacturing process as an example demonstrates that the first thing to consider is the patient. So, the product CQAs need to be defined as an initial step - *Figure 5*. The CPPs of the manufacturing process can then be identified and understood after certain systematic development work (e.g., application of DoE).

The definition of these CPPs is an iterative process and will result in a set of controls to be implemented in manufacturing. These initial activities are all carried out during the development phases with the major workload in Phases 2 and 3. Chemists and formulators should use 'smart' and fast experimental design tools such as DoE to get the maximum amount of information from their development experiments. In order to understand more about the product and processing, formulation scientists will need to collect much more data to understand how their experiments are performing. Different analytical and other data recording tools should be used, bringing the analytical laboratory into the formulation area to provide real or near real-time information using on-line or at-line techniques.

Another example of this might be in the development of a chemical API process. Following a reaction in real-time – like watching a movie, is now possible. Traditionally, samples had to be taken on a regular basis, sent to the laboratory, and analyzed using time and solvent consuming techniques such as HPLC analysis. Now a reaction can be followed applying a spectroscopic technique such as IR, NIR, UV, or Raman - *Figure 6*. Most often the reaction process can be followed directly without prior modeling work making it quick to set up in many different situations. The benefit and result is that the bench chemist can quickly understand what changes are occurring and can challenge the process and investigate it systematically and quickly. For example, the same bench chemist could apply DoE and thereby collect much more data than was possible under classical empirical design. By applying this methodology the speed of process development is increased; simultaneously process knowledge is improved.

This additional data (and the related understanding) can be used to help coordinate with the processing laboratories as they begin to develop the manufacturing process and begin scale up for the live manufacturing plant. The extra data collected will allow for a real understanding of what processing occurs and how multiple parameters correlate and can be simultaneously adjusted to give good product quality. In conventional development work, parameters are assumed and treated as individual non-correlating parameters which we in advance know is wrong! This extra data is the foundation for establishing the design space, i.e., the confined space where in the various process parameters can operate under normal operation resulting in a final product with the right quality. A reference to the development report and submission of the design space as well as the how to ensure the process parameters maintained within the design space (control strategy) is needed in the regulatory submission to demonstrate process understanding and to gain regulatory relief from the authorities.

This regulatory relief will have a major impact on the type

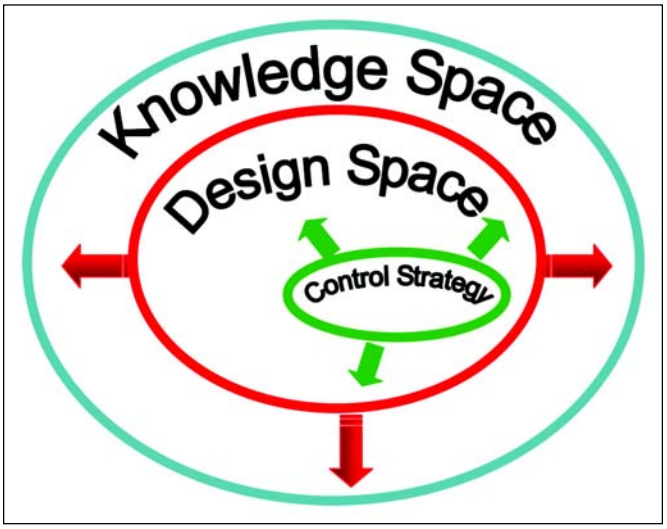

Figure 7. Knowledge and design space.

of data submitted to the authorities. The submission process will be radically streamlined and requires data and scientific rich information, rather than the reams of paper based on systems and validation with little fundamental understanding. Another big advantage of development collecting the extra data to really understand the product and processing is the fact that the regulatory authorities will allow process changes and continuous improvement within the Design Space in full scale manufacturing. This can be done under the companies own modern quality system (ICH Q10[6] being finalized by regulatory authorities) without prior approval.

So what does all this change mean for the development laboratories? In summary:

Chemical and formulation development laboratories will:

- Work cross organizationally as the final product CQA will be dependent on controlling CPPs of the API process.
- Increase process understanding when designing a new product.
- Consider how to manufacture at full scale and search for data and information that will help improve scale-up.

Analytical development laboratories will:

- Develop real-time analytical methods that will be cost-efficient, give increased process understanding in development and be easily transferable to the manufacturing environment.

Process development will:

- Develop processes that are relevant for full scale manufacturing (use of DoE, Evolutionary Operations (EVOP), and potentially radical process design such as continuous processing).
- Bring manufacturing process technology into the laboratory so development more closely replicates a real manufacturing environment.
- Initiate control models (feed forward and feedback loops).

Pulling it Together – What Does PAT and QbD Mean for Laboratories and the People Who Work in Them?

If a life science facility were to be designed from scratch, taking into account how PAT and QbD will be used to redefine how products are developed and manufactured, it would look different than what we see today.

The traditional compartmentalized thinking of separating analysts from formulators from chemists from process scientists would disappear out of necessity. The formulators, chemists, and process scientists would need so much more understanding that sending samples off to a different department for analysis would not work. The tools needed to give

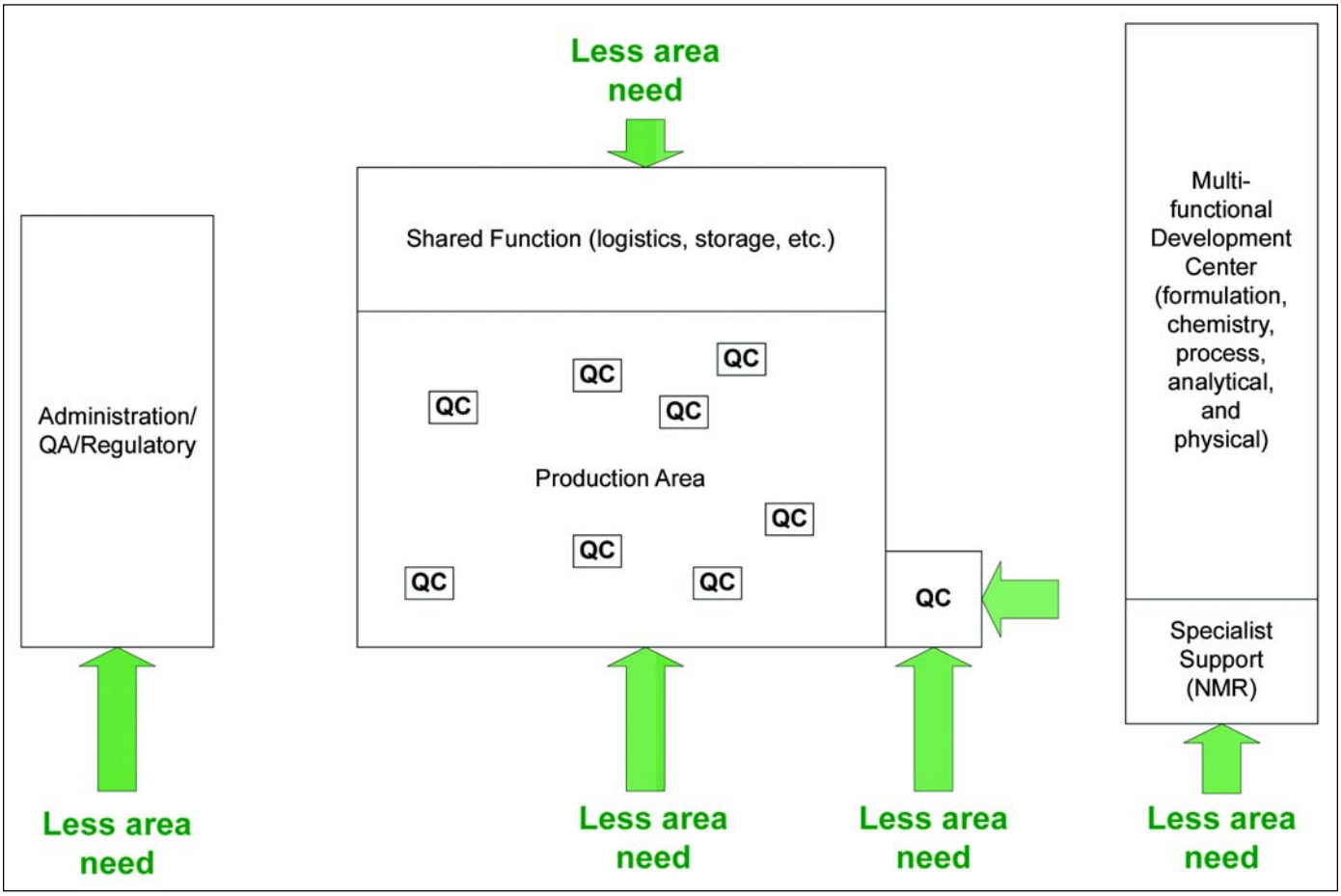

Figure 8. A future facility layout; PAT and QbD reduces area need and redefines the laboratory.

them the product and process understanding would need to be there in real-time. The 'real' process needs to be brought back into the development phases as much as realistically possible. Chemists and formulators developing things on a laboratory scale with the laboratory equipment easily available and then expecting this to be scaled-up into real manufacturing is a very strange state of affairs. The sensible approach is to consider how the product will be made on a large scale and then adapt the development laboratory to take account of this. This will lead to a seamless integration between chemical and formulation development, process development, and full-scale manufacturing.

The QC laboratory will have to change significantly to support manufacturing influenced by PAT and QbD. The current situation of mass sampling to take samples away to a separate QC area will not be suitable for an optimized, robust, and flexible manufacturing process hoping to achieve 6 sigma. QC needs to be incorporated into the manufacturing control strategy to give real-time feedback and control. The rest of the QC laboratory not brought into manufacturing will cover a new role of scientific ownership for tests in production as well as those tests that are not cost-effective to bring into manufacturing. Great skill, effort, and teamwork will be required by QC personnel to take on this role.

Technology and tools also will play a crucial role. In the development laboratory, new ways of generating, capturing, and reviewing data will have to be commonplace. The use of rapid analyzers which provide a rich amount of information in real-time will replace a good proportion of off-line analyzers dependent on the time consuming work flow of sample, prepare, analyze. These types of analyzers will be essential in manufacturing where production speeds require them. They also will be needed in development to provide more information and to allow realistic methods to be developed for manufacturing. The planning, collection, and analysis of data will move into tools such as DoE, automation systems, and multivariate analysis to make the complex simple.

Finally, what of the scientists and engineers working in the laboratories themselves? This article has already alluded to the need for increased skills in specialist areas such as data analysis and modern analytical techniques. This is allied to the fact that the team will need a more rounded approach and stop working in isolation. The development of hardcore specialists and skilled generalists is undoubtedly going to happen. These generalists will have to know much more about science than before – a generalist chemist will have to know his or her chemistry, but also how to integrate this with process development and analytical development effectively. The emphasis on what specialists will be required to know will shift also – the amount of analysts who have specialized in bench HPLC will simply outstrip demand in the future. The requirements will be specialists in NIR and other at-line and in-line techniques which provide rapid feedback.

Perhaps the most interesting aspect of this for the scientists and engineers is the work itself. A lot of the 'grunt' work will disappear. Routine work will be replaced with challenging assignments. Paperwork associated with submissions will alter radically to allow scientific rich submissions rather than the 'paperwork quantity' driven submissions of today. Continuous improvement will facilitate the implementation of new ideas that previously needed to be parked in the 'not-possible department.' Scientists and engineers will talk about exactly that – how to better understand the processes and the products rather than get bogged down in the operational systems of development and manufacturing. In summary, it is time for the scientists and engineers to get on with what they are good at – exciting science and engineering.

Specification	Traditional Test	21st Century Testing
Dissolution	Dissolution Test	NIR
Disintegration	Physical Test	NIR
Assay	HPLC	NIR/other
Hardness	Physical Test	NIR
Content Uniformity	HPLC	NIR
Impurity	HPLC	On-line HPLC/HPLC
Stability	Testing Program	NIR/Accelerated Testing Program
Appearance	Appearance	Colorimetry/NIR
Identification	IR/UV	NIR
Water	Karl-Fischer	NIR/NMR/Others

Table B. Traditional vs. 21st century testing.

Acronyms

5S	Sort, Set In Order, Shine, Standardize, Sustain
API	Active Pharmaceutical Ingredient
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
DMADV	Define, Measure, Analyze, Design, Verify
DMIAC	Define, Measure, Improve, Analyze, Control
DoE	Design of Experiments
EVOP	Evolutionary Operations
FBRM	Focused Beam Reflectance Measurement
IR	Infra-Red
LEAN	the short definition of LEAN is 'lean principles, practices, and tools create precise customer value – goods and services with higher quality and fewer defects – with less human effort, less space, less capital, and less time than the traditional system of mass production.'
NIR	Near Infra-Red
NMR	Nuclear Magnetic Resonance
PAT	Process Analytical Technology
QbD	Quality by Design
QFD	Quality Function Deployment
UV	Ultra-Violet
VSM	Value Stream Mapping
XRD	X-Ray Diffraction

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About the Authors

Dr. Alex Brindle holds a BSc in chemistry, a MSc in analytical science, and a PhD in process engineering. He has 10 years of experience at the interface between analytical science, materials science, and processing to characterize processes and products. Dr. Brindle has experience in petrochemicals, consumer healthcare, and life sciences (in both development and manufacturing), and has worked with process understanding and PAT at AstraZeneca and GlaxoSmithKline, before joining NNE Pharmaplan. Since joining NNE Pharmaplan, he has been involved in projects for PAT, facility design, and investment analysis. He can be contacted by telephone at: +45-30755734 or by e-mail at: axbr@nnepharmaplan.com.

NNE Pharmaplan, Vandtarnsvej 108-110, DK-2860 Soeborg, Denmark.

Dr. Line Lundsberg-Nielsen holds a BSc in mathematics, a MSc in physics and a PhD in NIR spectroscopy. She has 12 years of experience within the pharmaceutical industry (QC lab management, QA, API production, as well as secondary manufacturing). She has theoretical as well as practical experience in Process Analytical Technology (PAT) and Quality by Design (QbD) from working at Novo Nordisk and Lundbeck, before joining NNE Pharmaplan. Since joining NNE Pharmaplan, she has been involved in projects for process review, PAT, and QbD. Dr. Lundsberg-Nielsen is the Membership Secretary of the ASTM Committee E55 on Manufacture of Pharmaceutical Products, member of the ISPE PAT Steering Committee, Chairs the ISPE UK/Irl PAT Community of Practice, and member of the ISPE PQLI Control Strategy team. She can be contacted by telephone at: +44-1932596955 or by e-mail at: llun@ nnepharmaplan.com.

NNE Pharmaplan, East Lodge, Knipp Hill, Cobham Surrey KT11 2PE, United Kingdom.

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Energy Savings in Pharmaceutical Facilities: A Risk-Based Approach

by Dave Goswami, PE and Mark Butler

This article provides an in-depth look at the general risk profiles in the pharmaceutical industry and evaluates the place of energy saving features within the context of risk management.

Introduction

Recent escalations in energy prices have prompted pharmaceutical companies to review their operating costs. When energy costs were lower, energy saving features had a much longer return on investments and accordingly, there was less incentive to incorporate them. The risk of compromising the reliability and integrity of the system has been cited to avoid the use of many energy saving schemes, energy saving devices, and new and innovative energy-efficient design. Even five to 10 years ago, many companies and engineers did not consider using variable speed drives even though they had excellent financial paybacks, due to problems in the field.[3] There is a renewed effort in the industry to reduce energy usage, partly because of extremely high energy cost and partly because of the desire to be more environmentally friendly with sustainable design and green buildings. It is a perfect time to revisit some of the so-called "sacred" and "traditional" criteria and requirements that have limited use of energy efficient designs in the past.

With the above background, it is high time to examine whether the industry has been too risk-averse and reluctant to follow basic principles of energy management and sustainable design. Practices such as green design, carbon mapping, sustainable design, etc. are being discussed everywhere, and are becoming more mainstream.[4] In many countries, there are stringent Green House Gas (GHG) emission regulations and there is no doubt that very soon all industries will be faced with increasing pressure on sustainability. The pharmaceutical industry has to develop a balanced approach to energy savings and sustainable design versus risk mitigation. We must start the process now.

Risk Profiles of the Pharmaceutical Industry

The pharmaceutical industry, as a whole, is a very conservative group. The pressure of conforming to stated and sometimes unstated requirements of government regulating agencies like the US FDA, European Union, and regulators of other countries have created an atmosphere of minimal innovation and more of "doing it the same way" attitude. Trying out new methods, even if it achieves the same result, is often considered too risky. This article will review the various elements of risks that are generally encountered by the pharmaceutical industry.

Drug Product Safety

The educated consumer expects that all drug products are manufactured in the safest way that is humanly possible. The stakes are very high. So, it is understandable that the FDA and European agencies are extremely concerned about the process, the environment, and the SOP related to manufacturing medicines. Predictably, the pharmaceutical industry has taken a very conservative stance so that the risk of product contamination or product failure is perceived as practically eliminated.

Personnel Safety

In addition to ensuring the safety of drug products, another area of risk for the pharmaceutical companies is the human exposure to certain chemicals during the manufacturing process. Most of the current drug products are made from manipulations and handling of various combinations of chemicals. A number of formulations require the use of solvents. Also, during the research and development stages of drug development, a variety of chemicals and agents are used that could pose threats to personnel if exposed. Biological agents with

The pharmaceutical industry, like many other industries, is feeling the pressure to reduce the cost of goods and lately has turned its attention to energy efficiency to help meet their goals.[1] However, unlike the other industries, the pharmaceutical industry is heavily regulated and modifications and improvements should undergo a risk assessment prior to implementation. The concept of "risked-based" analysis is not new to the industry, and as a result, decisions on energy saving features can not simply be a financial decision. The decision also must ensure that the systems, equipment, or design is reliable and will not compromise the very essence of drug efficacy and drug safety.

The intent of this article is to give an in-depth look into the general risk profiles of the pharmaceutical industry, and assess the place of energy saving features within the context of risk management. A quantitative methodology has been proposed to consider all the elements affecting the use of energy saving features, including the risk element. This methodology can be a useful tool in making decisions on energy saving opportunities and sustainable design, as more and more pressures from society is put on all industries. Detail ed discussions on various energy opportunities have been purposely avoided as there are plenty of articles and seminars which have addressed them. However, certain applications and opportunities of energy management have been discussed only to exemplify base issues on risk versus applications.

various degrees of biohazard levels (BL-1 thru BL-4) are routinely used in the research. Recently, there has been tremendous increase in the use of "potent" and "cyto-toxic" compounds. Most of these chemicals are highly toxic and must be contained. Sensitizing compounds such as penicillin and cephalosporin have such adverse effects that they are typically manufactured in dedicated facilities. Government agencies such as OSHA have guidelines for the exposure limits and "right to know" laws.

Environmental Implications

These chemicals also pose threats to the environment. Release of these chemicals in the air or in wastes (solids and liquids) must be minimized. In the United States, the Environmental Protection Agency (EPA) provides guidelines and regulations for any release of such pollutants to the atmosphere. The pharmaceutical companies have the added responsibility to be "environmentally friendly."

Reliability

In terms of risk management, the concern of reliability in the manufacturing or R&D facilities is an important issue which often comes into play in the pharmaceutical industry. Certain design elements are deemed too risky as it may compromise reliability of the plants. Some of the issues are real, for example, ensuring almost "zero-failure" for long term pre-clinical studies. At the same time, criticality of some of the issues are sometimes over-emphasized. An example would be sizing the cooling and heating systems for manufacturing facilities to the maximum capacity required for extreme ambient conditions so that manufacturing operation is not interrupted at any time. In most cases, the unit operations of a batch manufacturing process can be interrupted with a little planning. This practice of sizing for the worst condition unduly increases the sizes of chillers and boilers; and, if not properly selected, will function very inefficiently most of its life span. Another example would be to design the air handling systems for coaters and fluid bed granulators for the worst ambient conditions when these pieces of equipment are not operated continuously. Is it not possible to ride through a "four-hour" peak condition and not operate the equipment at that time? In some cases, the answer is yes; but no one wants to analyze the risk and make that decision.

Currently, the facility design decisions are heavily weighed to support a low risk tolerance of the industry. Interestingly, there are only a handful of written requirements from regulatory agencies which actually affect the design. However, there are traditions based on "unwritten" rules which have created an environment of fear of the unknown, resulting in repetitive design concepts without much thought toward innovation.

Energy Usage in Pharmaceutical Industry

The pharmaceutical industry consumes on average about $1 billion of energy annually.[2] This staggering figure gives us an idea of the potential savings that can be achieved by focusing more attention to the energy usages. Figure 1 illustrates how the energy usage has been escalating consistently.

The process of drug making consists of several discreet steps starting from discovery research to pre-clinical testing, clinical manufacturing to bulk active substance manufacturing, and then to formulations/finishing facility. In addition, there are needs for warehousing and administrative offices to support the drug discovery and drug manufacturing. These functions, facilities, and processes vary widely and have very different energy requirements and usages. Figures 2 and 3 are illustrations of how energy consumptions in such facilities vary. These charts also show a typical breakdown of energy usages between the various user categories such as processes, lighting, and Heating, Ventilating, and Air-Conditioning (HVAC).

Energy Cost Savings

Due to the recent surge in energy prices, every company is looking for ways to reduce energy consumption and lower the energy bill. There are two distinctly separate ways of saving energy costs. One is the energy procurement management and the other is the energy user side management. Energy procurement management consists of reviewing energy procurement contracts and finding ways to reduce the supply side rate structure or suggest alternate procurement methods. Another way is to use plant resources (such as waste) to

provide energy sources for the facility. Cogeneration, captive power generation using various types of turbines, etc. are some of the ways to reduce operating costs.

The energy user side management may include peak demand management, such as peak shaving with the use of on-site generators during peak loading, thermal storage, etc. But the primary focus of user side management is to reduce energy consumptions of various plant users like HVAC, lighting, processes, and operations. Investigations of these Energy Conservation Opportunities (ECOs) form the basis of most of the energy saving and green building discussions. Based on the illustrations above, the largest opportunities are in the HVAC field, which includes generation and distribution of central utilities such as chilled water systems, steam systems, compressed air systems etc. However, the ECOs are not limited to HVAC and lighting. Process, critical utilities, and operating philosophy of a facility also have a significant effect on energy consumption, and must be investigated. Examples of this category would be re-use of reject water from Reverse Osmosis (RO) systems, efficient use of hot and cold WFI systems, re-use of dumped water from purified water or WFI systems, etc. It should be noted that these energy conservation features often present risks to the company in a certain way, whether on product safety, personnel safety, reliability, or other issues.

Risk versus Energy Savings

Over the years, there have been several misapplications of energy recovery systems, which have added fuel to the notion of unreliability and risky applications in terms of energy saving features. The authors have knowledge of two facilities, which installed rotary air-to-air heat recovery system, but were soon abandoned for the fear of exhaust air being entrapped in the rotary energy wheel and getting mixed with the fresh air. There are many other examples of misapplications which have added to the apprehension of using energy saving features. We often find that energy engineers who are not familiar with the pharmaceutical industry recommend energy saving features that compromise the current Good Manufacturing Practice (cGMP) or Good Engineering Practice (GEP) associated with the pharmaceutical world. Even the usual energy saving opportunities commonly practiced in other industries must be reviewed carefully and critically for the specialized application of the pharmaceutical industry. On the other hand, the pharmaceutical industry itself has become very conservative and does not accept something that may present a hint of risk to the operation. Consequently, the industry has been consistently making the most conservative decisions on energy features. Some examples of such conservative decisions are:

1. 100% Outside Air (OA) versus re-circulated air for multi-product manufacturing facilities – *product safety*
2. 100% OA versus re-circulated air for Labs – *personnel safety*
3. High Purity Water Systems – Hot USP or hot WFI; Cold WFI; how to cool; heat it back – *inefficient design is accepted to avoid validation issues*
4. Micro environment – isolators in aseptic facility in non-potent applications; ventilated cages in animal facilities – *rarely thought of in terms of energy saving feature*
5. Room Classifications for solid dosage spaces – *overkill for the ease of compliance*
6. Air change rates versus room classifications – *Still using the vertical laminar flow techniques when the semi-conductor industry has changed the way clean spaces are designed - afraid to change*
7. Chilled water temperature reset – *rarely done*
8. Air handling unit discharge temperature reset – *rarely done*

Item #	Energy Conservation Opportunities	Energy Saving Potential			Initial Cost of Installation			Environmental Effect			Controllability			Risk Factor			Total	Remarks
		Importance Factor	Score	Weighted Score	Importance Factor	Score	Weighted Score	Importance Factor	Score	Weighted Score	Importance Factor	Score	Weighted Score	Importance Factor	Score	Weighted Score		
1	Change the current 100% OA system to recirculated system for a multi-product solid dosage manufacturing facility.	2	4	8	-1	2	-2	1	3	3	-2	2	-4	-4	1	-4	1	Acceptable
1 alternate	Change the current 100% OA system to recirculated system for a multi-product solid dosage manufacturing facility.	2	4	8	-1	2	-2	1	3	3	-2	2	-4	-4	2	-8	-3	Not Acceptable
2	Lower air change rate for Grade B clean rooms in a Sterile Facility	2	4	8	-1	-1	1	1	1	1	-2	0	0	-4	4	-16	-6	Not Acceptable
3	Lower air change rate for Grade C clean rooms in a Sterile Facility	2	3	6	-1	-1	1	1	1	1	-2	0	0	-4	2	-8	0	May be Acceptable
4	Unoccupied Mode in terms of temperature, RH and air change for Processing Rooms	2	3	6	-1	1	-1	1	2	2	-2	0	0	-4	2	-8	-1	May be Acceptable
4 alternate	Unoccupied Mode in terms of temperature, RH and air change for Processing Rooms	2	3	6	-1	1	-1	1	1	1	-2	0	0	-4	3	-12	-6	Not Acceptable
5	Remove room classification & Lower air change rates in a Solid Dosage Facility	2	2	4	-1	0	0	1	1	1	-2	0	0	-4	1	-4	1	Acceptable
6	Reuse reject from Animal Drinking water Reverse Osmosis (RO) system for Large Animal Trench washing in a Vivarium	2	2	4	-1	2	-2	1	3	3	-2	1	-2	-4	0	0	3	Acceptable
7	Reset of Chilled Water Temperature during relatively lower ambient conditions	2	2	4	-1	0	0	1	1	1	-2	0	0	-4	1	-4	1	Acceptable
8	Reset of Discharge Air Temperature for air handling units serving Manufacturing Rooms	2	2	4	-1	0	0	1	1	1	-2	0	0	-4	3	-12	-7	Not Acceptable
9	Reset of Discharge Air Temperature for air handling units serving Laboratory & Lab support spaces	2	2	4	-1	0	0	1	1	1	-2	0	0	-4	1	-4	1	Acceptable
10	Use of economizer control in air handling units serving manufacturing spaces with critical pressurization requirements.	2	3	6	-1	1	-1	1	1	1	-2	0	0	-4	3	-12	-6	Not Acceptable

Table A. Examples of quantitative analysis of energy conservation opportunities.

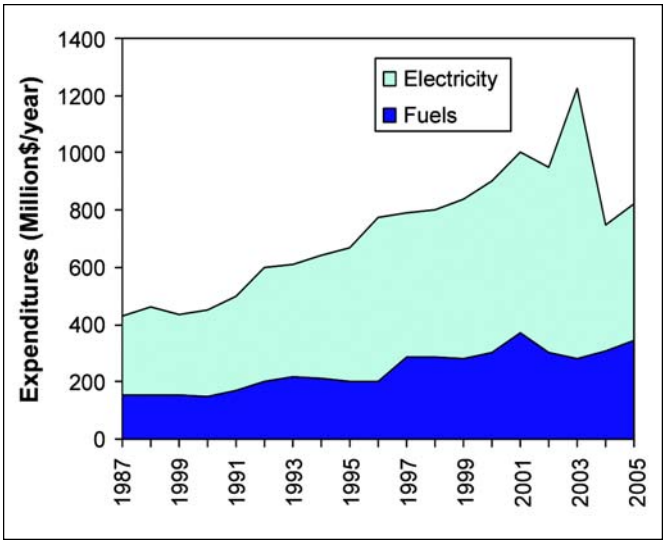

Figure 1. Historical energy expenditures of the US pharmaceutical industry. (Source: US Census)

9. Night setback for process rooms – *rarely done due to validation issues*
10. Lower face velocity or vortex controlled fume hoods – *still considered too risky by many*

Energy and Environments

Most energy related projects directly or indirectly affect the environment. In many cases, energy recovery or saving features are equated to reduced environmental discharge or emission. In addition to the usual NOx, CO, particulate matters, and other listed emission limitations, there has recently been a lot of discussion on greenhouse gases. Carbon dioxide is a major source of greenhouse effect, and most likely, will shortly be listed as a pollutant. Most multinational companies are already reporting their carbon footprint. The other companies are considering implementation of the "carbon mapping" program to monitor and perhaps control CO2 discharge. In most cases, the energy saving features will have a direct impact on carbon footprint. This is an important side advantage of energy saving features and must be considered in the evaluation of ECOs.

Evaluation Methodology Using Quantitative Analysis

As noted in the previous discussions, the energy saving features may have direct impacts on several important areas, including adding risks to the process, reliability, safety, and environment, etc. Each of the affected areas may have different importance and sensitivity to the project, company, or the industry. The evaluation must consider all of these aspects with varying importance or significance. The following is a suggested methodology that can be used for the decision making process. It is suggested that this is done before a true Return On Investment (ROI) analysis is conducted. The ROI analyses can take considerable engineering time and effort. Instead, a more judgmental analysis can be done to filter out most of the energy saving candidates. The full ROI analysis then can be performed for the energy saving candidates that pass the first scrutiny.

It should be noted that there are several energy conservation items that add little or no risk to the business. Examples are Low-E glass, additional insulations, white roofs, high efficiency, and energy star rated equipment, etc. These "non-risk" energy conservation opportunities do not need to pass through the above stated methodology of filtering the risk elements of various ECOs.

Methodology

The following describes the methodology for risk analysis of the energy conservation opportunities:

A. The significant areas (categories) affected by energy saving features:
   a. Risk to product, personnel, facility, reliability, etc.
   b. Energy Saving Potential
   c. Installation Cost
   d. Environmental Effect – positive or negative
   e. Constructability – in an existing condition

   Note: There may be a few other categories such as "maintenance" that can be added to the list, but the above five categories are by far the most significant in the decision making process.

B. Importance factor or weight of each category: An Importance Factor (IF) must be assigned for each of the affected area. For example:
   a. Risk Factor: IF = (-)4
   b. Energy Saving Potential: IF = 2
   c. Installation Cost: IF = (-)1
   d. Environmental Effect: IF = 1
   e. Constructability: IF = (-)2

C. Score: Assign scores for each ECO under each category. The scores could be assigned based on a scale as follows:
   a. Risk Factor: Score between 0 to 4: 0 when there is no risk; 1 when it is low risk; 4 is when it very high risk.
   b. Energy Saving Potential: Score between 1 to 4: 1 means low savings and 4 means high savings.
   c. Installation Cost: Score between (-)1 to 4: (-)1 means reduced installation cost; (+)1 means low installation cost and 4 means high cost.
   d. Environmental Effect: Score between (-)1 to (+)4: (-)1 for being negative or adverse impact; 0 would mean no impact; (+)4 means high positive impact.

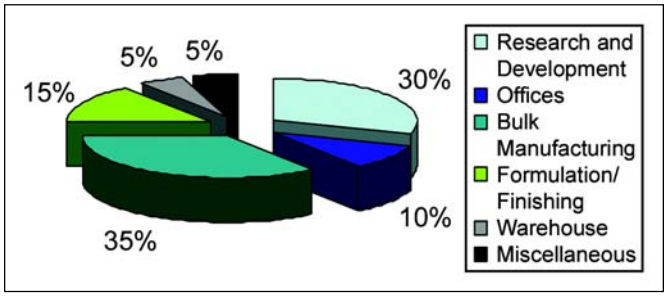

Figure 2. Breakdown of energy usages within pharmaceutical sector.[2]

e. Constructability: Score between 1 to 4: 1 for easy installation and 4 for difficult installation.

D. Assigning Scores: It is extremely important to assign scores properly. As with any numeric analysis such as this, the scores should be established with well thought out logistics and not picked arbitrarily. As is evident from the above, risks to product or personnel have the highest importance factor of 4. So, the score assigned to risk factor has a great effect on the outcome or result of the analysis. Table A gives examples of how to assign scores for risk factors.

E. Total Weighted Score: Total weighted score is the summation of each weighted score under each category which is derived by multiplying the assigned score with the weight, i.e., the importance factor.

F. Decision Making Process: Decision can be made based on the total cumulative score for each ECO. Higher positive total weighted score will signify better expected result with high ROI, low environmental impact, and most importantly low risk. Low cumulative weighted score or negative total score will signify higher risk or low ROI and should be discarded. The high scoring ECOs should then be pursued further to calculate the actual ROI and justified through financial benefits.

Table A shows some examples to illustrate the methodology. The actual weight and scores should be adjusted based on the actual situation, risk taking profile of the company, local environmental limitations, etc.

Suggested Implementation Program

It is important to develop a solid program to plan, evaluate, and implement various energy saving ideas. In most cases, the program will require significant investments on the part of the company. Usually, there is a minimum ROI that a company expects before the spending is approved. However, as pointed out here, many of the opportunities have additional benefits such as reduction in emission, including lowering of carbon footprint, sustainable design, etc., which go beyond just the ROI filter.

The implementation plan should follow the following logistics:

New Facility

1. Energy use should always be on the table during the design phase as well as construction phase. There should be an energy budget during the initial design phase.
2. Perform a risk-based study similar to the methodology suggested in this article.
3. Ensure the energy saving features that passed the initial test is considered and applied during the design phase. Often, energy savings features are easy targets for value engineering.

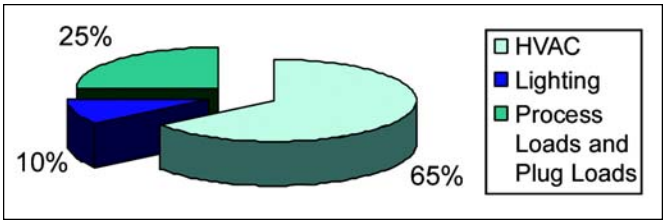

Figure 3. Typical energy consumption breakdown.[2]

Existing Facility

1. Implement an energy audit.
2. Make sure you hire capable engineers who understand both energy saving ideas as well as the type of pharmaceutical facility under audit.
3. Make sure the audit is comprehensive and includes process based systems and energy consuming operations.
4. Expect the firm to go beyond the "norm" in the pharmaceutical industry, within the constraints and boundaries of cGMP and GEP regulations in identifying energy saving potentials.
5. Perform a risk-based study for implementing the energy saving candidates, similar to the methodology suggested in this article. The client must be involved in this risk-mitigated analysis of energy candidates, and must be responsible for the decisions.
6. Based on the initial assessment, the ECOs with higher positive total scores (passing through the initial filter) should be analyzed further for actual ROI.
7. Implement the ECOs with reasonable ROI.
8. Measurements: It is important to have a baseline before the implementation of any energy saving opportunities. Have another measurement of energy consumption after the implementation. However, it is tricky as a large number of energy saving opportunities are influenced by the outside (ambient) environment, which is not controllable. Also, a high numbers of ECOs are dependent on a combination of situations and environments that are difficult to duplicate.

Conclusion

The time has come to revisit the system design and philosophies traditionally used in the pharmaceutical industry. The high cost of energy has given impetus to this movement. FDA and other agencies are also much more flexible with their new "21st century initiatives" and "Risk-Based Approach" subset for compliance and conformance. In addition, the industry collectively has the responsibility to ensure the sustainability of our environment. We need to join the "green" movement without sacrificing the efficacy and safety of the medicinal products. This article is intended to merely give ideas on how we can evaluate each scenario objectively and make the correct decisions. It is too easy to say that the industry is restricted and bound by all the compliance regulations, and there is no scope to save energy and become "greener."

At the same time, it should be realized that this industry is not suited for "overzealous" energy engineers to direct energy saving programs without understanding the risk. The

authors strongly agree that there is an opportunity to achieve reduced energy usage and balance energy savings and the various risks associated with making drug products. The decisions to implement energy saving opportunities must be made with proper engineering knowledge, risk assessments, and financial considerations instead of "it does not work" or "it is too risky" statements.

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About the Authors

Dave Goswami, PE President and Chief Operating Officer of IPS. His experience includes more than 22 years of leadership experience in facility design and engineering for pharmaceutical and high-tech, high performance facilities. Throughout his career, he has specialized in biohazard facility design, high-tech laboratories, utility plant design, wastewater recovery, and energy based projects. In addition, he has extensive experience in designing and coordinating systems for sterile and oral solid dosage facilities, R&D facilities, pilot plants, large corporate headquarters, hi-tech laboratories, animal facilities, and data centers. He can be contacted by telephone at: +1-610-828-4090 or by e-mail at: dgoswami@ipsdb.com.

Mark Butler is Principal and General Manager Engineering of IPS. He has more than 24 years of experience in facility design, construction, and operations. His expertise is in the engineering and leadership of large, technically complex, engineering-intensive facilities. In addition, he is presently a member of the ISPE Baseline® Guide for Quality Laboratory Facilities Task Team and has written and collaborated on several chapters for the new Guide. He can be contacted by telephone at: +1-610-828-4090 or by e-mail at: mbutler@ipsdb.com.

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Dr. Carl Lawton discusses how academia, industry, and government are working together to help biopharmaceutical companies in Massachusetts transition from drug discovery to manufacturing quickly and efficiently. He also discusses related training programs that are educating future and current biomanufacturing employees in process development and process validation.

PHARMACEUTICAL ENGINEERING Interviews

Dr. Carl Lawton, Director of Massachusetts BioManufacturing Center (MBMC) and Associate Professor, Department of Chemical Engineering, UMass Lowell

by Cathy Middelberg, Member, *ISPE Pharmaceutical Engineering Committee*

Dr. Carl Lawton is the Director of the Massachusetts BioManufacturing Center (MBMC) and Associate Professor in the Department of Chemical Engineering at UMass Lowell. He has a BS in microbiology from Purdue University and a Masters in microbiology and PhD in chemical engineering from University of Connecticut.

Dr. Lawton works closely with companies on the verge of biopharmaceutical production to give them the opportunity to utilize the Center's process development, applied research, and education services to optimize time to market and to improve the quality, cost, and productivity of their operations. In the 15 years that Dr. Lawton has been at UMass Lowell, he has helped more than 15 companies bridge from biotech research to manufacturing.

Dr. Lawton in collaboration with industry and other University faculty co-developed the Graduate Certificate Program in Biotechnology and Bioprocessing. Students that Dr. Lawton advises and mentors through this program and the chemical engineering degree programs are in demand by leading biopharmaceutical firms, including Genzyme and Wyeth, as well as by startups and industry supplier companies. Dr. Lawton also has developed customized training programs to uniquely address the workforce needs of specific biopharmaceutical manufacturers.

Q Could you tell us a little about yourself and what led you to your current position at the University of Massachusetts?

A I joined the faculty at the University of Massachusetts Lowell after 15 years of working and being educated in the field of biotechnology, microbiology, and chemical engineering. In the early days of my industrial career, I served as a consultant to companies for the biological production of ethanol. The insight I gained during this time led me to seek out a more engineered approach to the application of biochemical principles for the commercial production of products.

After working and receiving patents on several government-funded ventures involving biologically engineered approaches to producing specialty chemicals and specialized materials, I joined the University of Massachusetts Lowell to help them establish a more comprehensive biotechnology program. This was at a time when the pharmaceutical industry was in a state of flux and biopharmaceuticals were

Dr. Carl Lawton, Director of Massachusetts BioManufacturing Center and staff analyze data for study of Glucose Feedback Control on CHO Cell Bioreactor.

just starting to come onto the market. While establishing a bioprocess development center and a bioprocessing graduate program, I continued to pursue my research interests in specialty materials, but eventually turned to more applied research endeavors as I became more knowledgeable of the biopharmaceutical industry needs. I spent periods of time working on site with Cambrex, Antigenics, and Cambridge Biotechnology, helping them while at the same time gaining expertise in process development and process validation.

Q Can you tell us about the UMass Lowell Massachusetts BioManufacturing Center (MBMC)? What is the mission of this center?

A The UMass Lowell Massachusetts BioManufacturing Center (MBMC) has a tripartite mission of education, applied research, and process development to facilitate growth of biomanufacturing. The Center works with biopharmaceutical firms to help them transition from drug discovery to manufacturing. As an interdisciplinary center, the Center assists biotechnology companies in developing procedures and processes that lead to validated cGMP-compliant manufacturing processes. Some of the capabilities of the facility include process development, large scale engineering production for pre-clinical materials, applied research focused on critical biomanufacturing, and education and customized training programs for developing process excellence and best practices.

Q How does the center compare to other training programs and facilities globally that you know of?

A MBMC is unique with our mis sion of helping companies transition from drug discovery to manufacturing quickly and efficiently, as opposed to a center that is primarily dedicated to one aspect of biomanufacturing, either training, research, or cGMP manufacturing. In addition, MBMC provides training as well as other services that combine technological and scientific expertise.

We are also fortunate to be a part of the Life Sciences Super Cluster – one of the largest in the world. The Massachusetts region generates many biotech start-ups each year based on inventions and technology created in our research universities and hospitals. The inter-related capabilities that support the Center's focus of bridging this biopharmaceutical research to product manufacturing operations within Massachusetts are process development services, large-scale engineering facility, education for company leadership and technical staff, applied research focused on critical biomanu-facturing issues, and networking industry and academic expertise to disseminate best practices.

Q Could you also tell us a little about the training programs? What kind of training is offered? What type of student is the state looking to educate through the center? What types of jobs does the program prepare them for?

A The Center offers a Graduate Certificate in biotechnology and bioprocessing. Courses cover the theory of industrial fermentations and cell culture, harvest and purification, regulatory compliance, as well as hands-on process development laboratory. Because of the timely topics, breadth of subject material and hands-on experience, students in this program as well as students I advise in the chemical engineering degree programs are sought by leading biopharmaceutical firms, including Genzyme and Wyeth, as well as by startups and industry supplier companies, such as Millipore. Graduates are successfully placed in a variety of jobs, including process development, manufacturing operations, quality control, and validation. We are playing a key role in providing this growing industry with employees equipped with the right skills and talent.

It is often advantageous for companies to seek our customized training programs to allow them to upgrade existing employees' skills, thereby resolving some of their hiring needs in a more cost efficient manner. Customized training can be developed in short course format to be delivered on company site.

An example of a training program we developed with Massachusetts Biologic Laboratories involved a need for CHO based monoclonal antibody production workers. We were able to design a comprehensive program to train their blood purification operators, which helped them to transition to the needed CHO- based monoclonal anti-

body production. We spent 64 hours at their facility lecturing on cell culture and purification after which 20 employees participated in 32 hours of hands-on activities at UMass Lowell MBMC process development laboratories.

Q How many students does the BioManufacturing Center train per year? Is the training part of the UMass curriculum? How long is the training program?

A We currently have approximately 40 students a year enrolled in the courses for the Biotechnology and Bioprocessing Graduate Certificate. Although the graduate certificate is a stand-alone program, the courses can be used for other degrees such as a Masters in biology or chemical engineering. There are four required courses that are offered and students can complete the certificate in one year. These four courses provide students with comprehensive theory behind biomanufacturing operations as well as hands-on process development experience.

Q What are the driving forces behind the decision to design and build expanded facilities and how large will the expansion be?

A The MBMC core team met with industry executives and our Advisory Board to determine a focus for our offerings. Using this input, we evaluated the facilities we are working in and determined the need for and best direction for an expansion.

The expansion will allow us to upgrade to state-of-the-art equipment in process development for cell culture, fermentation, and purification. Added laboratory space includes space for MBMC faculty to work on applied research projects as well as space for additional process development and analytical equipment and services. There also will be space for conference rooms and offices. The total will be about 16,000 square feet.

The existing facilities of MBMC at UMass Lowell allow us to effectively work on process development projects. We pride ourselves on the quality we provide and our clients expect it. We will implement ISO 9001-2000 guidelines as a base to ensure our quality The new facility will have more defined areas to evaluate new technologies, such as disposable bioreactors and purification methods. Pilot scale reactor runs will provide ample material for evaluating novel purification strategies.

Q How do you help companies get into clinical production?

A There are two strategies for getting into clinical production depending upon the host organism. For *E.coli* and yeast, we help companies starting with process development. The process is then transferred to our large-scale engineering facility. Using similar equipment, process, and methods, we can then transfer the process to a partner cGMP contract manufacturer. This affords client companies speedy and economical transition to clinical trials.

For CHO-based processes, we will start with process development to help companies develop an efficient process and then help lead them to self-manufacture of Phase I and II clinical material through instruction and consultation. Our partnerships and Advisory Board provide us guidance and allow us to draw on the experience of companies that have successfully followed this path using disposable technology.

This is another example of our good fortune to be part of the Life Sciences Super Cluster, and we seize upon that by being a reliable partner to innovators and entrepreneurs and help them move brilliant science from laboratory to market.

Q What are your current applied research programs and what do you envision for the future?

A We currently have two projects focused on improving the productivity of CHO cells in the bioreactor. The first is based on glucose feedback control to keep glucose concentrations low in order to minimize lactic acid production. We are interested in the effects of this type of automation on product titre and quality. The second is to develop perfusion technology coupled to stir tank bioreactor that is easy to validate and operate. We are also interested in product titre and quality.

Future projects will focus on reducing equipment, capital investment, and risk. Technical challenges we are addressing include optimization of expression at industrial scale, molecule stability, downstream purification, and characterization of molecules. The upgraded facilities and capabilities the expanded Center will provide will allow us to further enhance our experience and knowledge of best practices, to increase our offerings, and provide a greater proportion of the biomanufacturing industry with innovative solutions.

Q How are programs funded and what are the funding sources for the expansion?

A The current operation of the Center is sustained through process development and customized training client programs. As we expand, we rely on equipment donations from compa-

Automated control of the pilot plant reactor.

nies, but more significantly the Massachusetts legislature passed an Economic Stimulus Bill that provides capital for the expanded facilities.

Q Who are partners and supporters of MBMC?

A Wyeth, a multinational biopharmaceutical manufacturer; Invensys, a multinational automation company; and Dakota Systems, a local supplier of bioreactors are helping us build our microbial pilot plant. Nova Biomedical and Waters, both multinational suppliers of analytical equipment, have donated analytical equipment to us.

We have support from many of the local biotech companies such as Wyeth, Genzyme, and Abbott in the form of Advisory Board Members, technical expertise, and adjunct faculty. A partner cGMP facility is with Lonza Hopkinton, Inc.

We are looking for additional partners to help with downstream purification, increasing our analytical capability, and building a mammalian pilot plant based on disposable technology.

Partnerships and support from industry allow us to work out processes with state-of-the-art equipment in a real world setting. The training on real-world equipment, such as the 190L reactor from Wyeth and the automation system from Invensys, ensures our students learn the necessary skills to be active players in the life sciences industry.

The partnerships we develop allow innovative technology to be more readily accessible to the industry and create an environment which allows us to help advance the next generation of products.

Q How do you intend to keep the center state-of-the-art?

A We plan to keep the Center state-of-the-art by continuing to evaluate technologies and to partner with leading companies in the industry. The 190 L reactor that Wyeth donated is a sister reactor to a current one in Wyeth's Andover facility pilot plant. Dakota will retrofit the reactor with state-of-the-art instrumentation donated by Invensys and others. An InFusion automation system donated by Invensys will enable easier process development, scale-up, and batch recordkeeping.

Waters Corporation donated state-of-the-art HPLC coupled with ion-spray mass spectrometry. We will continue to add equipment and faculty expertise to develop an analytical facility that can fully characterize biopharmaceuticals.

In downstream purification, we will evaluate resins and hardware from different manufacturers and investigate the use of newer disposable technologies.

Many of the suppliers of analytical equipment, purification, and automation systems who partner with us are headquartered in Massachusetts. They are continually introducing new products that are state-of-the-art. The high density of these companies creates an environment of innovation of which we benefit from and help to advance.

Q What are your expectations for company donations and how does this meet your state-of-the-art objectives?

A In order to outfit the Center, we will purchase some equipment, but are looking to industry to donate key items. These donations need to be state-of-the-art, readily accepted by industry, and the donor company needs to have the ability to build a trusted relationship for service and training.

Part of the bioreactor suite at the Lowell, Massachusetts campus BioManufacturing facility will be automated with a system from Invensys that will be used for training and optimization. The InFu-sion ECS system donated from In-vensys will enable easier process development, scale-up, and record keeping, as well as faster start-up leading to optimized and validated cGMP-compliant manufacturing processes. With the InFusion ECS system, control, batch documentation, process tracking, traceability for scale-up, and production is optimized and quality is ensured.

Q Do you believe that the center helps create new jobs in Massachusetts?

A The Center is only a part of the solution to create new jobs in Massachusetts. Equally important are tax reform and streamlined permitting.

Bristol-Myers Squibb cited the state's pool of life science graduates as a key factor in its decision to locate their newest $750 million biopharmaceutical manufacturing facility in Devens, Massachusetts. As Director of MBMC, I was a member of the UMass contingent that, along with members of community colleges and other universities such as Worcester Polytechnic Institute, was involved in state efforts to recruit that firm.

By helping companies develop efficient manufacturing process, providing state-of-the-art analytical facilities and expertise, and providing motivated trained workforce, we help to create a successful environment for biopharmaceutical manufacture in Massachusetts.

Future Plans

Q Are there any future plans in Massachusetts for other types of biotechnology facilities or training centers once this facility is completed?

A Governor Deval Patrick has put forward a $1 billion Life Sciences Initiative to help keep Massachusetts at the forefront of the life sciences industry. Regional "Innovation Centers" have been proposed to enable research collaborations. Funds would be available for "shared use" equipment and instrumentation. One such center would be the Massachusetts Stem Cell Bank, the largest repository of stem cell lines in the world. Another would be an RNAi Center to capitalize on the groundbreaking work of Nobel Laureate, Dr. Craig Mello of UMass Worcester.

Q What do you envision the future will be like once your center is completed?

About the University of Massachusetts

The University of Massachusetts educates 60,000 students at its five campuses in a given year and, together with UMass Online, generates an estimated $4.2 billion in annual economic activity, and spends more than $400 million annually on research. UMass ranks 11th among American universities in technology licensing revenue – generating $28.7 million in fiscal year 2005, second in the state only to the Massachusetts Institute of Technology.

UMass Lowell, www.uml.edu, a comprehensive university with a national reputation in science, engineering, and technology, is committed to educating students for lifelong success in a diverse world and conducting research and outreach activities that sustain the economic, environmental, and social health of the region. UML offers its 11,000 students more than 120 degree choices, internships, five-year combined bachelor's to master's programs, and doctoral studies in the colleges of Arts and Sciences, Engineering and Management, the School of Health and Environment, and the Graduate School of Education.

A The Center, along with tax reform and streamlined permitting, is part of the solution for creating a favorable manufacturing environment in Massachusetts. The expanded Center will continue to help companies develop efficient manufacturing process, provide state-of-the-art analytical facilities and expertise, and provide training for a motivated workforce.

The expanded facilities will allow us to reach out to more companies and offer more services. The pilot plant will allow for more efficient transfer of process development. We will see quicker turnaround times and cost will be lowered for clients when they get to cGMP stage.

The expansion makes us state-of-the-art and provides us with analytical facilities so we can offer full protein characterization. It allows us to demonstrate innovation, such as disposable technology, and build our expertise with new technologies so we can disseminate best practices to the industry through solutions and services we provide.

Q Would you like to work with ISPE to help train biotech professionals?

A ISPE has many training programs for biotech professionals that complement our training programs. I would like to work with ISPE to formalize this opportunity and make the Center available to ISPE classes.

The Center's hands-on facility can enhance many of the biopharmaceutical product training ISPE offers.

Q What do you see as the future of biotechnology in Massachusetts and the US? Do you believe the US biotech manufacturing industry can compete with international or third world companies?

A Massachusetts will never be the lowest cost producer of products. However, there are many other considerations biopharmaceutical companies take into account when making the decision of a manufacturing plant location. Of equal importance are trained motivated employees, tax reform, streamlined permitting, a community of skilled professionals, and quality of life issues. Many companies have based their decision to build or expand in Massachusetts based on having these attributes available. The Center now, and even more so as it expands, is playing its part in helping to create a fertile environment for company success – where quality of the product is paramount.

Dr. Lawton can be contacted by telephone at: +1-978-934-3158 and by e-mail at: mbmc@uml.edu.

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Commissioning and Qualification: A New ASTM Standard – GMP Regulations

This article clarifies the principles and practices in the new ASTM Standard and presents how the new standard will impact the ISPE C&Q Baseline® Guide Revision.

by Robert E. Chew and David Petko

In May, 2007, the ASTM Committee E55 voted to approve a new standard, "A Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment." This recently published standard has the ASTM designation of E2500. It has been three years since the risk-based concept for this standard was first discussed at a meeting at ISPE headquarters in Tampa. Several draft versions have been issued in the intervening time, and people at a number of conferences and speaking engagements have addressed the concepts in the standard to audiences around the world. It is ISPE's intent to update the Commissioning and Qualification Baseline® Guide to reflect the principles and practices outlined in this standard; other Baseline® Guides will be updated in due time. Due to the general guidance nature of this standard, there is significant room for interpretation. This article is intended as a precursor to the update of the C&Q Baseline® Guide in order to clarify certain aspects of the standard and to help ensure that industry ***doesn't misinterpret and then misapply the new standard.***

For most companies, qualification is a costly and time consuming process that in some cases can delay the launch of critical medicines to patients. There are aspects of qualification that can add value in terms of ensuring the equipment and systems are ready to reliably manufacture a quality product. There are other aspects and documentation practices that clearly do not add this value. And it can be argued that the rigid rules that surround qualification (as practiced today) can detract from its overall effectiveness. If one examines GMP regulations, one can easily find the basis for what we call qualification, but no specific requirements that relate to *how* qualification is practiced *today* - *Sidebar 1*. Furthermore, if one reviews the 1987 Guideline to Process Validation, which is where installation qualification was first mentioned, one finds qualification concepts discussed, but not specific "how to" implementation nor the controls and practices typically applied today.

It can be argued that many of the non-valued-added aspects of qualification as practiced today stem from a lack of understanding as to the intent of the GMPs related to equipment suitability. Instead of acquiring and deploying this understanding, companies have chosen to avoid ill perceived risk, seeking to create procedures that are at least as onerous if not more so than those of their fellow manufacturers (safety in numbers). Thus, they have implemented a plethora of structural, oversight controls, and other rigid practices, which when taken to the extremes many companies take them, obscure the underlying value that can and has been added by the intent of current Good Manufacturing Practices (cGMPs). ***This concept is simple: were the equipment and systems properly installed, do they operate properly, do they perform to meet process requirements, do they control risks to product quality, and will they support process validation?***[1] It is the spirit and practical application of this concept that is addressed by the ASTM Standard.

The ASTM standard adheres to the current Good Manufacturing Practice (cGMP) regulations and describes a high level process to ensure manufacturing systems and equipment (including automation) are fit for intended use such

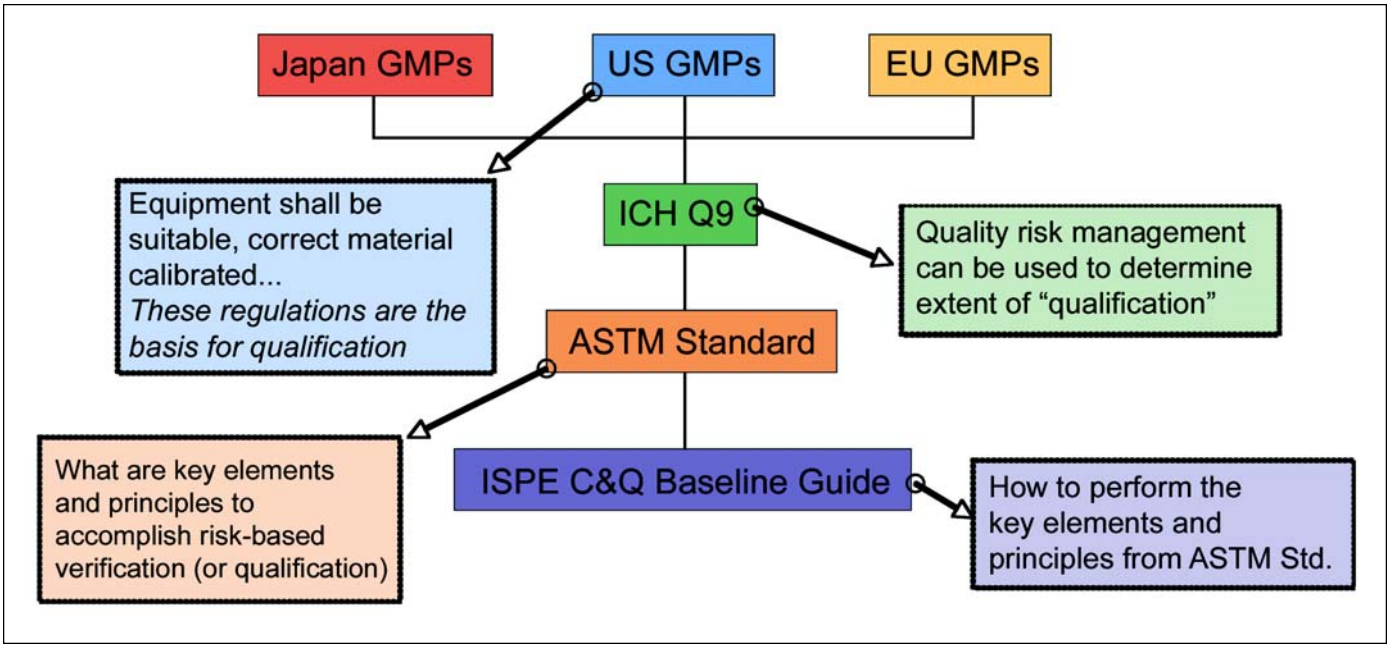

Figure 1. Relationship of ASTM Standard to GMP regulations and guidance documents.

that risks to product quality and public health are effectively managed. To accomplish this, the standard (1) specifies a minimum set of activities that meet GMP regulations to form a framework for specifying, designing, and verifying manufacturing equipment, systems, and associated automation; (2) describes an approach to specifying, designing, and verifying that incorporates the science and risk-based concepts of ICH Q8 and Q9. The standard is based on a set of 10 principles that were first presented to the Society's International Leadership Forum in April 2005 - *Sidebar 2*. The standard was purposefully written at a relatively high level to allow firms the flexibility to adapt to their particular organizational breakdown of responsibilities, and to allow firms to develop innovative approaches to implementing these principles. Figure 1 illustrates how the standard fits within a regulatory framework and incorporates principles of Quality Risk Management (QRM).

The preceding paragraphs give us cause to celebrate, but also pause to exercise caution. By studying both the letter *and understanding the intent of* the GMPs, and by understanding this ASTM standard, we can expunge many of the non-value added qualification practices of today. We can even redefine what we mean by the term "qualification" or "to qualify." Several projects have taken the step of deleting IQ/OQ per se, and have passed an FDA pre-approval inspection. However, we cannot use this standard as an excuse for not meeting GMPs. But we can use this standard to separate GMP requirements from "folklore" qualification practices and expectations we ourselves have invented over the past 20 years, not to meet the intent of GMPs, but in an ill-designed attempt to avoid regulatory risk. Frequently, systems that were qualified via formal qualification protocols simply did not work correctly, even though they had been signed off as "qualified." We can use this standard to help us devise and implement better, more effective ways of ensuring our facilities, equipment, systems, and associated automation are delivered in an efficient manner using good engineering practices. Regardless of which methodology we choose, at the end of the day our manufacturing systems must be fit for purpose – able to support the reliable manufacture of quality products and able to control risks to the patient to an acceptable level.

The standard was developed using a consensus approach, with content based on science and sound quality assurance principles. The ASTM organization and the consensus process mean this standard can be traceable to the World Trade Organization. Objections to any portion of the standard must be justified based on science; good science was the same criteria by which comments to the draft standard were assessed. Use of the standard is voluntary. However, if one chooses to use the standard, it must be implemented in its entirety; a piecemeal or partial approach is the same as not implementing the standard at all.

ASTM E2500 and the GMPs

The first thing to note about ASTM E2500 is absence of the term "qualification." The term appears, but once, in the definitions section: "Verification... is an umbrella term that encompasses all types of approaches to assuring systems are fit for use such as Qualification, Commissioning..." ***It is interesting to note that the US GMPs do not mention the term "qualification," nor do the US GMPs require documents labeled "IQ," "OQ," or "PQ" and hence, neither does the standard.*** Instead, the standard describes a process, backed by key concepts, that allows a project team to meet the intent of what the GMPs do require - *Sidebar 1*.

1. The GMPs (211.22c) require the quality unit to approve procedures

and specifications that impact the identity, strength, purity… of the drug product. Here is how ASTM E2500 supports this requirement:

a. §7.4.1.3 specifies that the quality unit approve verification "acceptance criteria of critical aspects (i.e., critical to product quality and patient safety)…" These critical aspects are defined earlier in §6.4.1 as "functions, features, abilities, and performance characteristics necessary for the manufacturing process to ensure consistent product quality and patient safety."
b. §7.4.2.3 describes use of an overall verification plan to define the verification strategy, what constitutes acceptable documentation, etc. The verification plan can be thought of as similar to what we find today in validation project plans, or commissioning plans, or other plans that govern how the quality of the installation, operation, and performance are to be inspected, tested, or otherwise verified. If the scope of the project verification plan includes systems with critical aspects, the quality unit should approve this plan. The verification plan, or related procedures, can be considered procedures that may fall within the requirements of 211.22c.
c. §6.8.3 requires quality unit approval when vendor documentation will be used to support verification of critical aspects.
d. §7.5.4 requires quality unit approval of the final documentation that confirms the manufacturing system is fit for its intended use. This documentation includes a review of the results of the verification activities, including any non-conformance with acceptance criteria for critical aspects. It should be noted that this does not infer use of deviation practices as we know them today, wherein problems encountered during start-up are treated the same way as batch record non-conformances, with formal investigations, corrective actions, etc. Instead, this requirement is meant to ensure any non-conformance of critical aspects that remain after all start-up, setting to work, adjustment, and testing have all been completed, are documented and that an assessment is made to determine the impact of this open non-conformance on patient safety.

The above does not imply that the quality unit should only become engaged at these specific times. Firms must ensure a responsible and effective quality program exists. For some firms, engineering project teams are diligent about ensuring the quality of system installation and operation. For other firms, project teams have viewed a structured and documented quality program based on good engineering practices as something to be done only because regulators expect it. This is not the case – try taking such a position while working for Intel or Motorola or Ford or any other world-class manufacturer! The quality unit is responsible to see that the project verification plan, which spells out the overall approach to verification and project quality assurance, is robust and is implemented properly. How such responsibility is discharged will depend on the confidence the quality unit has in the project delivery team.

2. The GMPs (211.25a) require the use of persons of appropriate "education, training, or experience, or combination thereof..." ASTM E2500 §6.7.1 defines Subject Matter Experts in similar fashion. In some circumstances, the quality unit is a subject matter expert, for example, on the application of appropriate levels of quality control. Hence, the quality unit must approve the overall project verification plan, which would describe the tasks necessary to apply various quality control and quality assurance strategies and practices. In other cases, engineering should be the subject matter expert, such as to determine how best to inspect or test a piece of equipment, review the results of these inspections or tests, and evaluate any departures from engineering specifications. A person from the quality department may or may not have the requisite education, training, or experience to be able to perform these often very technical functions; hence quality unit involvement in these aspects of verification is not required. This is perhaps one of the more significant changes from current qualification practices of today.

The role of quality is focused on three things: (1) ensuring that critical aspects and associated acceptance criteria have been identified, based on scientific knowledge of the process and an analysis of risks to the patient that may arise through the manufacturing process, equipment, or systems; (2) as a subject matter expert on the application of quality principles, the quality unit approves the overall project verification plan; (3) the quality unit approves the final determination that a manufacturing system containing critical elements is fit for its intended use. All other aspects of the specification, design, and verification process described by the standard are to be performed by other appropriate subject matter experts such as engineering, product/process development, operations, etc. – in many cases, using a multi-disciplined team that may or may not involve the quality unit as deemed appropriate by the individual firm.

3. The GMPs, both US and EU, spell out requirements for certain items such as materials of construction, calibration of critical instruments, etc., that have typically been a part of what is called IQ/OQ/PQ. While ASTM E2500 does not list specific verification activities, it describes verification as "A systematic approach…to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly." It goes on to incorporate the idea of quality

risk management as found in ICH Q9 and EU Annex 15, along with engineering and business risk: "The extent of verification and the level of detail of documentation should be based on risk, including that associated with product quality and patient safety, and the complexity and novelty of the manufacturing system." (§7.4).

4. Documentation has traditionally been viewed as an onerous requirement carried out "because the regulators demand it." Even the current version of ISPE's Commissioning and Qualification Baseline® Guide uses the term "enhanced documentation... to satisfy the demands of the regulators." It is unfortunate that our industry has adopted this viewpoint, for it leads to the misapplication of people's time (and hence cost) in how documents are created and controlled. Instead, documents should be viewed as serving a useful, practical purpose. Documents help ensure the intended actions are performed in the field in a deliberate, controlled manner. Details in documents are an invaluable tool when a person is standing at a machine inspecting or testing it; hence, "on-the-fly" field research is not needed because the document creator did the research. Recording of operational or performance data serves as a valuable record for future operations, maintenance, or change. Where we have gone astray is the rigid nature of our qualification protocols, including computer system validation documentation. Current documentation practices are based on the premise that the detailed engineering specifications are perfect; there is no allowance for learning, adjustments, or changes to the physical or functional design during start-up. This is not to say that uncontrolled changes may be made (see below).

Commissioning, as described in the current ISPE Baseline® Guide, is to be a more flexible exercise, and acknowledges the learning and adjustments and cycle development that occur during any project. Qualification does not have that same flexibility, and this distinction has lead to a two-phase activity, commissioning followed by qualification, or a one-phase activity that was just qualification with a new name, but the same old constraining practices. More recently, the use of Process Analytical Technology (PAT) has highlighted the issue of learning during installation and operational checkout; such projects often require significant changes to the original design, and trying to accomplish this under a traditional qualification and/or computer validation regime can quickly kill such projects. As PAT applications become more sophisticated, moving from simple feedback loops to a process controller that is programmed to adapt a process based on a complex mathematical model of many raw materials and in-process variables, the traditional computer validation model just won't work. Hence, documentation must be used in a way that serves both purposes: inspection and testing control and record-keeping, along with adaptability for start-up learning and adjustment.

ASTM E2500 requires that verification activities be documented. Many different sections require documentation, from critical aspects, to verification activities, to results. The standard is purposefully vague on what constitutes acceptable documentation, leaving that to the individual firm and to be spelled out in the overall verification plan. An earlier draft version of the standard defined acceptable documentation as that which clearly demonstrates to a subject matter expert that the acceptance criteria were met. The current standard requires that verification results be reviewed by appropriate subject matter experts, which implies that the documentation need be understandable by a subject matter expert. The only specific requirement regarding documentation in the standard is found under Acceptance and Release §7.5.3, "The documentation should contain a clear statement as to whether or not the manufacturing system is fit for intended use…"

5. The GMPs require pre-approval by the quality unit of changes once manufacturing operations have commenced. Many project teams have extended this pre-approval further and further into the early stages of inspection and testing, even as far back as design. The ASTM standard makes the distinction between pre-approval by the quality unit, and change management as may be practiced by subject matter experts. The standard requires that change management processes be established throughout the project. Change management includes use of appropriate subject matter experts to approve changes with notification of the quality unit of changes to critical aspects. This is acceptable, as the manufacturing systems, during these stages of the project, are not yet producing product.

Additional ASTM E2500 Requirements

While ASTM Standard E2500 does much to eliminate the "folklore" wasteful practices such as excessive focus on documentation practices that have come to permeate qualification, it also contains provisions that are not typically part of many projects, or if used, aren't given as much attention as "GMP requirements." These provisions include science-based process requirements, specification and design reviews, risk management, and application of good engineering practices. With ASTM E2500, they are not optional. Proper application of this standard requires all provisions to be carried out although there can be much latitude as to "how" these provisions are met.

Many projects develop user requirements specifications slanted toward the V-model: system by system so that system PQ's can easily line up one for one. While system-based user requirements specifications can serve useful procurement functions, they are often very detailed and cover a range of requirements well beyond those necessary to assure product quality and patient safety. ASTM E2500 focuses on what one could call process requirements, those that are relevant to prod-

uct and process safety, and which are based on scientific understanding of the product and process. If a firm has employed the principles of Quality by Design (QbD) to develop a well-characterized process design space, then process requirements become defined by this multi-dimensional space. Whether QbD is used or not, these manufacturing process requirements must include anything impacting the ability to meet critical product quality attributes, and include the critical process parameters.

The project team should develop a process by which the process requirements are communicated to the design team, to ensure that the design is developed from this knowledge of product and process requirements. As part of the design effort, those aspects that are critical to product quality and patient safety must be identified. Design reviews (plural) are conducted throughout the project with a number of criteria to be checked (standard §8.2). The design reviews are performed by appropriate subject matter experts and are documented.

Risk assessments should be performed by appropriate subject matter experts. Several kinds of risks can be evaluated. Risks to the patient and product quality are a must. In addition, business risks such as vendor or construction risk, and technological risks, especially as they pertain to product quality, also should be evaluated. Risk management is an iterative process, and will likely result in design changes. The degree of verification checks and the nature of the verification documentation also is based on the outcome of risk assessments. The entire verification effort is thus risk-based.

Risk assessments can help identify the critical aspects, and thus can replace the generic criteria used in the current ISPE Commissioning and Qualification Baseline® Guide impact assessments. A top-down risk assessment has been shown in real project case studies to be a more effective and efficient way (vs. system and component impact assessments) to identify the critical aspects that control risks to the patient and otherwise support meeting process requirements.

If a project team uses a solid design development and design review process, integrated with a risk-based understanding of the product and process upon which the design is based, then what can be achieved is a dimension of Quality by Design. The term "Quality by Design" is meant to refer to the design of the manufacturing process and an understanding of the process design space within which successful manufacture of a quality product can occur. However, this term can be just as appropriately applied to the infu-

US GMPs

§210.3, Definitions – (20) *Acceptance criteria* means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

211.22 Responsibilities of the Quality Control Unit. (c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.

211.25 Personnel Qualifications. (a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions…

211.42 (Facility) Design and construction features. (a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.
(several specific items are listed in subsequent sections and subsections)

211.63 (Equipment) Design, size and location. Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.

211.65 Equipment construction.
(a) Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.
(b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

211.68 Automatic, mechanical, and electronic equipment.
(a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.
(b) Appropriate controls shall be exercised over computer or related systems to assure those changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas

Continued on page 6.

Sidebar 1. GMP Regulations Relating to Qualification.

sion of quality principles into the engineering design. The ASTM Standard requirements for a design basis, design development, design communication, and design review process based on process understanding and risk management principles provides us a clear program for achieving this infusion of quality principles: *"Facility and Equipment Engineering Quality by Design."*

While nearly all projects at least pay lip service to the application of good engineering practice, this standard requires the use of good engineering practice throughout the specification, design, and verification phases. A complete discussion of good engineering practice is beyond the scope of this article; additional information may be found in current and soon-to-be released ISPE Baseline® Guides and Good Practice Guides.

Implementation Options and Case Studies

What follows are some suggestions and a case study for restructuring qualification, while meeting GMPs and ASTM E2500. Other approaches are also possible. Again, it is important to note that to be in conformance with the standard, one does ***not*** have the option of picking and choosing which aspects of E2500 to implement on a particular project.

Alternative Approach #1

One could simply follow the ASTM standard and not worry about whether documents are called "IQ/OQ" or commissioning or verification. Inspections and testing to demonstrate equipment is fit for purpose, performed under a reasonable level of control with documentation sufficient to control and record the relevant information and reviewed by subject matter experts, is what is required. A rose, by any other name, is still a rose. Activities, and the associated documents, should be structured in a manner that constitutes the most effective approach to inspecting and testing each piece of equipment, each system, and associated automation - based on sound engineering practices. Don't try to force fit these activities into traditional IQ/OQ/PQ structures, as that approach may be suboptimal for any given piece of equipment.

Alternative Approach #2

Follow the ASTM standard, and consider the final acceptance phase the "act of qualifying." There is some logic to this approach. If the purpose of qualification was to demonstrate that equipment and systems were fit for their intended use, then one would need to show that the equipment and systems can support manufacture of a particular product using a particular process.

Continued from page 5.

or other records or data shall be checked for accuracy…

EU GMPs

Annex 15.

It is a requirement of GMP that manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations… A risk-based approach should be used to determine the scope and extent of validation.

The key elements of a validation program should be clearly defined and documented in a validation master plan or equivalent documents.

After completion of a satisfactory qualification, a formal release for the next step in qualification should be made as a written authorization.

The first element of the validation of new facilities, systems or equipment could be Design Qualification (DQ). The compliance of the design with GMP should be demonstrated and documented.

Installation qualification, operational qualification, and performance qualification are specified and defined as to typical content focus.

Qualification of existing facilities is discussed in terms of verifying the operating parameters and limits for the critical variables of the operating equipment.

Annex 11 Computerized Systems

Where a computerized system replaces a manual operation, there should be no resultant decrease in product quality or quality assurance.

Persons should be appropriately trained and have appropriate expertise as applicable to a computerized system. The extent of validation necessary will depend on the intended use, whether validation is to be prospective or retrospective, and whether or not novel elements are incorporated.

The computerized system is further discussed, including, but not limited to, topics such as:

- Software should be produced in accordance with a system of Quality Assurance.
- Access to data should be limited.
- When critical data is entered, there should be a check on the accuracy.
- The identify of operators editing or confirming critical data should be recorded.
- Alterations should be via a defined procedure.
- Data should be secure and protected by backup, etc.
- Procedures to be followed when the system fails should be established.
- When outside agencies are used, there should be a formal agreement, including responsibilities of the outside agency.
- Only authorized, Qualified Persons should have the ability to release a batch.

ICH Guidance Documents

ICH Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Before initiating process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined: DQ, IQ, OQ, PQ.

ICH Q9 Quality Risk Management

[Quality Risk Management can be used] to determine the scope and extent of qualification of facilities, buildings, and production equipment… To determine design of facilities/equipment.

Sidebar 1. GMP Regulations Relating to Qualification. (continued)

1. Focus on that which affects product quality.

2. Requirements. User requirements, based on the process (and not on equipment or systems), are the key to acceptability.

3. Risk assessments, process development, and experimental design are used to identify critical features, functions, and critical process parameters.

4. Only critical process parameters will be used as the basis on which to define the formal "qualification information."

5. All activities must contribute value to the start-up and delivery of manufacturing capacity. We won't do anything just for the sake of regulatory compliance.

6. Risk-based asset delivery. Different types of equipment and systems (custom, off-the-shelf, simple, and complex, etc.) require different levels of attention to ensure quality.

7. Value-added documents. Documents serve a useful purpose of controlling activities, they ensure completeness, and they serve as a record of what occurred. Only data which serves a useful purpose should be collected.

8. Use of supplier documentation. Supplier's standard inspection and test documentation may be used and no other documents be produced that duplicate this information, provided that documentation clearly shows the items of interest have been verified or tested in an appropriate manner.

9. Test planning. Defined tests should only be carried out once, unless there is a clear justification for undertaking further tests at a later stage of commissioning.

10. Fostering innovation. Any program must remain flexible enough to apply sound and qualified scientific and engineering judgment based on the situation at hand.

Sidebar 2. ISPE International Leadership Forum (ILF) White Paper Guiding Principles.

The final acceptance phase includes a review of the verification work to confirm that process requirements have been met and risks to the patient adequately controlled. In short, "progressively qualified."

Imagine a multi-product facility for which no product has yet been identified. How can one qualify it? In the past, the approach has been to base IQ/OQ/PQ on engineering specifications, perhaps related to a generic future product/process. But qualification is not about meeting engineering specifications, it is about being fit for purpose. Hence, qualification should be tied directly to a particular product manufactured via a particular process. Each product/process combination has a potentially unique set of process requirements, and a potentially unique set of risks to the patient inherent in the manufacturing process. Hence, the act of verifying should be to define those process requirements, identify the risks and how they are to be controlled, and then review commissioning/verification documentation to confirm those items can meet the specifications for that product/process. Of course, for a multi-product facility, the product/process requirements and risks will be similar across all products manufactured therein. Regardless, the act of qualifying now becomes a review of the verification work, which is how ASTM E2500 describes the Final Acceptance phase (§7.5).

Alternative Approach #3

Follow the ASTM standard, and label the verification documentation IQ/OQ/PQ as appropriate. However, if this approach is to achieve cost/schedule/quality improvements over today's practices, then the current non-value-added qualification practices need to be stripped away. This is easier said than done since current qualification practices that would need to be eliminated can be many, but the major ones that impact cost/schedule/quality are:

- A discrepancy handling process that mimics batch record deviations – instead, let the subject matter expert deal with the situation. If a critical aspect can't be met AFTER efforts have been made to correct, then quality needs to be involved to review the impact on patient safety with implementation of other measures to control a particular risk or otherwise meet a process requirement.

- Pre-mature implementation of QA pre-approved change control – this is not required if product for human use is not yet being manufactured. However, project teams must implement a workable system of change management using good engineering practice to ensure changes are noted, appropriate documents updated, and appropriate groups, including QA when warranted, are notified of the change.

- Use of a rigid IQ/OQ/PQ protocol template and procedures that require a laundry list of inspections or tests and a laundry list of documents for the turnover package – such prescription means every piece of equipment is subject to the same inspections or tests, leading to both unnecessary testing and also gaps in testing. There is no requirement for an enhanced turnover package in order to qualify a system. There is an expectation that firms will have accurate drawings and sufficient information to operate, maintain, and change their equipment and systems. A signature by the operations and maintenance managers should be sufficient to signify an acceptable documentation package for these purposes. Other common turnover package contents include records of pre-start-up activities and pre-commissioning inspections and checks. Having these on hand to support start-up and commissioning is a good engineering practice.

- Having QA pre-approve IQ/OQ protocols – instead, have QA pre-approve the acceptance criteria of critical aspects, and the process requirements. It is up to subject matter experts to determine how to inspect

The following is a proposed approach to aligning ISPE's GAMP® guidance with the principles embedded in ASTM E2500 and the associated update to the ISPE Commissioning and Qualification Baseline® Guide.

1. Common elements. GAMP guidance documents and ASTM E2500 share many common elements and underpinning principles. First, both advocate a life cycle that is based on requirements definition, design and design reviews, inspection and testing, and acceptance. Second, both advocate use of risk management principles to determine the scope and extent of inspection and testing (whether one calls it "validation," "verification," or "qualification."). In the case of GAMP, there are categories of automation systems. Depending on the category, one engages a set of activities designed to assure the robust operation of the system. This categorization and the quality assurance activities associated with each category is, in and of itself, a form of risk management. "Riskier" custom software is subjected to a full set of requirements, design, design review, code development, coding standards, and verification activities. Less risky off-the-shelf software is subjected to a reduced set of these activities. These and other risk analysis methods have been a part of GAMP for some time.

2. Risk. GAMP categories are one dimension of risk. Other risks assessment dimensions can include:

   a. The intended use (Is the system, feature, or function impacting to product quality? What is the nature and stage of the process?)

   b. The genesis of the function, feature, or system

   c. The ability to detect a defect or Out of Specification condition, e.g., downstream quality checks in place

Thus, automation, software, and computers must be managed within the intended use environment using an appropriate set of practices and documentation.

3. Role of Quality. GAMP guidance should revisit any specified quality unit touch points and realign those touch points with those specified in ASTM E2500 or as otherwise mandated by GMP regulations.

4. Documentation practices. GAMP guidance should revisit any recommended documentation practices and provide guidance that is consistent with minimum GMP regulations and the intent of the ASTM E2500 standard. The principle of ICH Q9 that states, "The level of effort and associated documentation should be commensurate with the risk to the patient" should be applied to all documentation practices.

5. Software delivery project controls. GAMP should provide practical guidance that aligns with practices from other industries relative to the control of software projects, such as configuration (change) management, software test reporting (discrepancy management), preliminary and critical design reviews (traceability of requirements to design, and the robustness of the logic design), etc.

6. Software verification. GAMP's most important contribution is in the area of verification strategies, based on the wide range of types of software/automation systems, from simple spreadsheet or data base applications, to enterprise systems, to MES, to DCS, and PLC-based controls, etc. GAMP guidance has been, and should continue to be, invaluable in how to approach verification of these various systems from both a structural and functional perspective. A critical analysis of the most efficient means to verify these systems may challenge the perhaps overly simplistic V-model; especially as complex PAT systems are developed and deployed which adapt a process based on a multitude of input variables. It is the authors' opinion that breaking free from the V-model so as to employ verification strategies tailored to the specific application will result in improved software quality and savings of cost and time.

Sidebar 3. Integrating ASTM E2500 and GAMP.

and test these items; QA will get to post-approve the fact that those critical aspects and process requirements were met. The GMPs require nothing more than this.

- A process that does not recognize the need to adjust the design during start-up and initial operations – some necessary initial operational checks don't have clear acceptance criteria, and in a rigid test environment, these are sometimes not performed because they don't conform to IQ/OQ/PQ structure very well. If we have a more flexible test program, a more robust test program will result. This is especially important when dealing with PAT or other complex, novel technologies.

If these practices are stripped away, then it doesn't matter what things are called; the process will be more efficient and will add more value. A rose, stripped of its thorns, is still just as beautiful and fragrant.

Integration with GAMP®

The Good Automation Manufacturing Practices (GAMP®) Community of Practice has over the years developed a number of guidance documents designed to address the software lifecycle, including the subject of computer validation. These documents have been widely accepted and used by industry. Efforts to integrate GAMP® guidance with this ASTM Standard and with the update to the ISPE Commissioning and Qualification Baseline® Guide are ongoing. At a minimum, industry needs to eliminate the duplication of effort whereby manufacturing systems and equipment are subject to an IQ/OQ/PQ program, and the associated DCS/PLC or other automation that runs this equipment is subject to a separate computer validation program. This is inefficient, costly, and time-consuming. See Sidebar 3 for a discussion of how these guidance documents might be harmonized.

Case Study

A biotech process development/clinical manufacturing facility was being

brought out of mothball status. It was desired to both leverage commissioning to streamline qualification, and also to use a risk-based approach to focus qualification. Risk assessments were used to identify the risks to the patient that could result from the manufacturing process. Risk control mechanisms were identified for each risk. These risk control mechanisms took the form of automation controls, detection mechanisms, design features, procedures, and other means. These risk control mechanisms became the substance of the IQ/OQ protocols. The protocols were developed as a checklist of these mechanisms – the protocol for a bioreactor ran all of 12 pages, with the first six being front matter. A thorough, documented commissioning of the mechanical and automation systems took place as part of start-up. Commissioning included inspections, tests, start-up procedures, setting to work activities, and anything else deemed necessary to bring the system to a fully operational state, verified to be installed and operational per engineering specifications. The execution of the IQ/OQ consisted of reviewing the commissioning work to verify each risk control element was checked satisfactorily, and that process requirements were met. The execution and report writing for an IQ/OQ protocol took all of a half a day (on average) to complete. Following IQ/OQ, a more traditional PQ was conducted for the sterilize-in-place performance, and for PQ of other typical aspects of clean utilities, etc.

Summary and Conclusion

ASTM Standard E2500, "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment" is a high level standard describing "what" must be done to deliver manufacturing solutions that meet process requirements and control risks to the patient. The details of "how" these activities are carried out are left to individual firms. ISPE's update to the Commissioning and Qualification Baseline® Guide will provide much guidance regarding these "hows." The ASTM standard is designed to conform to US and EU GMPs, and to provide an approach that is in accordance with GMPs for the 21st Century and ICH Q8 and Q9.

Teams that make use of this new standard, and who do so in a manner that does not impose the inefficient practices of qualification on what can be called "commissioning" or "verification," stand to gain significant competitive advantage in terms of time to market and facility cost, while improving the design to better meet process requirements and control risks to the patient. Manufacturers and consumers should both win as a result of this standard. ASTM E55 committee is currently working on a number of other standards relating to pharmaceutical manufacturing. The future looks promising!

Reference

1. In similar vein, process validation is the confirmation that the overall manufacturing process has been properly designed, monitored, and controlled so that the resulting drug product is of consistently high quality and meets all of its specifications.

About the Authors

Robert E. Chew, PE, is Vice President of Commissioning Agents, Inc. He initiated the effort to develop this standard, and was involved in the ASTM E2500 writing effort throughout its three year process. Chew has a BS in Chemical Engineering and is a registered Professional Engineer. He can be contacted by telephone at: +1-317-710-1530 or by e-mail at: Robert.Chew@CAgents.com.

Commissioning Agents, Inc., 1515 N. Girls School Rd., Indianapolis, Indiana 46214, USA.

David E. Petko, PE was chairman of the committee that created ASTM E2500. Petko is Senior Director of Auxilium Pharmaceuticals, Inc. He is a licensed professional engineer and holds a BS in engineering from Drexel University in Philadelphia, Pennsylvania. He can be contacted by telephone at: +1-267-960-1865 or by e-mail at: dpetko@auxilium.com.

Auxilium Pharmaceuticals, Inc., 102 Witmer Rd., Horsham, Pennsylvania 19044, USA.

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US FDA Office of Generic Drugs' Pharmaceutical Quality Initiative: Progress and Feedback on Question-based Review

by LaiMing Lee, Robert Lionberger, Lawrence Yu, Christine Mundkur, Gordon Munro, Gordon Johnston, and Joseph Famulare

This article presents the US FDA-Office of Generic Drugs' Pharmaceutical Quality Assessment Initiative that was presented at the February/March 2007 Pharmaceutical Quality Workshop in Bethesda, Maryland. At the meeting, ISPE representatives invited the FDA to submit an article on OGD's new CMC review paradigm for publication.

Introduction

The US FDA Office of Generic Drugs (OGD) developed a Question-based Review (QbR) for its Chemistry, Manufacturing, and Controls (CMC) evaluation of Abbreviated New Drug Applications (ANDAs).[1] QbR is a new quality assessment system that focuses on critical pharmaceutical quality attributes. It concretely and practically assesses a sponsor's implementation of concepts and principles of Quality by Design. QbR is transforming the ANDA CMC review into a modern, science- and risk-based pharmaceutical quality assessment. At the February/March 2007 Pharmaceutical Quality Workshop sponsored by the American Association of Pharmaceutical Scientists (AAPS), International Society for Pharmaceutical Engineering (ISPE), and the FDA, participants discussed the quality initiatives, shared progress of Question-based Review, and sought input and recommendations from the stakeholders during a breakout session. This article reports on the progress of the FDA OGD's Question-based Review paradigm and early industry feedback.

Background

The FDA has the responsibility of approving safe and efficacious drugs through the review of information in a submission package and inspection of manufacturing facilities for compliance to current Good Manufacturing Practice (cGMP). For over two and half decades, the regulation of pharmaceutical manufacturing and product quality has remained unchanged despite scientific advancements.[2] In August 2002, the FDA announced a new initiative – Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach – intended to enhance and modernize the pharmaceutical manufacturing industry and the CMC regulatory process. The pharmaceutical cGMPs for the 21st Century initiative envisions a future in which the FDA recognizes that manufacturers have the ability to link process variability to product attributes and are capable of controlling changes; therefore, can allow manufacturing changes to be made with less restrictive oversight.

The FDA OGD is encouraging their stakeholders to begin to implement FDA's Pharmaceutical cGMPs and Quality by Design (QbD) initiatives by submitting their development and manufacturing activities in their ANDAs. It is through the sharing of additional information that the FDA will better understand how generic drug sponsors design their products, develop their manufacturing processes, and establish the capability to consistently produce high quality products.

Question-based Review

The FDA Office of Generic Drugs developed a Question-based Review (QbR) for its Chemistry, Manufacturing, and Controls (CMC) evaluation of ANDAs in early 2005. QbR is an assessment system that can assess a sponsor's implementation of QbD. QbR is intended to transform the ANDA CMC review into a modern, science- and risk-based pharmaceutical quality assessment.

The goal of the CMC review of ANDAs is to ensure that the generic product is appropriately designed (a pharmaceutical equivalent to the Reference Listed Drug or RLD) and that sponsors have methods and controls in place for the manufacture, processing, and packaging of a drug that are adequate for assuring and preserving the identity, strength, quality, and purity of the proposed generic drug product. In this context, pharmaceutical quality means that consumers will

Questions to be completed by ANDA Sponsors for the Preparation of a QbR-Quality Overall Summary

2.3 Introduction to the Quality Overall Summary

- Proprietary Name of Drug Product
- Non-Proprietary Name of Drug Product
- Non-Proprietary Name of Drug Substance
- Company Name
- Dosage Form
- Strength(s)
- Route of Administration
- Proposed Indication(s)

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

- What are the nomenclature, molecular structure, molecular formula, and molecular weight?
- What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

2.3.S.2 Manufacture

- Who manufactures the drug substance?
- How do the manufacturing processes and controls ensure consistent production of drug substance?

2.3.S.3 Characterization

- How was the drug substance structure elucidated and characterized?
- How were potential impurities identified and characterized?

2.3.S.4 Control of Drug Substance

- What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?
- For each test in the specification, is the analytical method(s) suitable for its intended use, and if necessary, validated? What is the justification for the acceptance criterion?

2.3.S.5 Reference Standards

- How were the primary reference standards certified?

2.3.S.6 Container Closure System

- What container closure system is used for packaging and storage of the drug substance?

2.3.S.7 Stability

- What drug substance stability studies support the retest or expiration date and storage conditions for the drug substance?

2.3.P DRUG PRODUCT

2.3.P.1 Description and Composition

- What are the components and composition of the final product? What is the function(s) of each excipient?
- Does any excipient exceed the IIG limit for this route of administration?
- Do the differences between this formulation and the RLD present potential concerns with respect to therapeutic equivalence?

2.3.P.2 Pharmaceutical Development

2.3.P.2.1 Components of the Product

2.3.P.2.1.1 Drug Substance

- Which properties or physical chemical characteristics of the drug substance affect drug product development, manufacture, or performance?

2.3.P.2.1.2 Excipients

- What evidence supports compatibility between the excipients and the drug substance?

2.3.P.2.2 Drug Product

- What attributes should the drug product possess?
- How was the drug product designed to have these attributes?
- Were alternative formulations or mechanisms investigated?
- How were the excipients and their grades selected?
- How was the final formulation optimized?

2.3.P.2.3 Manufacturing Process Development

- Why was the manufacturing process described in 2.3.P.3 selected for this drug product?
- How are the manufacturing steps (unit operations) related to the drug product quality?
- How were the critical process parameters identified, monitored, and/or controlled?
- What is the scale-up experience with the unit operations in this process?

2.3.P.2.4 Container Closure System

- What specific container closure attributes are necessary to ensure product performance?

2.3.P.3 Manufacture

- Who manufactures the drug product?
- What are the unit operations in the drug product manufacturing process?
- What is the reconciliation of the exhibit batch?
- Does the batch formula accurately reflect the drug product composition? If not, what are the differences and the justifications?
- What are the in-process tests and controls that ensure each step is successful?
- What is the difference in size between commercial scale and exhibit batch?
- Does the equipment use the same design and operating principles?
- In the proposed scale-up plan, what operating parameters will be adjusted to ensure the product meets all in-process and final product specifications?
- What evidence supports the plan to scale up the process to commercial scale?

2.3.P.4 Control of Excipients

- What are the specifications for the inactive ingredients and are they suitable for their intended function?

2.3.P.5 Control of Drug Product

- What is the drug product specification? Does it include all the critical drug product attributes?
- For each test in the specification, is the analytical method(s) suitable for its intended use, and if necessary, validated? What is the justification for the acceptance criterion?

2.3.P.6 Reference Standards and Materials

- How were the primary reference standards certified?

2.3.P.7 Container Closure System

- What container closure system(s) is proposed for packaging and storage of the drug product? Has the container closure system been qualified as safe for use with this dosage form?

2.3.P.8 Stability

- What are the specifications for stability studies, including justification of acceptance criteria that differ from the drug product release specifications?
- What drug product stability studies support the proposed shelf life and storage conditions?
- What is the post-approval stability protocol?

Appendix A.

receive a product free from contamination that will reproducibly deliver the therapeutic benefit promised in the label.[3]

The QbR, a general framework for the CMC assessment of ANDAs, incorporates the most important scientific and regulatory review questions that focus on critical pharmaceutical attributes essential for ensuring generic drug product quality. The QbR serves two purposes for the CMC assessment of ANDAs. First, it provides a guide to the reviewer in the evaluation of whether a product is of high quality and in the determination of the level of risk associated with the manufacture and design of the generic product. Second, it provides transparency to sponsors about the logic that reviewers invoke in their CMC reviews.

The FDA OGD publicized its QbR approach beginning in 2005 and has been communicating the progress with stakeholders through various workshops, web casts, meetings, and individual industry talks. The major changes that have resulted from the QbR initiative include:

- Implementation of ICH Q8 guidances. It emphasizes that quality cannot be tested into products, i.e., quality should be built in by design.

- Submission of ANDAs in Common Technical Document (CTD) format with a Quality Overall Summary (QOS) that addresses all QbR questions. The sponsor-prepared QOS provides the primary reviewer with a quick overview of the entire CMC package and reduces the review time spent on documentation.

- Change of CMC review from the old traditional 36 point review that focuses on specification establishment to CTD-based QbR review that concentrate CMC review to product and process design and manufacturing as well as establishment of clinically relevant specifications.

- Implementation of risk-based assessment that is intended to reduce CMC supplements.

During 2006, some sponsors began to submit QOS that addresses the QbR questions in their ANDAs. Since that time, there have been many opportunities for the FDA and ANDA sponsors to meet to provide feedback to each other on the experience with this new review process. For the month of July 2007, 90% of ANDAs are in QbR format.

Workshop Questions

At the February/March 2007 Pharmaceutical Quality Workshop sponsored by AAPS, ISPE, and FDA, the FDA OGD and Office of Compliance (OC) and the generic industry had the opportunity to discuss the progress of Question-based Review during a breakout session. The session began with a brief introduction of QbR and how it is intended to assess a sponsor's implementation of QbD. Contributions from both ANDA and NDA sponsors about the use of directed questions to guide sponsors in preparing Quality Overall Summaries that lead to efficient application review were welcomed. During the session, the following questions were discussed:

1. How has the QbR made the FDA's expectations clearer? Where is there a need for additional clarification?
2. How has the need to address the QbR questions changed the generic drug development process at your company?
3. How has Quality by Design been encouraged by the QbR process? And how does QbR promote product lifecycle management?
4. What benefits has your company observed from providing a reviewer with a QOS and pharmaceutical development report? Have reviewers demonstrated a better understanding of your scientific approach and how your specifications were developed?
5. What can be done to improve the QbR process?

Even though both the FDA and ANDA sponsors had limited experience with the new review paradigm, both parties were optimistic about the QbR system. Initial feedback from some generic sponsors indicated that the QbR paradigm had somewhat impacted their existing Research and Development (R&D) practices and how they share this information with the FDA. OGD has asked generic sponsors to complete before filing some development work that previously was conducted after filing.

Workshop Findings

At the conclusion of the workshop, shared understanding and agreements between OGD and the sponsors were presented in a plenary session and included the following:

QbR has affected what ANDA sponsors do to prepare ANDA applications.

The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Waxman-Hatch Act, established the legal pathway for the marketing of generic drugs without requiring costly clinical studies. In lieu of clinical studies, demonstration of equivalent clinical performance is evaluated with bioequivalence studies. In addition to the successful demonstration of bioequivalence, the generic product also must demonstrate that it is pharmaceutically equivalent (e.g., same amount of active ingredient, same dosage form, and similarity in the inactive ingredients).

Historically, a dossier is prepared for submission by the Regulatory Affairs (RA) department of an ANDA sponsor. ANDA information, in the form of data and tables, are collected from the different departments within a company and compiled for submission by the RA officers. With the directed questions and a greater emphasis on how and why, scientists in R&D play a bigger and more important role in explaining the development history of a particular product. QbR has promoted communication among different functional teams within the company because the questions directed at the development and manufacturing processes were previously not conveyed to RA or submitted in the ANDA.

To effectively answer the QbR questions and to prepare a QOS that is most meaningful to FDA reviewers, sponsors have had to bridge the communication gap between R&D and

RA. This could be done by moving some development scientists to technical writing positions. Investing in technical writers trained in Chemistry, Pharmaceutical Sciences, or Engineering who are capable of preparing the QOS and pharmaceutical development report meant dedicating additional resources and changing hats for selected individuals.

Furthermore, the QOS is part of the International Conference for Harmonization (ICH) CTD-formatted application and unfamiliar to many sponsors. Most ANDA sponsors had to first become familiar with the adopted submission format. The FDA OGD posted on their Web site an ANDA checklist in line with CTD. QbR changed the sponsors' internal data management.

QbR questions have changed the pharmaceutical development process.

Pharmaceutical development activities include, in part, understanding the physical and chemical properties of the drug substance well enough to determine the effect they will have on the development, manufacture, and performance of the final drug product.

In the competitive nature of the generic drug industry, the time spent on exhaustive pharmaceutical development activities has been limited. When product failure arises (e.g., comparative dissolution is not satisfied), time and resources are directed to investigate and understand the cause(s). This reactive scientific investigation costs more time and money than if development work were conducted methodically early on. With QbR, development activities are conducted upfront in order to address OGD's questions. The result is more product and process understanding when the ANDA is submitted and upon approval, risk to problems like process scale-up is reduced.

For example, the FDA OGD will ask the following product design questions:

- What attributes should the drug product possess?
- How was the drug product designed to have these attributes?
- Were alternative formulations or mechanisms investigated?
- How were the excipients and their grades selected?
- How was the final formulation optimized?

The following process design questions will be asked:

- Why was the manufacturing process selected for this drug product?
- How are the manufacturing steps (unit operations) related to the drug product quality?
- How were the critical process parameters identified, monitored, and/or controlled?

With the use of these product and process design questions in QbR, the FDA has made the expectations clearer to the sponsors.

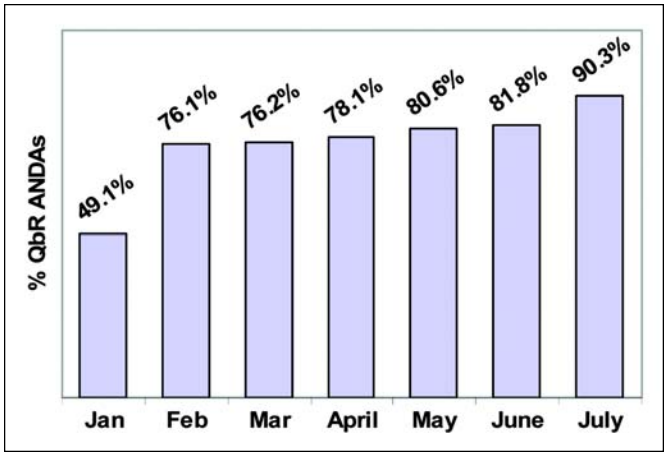

Figure 1. QbR submissions in 2007.

QbR encourages use of QbD elements and principles.

In early 2005, OGD publicized the QbR paradigm and posted the review questions on their Web page. With the directed questions, OGD encourages generic sponsors to adopt QbD to design, develop, and manufacture generic drugs. Pharmaceutical QbD means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives.[2] QbD identifies characteristics that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired attributes.[4]

Under QbD, the relationship between formulation and manufacturing process variables (including drug substance and excipient attributes and process parameters) and product quality is established and sources of variability identified. This knowledge is then used to implement a flexible and robust manufacturing process that can adapt and produce a consistent product over time. Thus, QbD consists of the following steps:

- Define target product quality profile.
- Design and develop product and manufacturing processes.
- Identify critical quality attributes, process parameters, and sources of variability.
- Control manufacturing processes to produce consistent quality over time.

Under the QbD paradigm, pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables. End product testing confirms the quality of the product and is not part of the product consistency strategy. Under the paradigm of quality by testing, a product specification is often set by observing data from a small number of batches believed to be acceptable and then setting acceptance criteria that required future batches to be the same. Since under QbD consistency comes from the design and control of the manufacturing process, the specification of

drug product under QbD should be clinically relevant and generally determined by product performance.

QbR has changed the quality assessment within OGD and has generated positive comments from the reviewers.

There are preconceived notions that more information submitted to the FDA generates more deficiency questions. This may be the primary reason why development information was not submitted in the past. The early experiences with reviewing QbR applications is that more information does not generate more questions; in fact, they generate less questions because ANDA sponsors reveal their depth of product and process knowledge in the development report. With QbR, reviewers have the confidence that critical aspects of product formulation and process development have been addressed which further assures the quality of the product.

Before QbR, many of the deficiency questions requested the sponsor to tighten the proposed specifications. This was often due to the limited understanding on the part of the reviewer on how the sponsor set the specification. As more information is being included in the ANDA and the reviewers have a more comprehensive understanding on how the specifications were determined, the deficiency questions are moving away from the numbers and are more science-based. These science-based deficiency questions inform the sponsor about what OGD considers important and are used to redirect R&D activity for future ANDAs.

And, finally, the Pharmaceutical Development Report (PDR) has been historically prepared for documentation and record keeping purposes. Having the QbR questions in mind, the development report is now more product and process designed focused. Inclusion of this information in the ANDA has provided the reviewer with a more comprehensive picture and explanation of the steps and thought processes. Sponsors are able to clearly present the rationale for the selection of excipients, selection of manufacturing process, and setting of specifications.

QbR is being developed for microbiology review and to a certain degree, bioequivalence review.

The total time for an ANDA to be approved includes the time for review by other disciplines. Even when the CMC review becomes more efficient, it will not result in faster approvals unless the other reviews also are complete. OGD is undertaking initiatives to improve the efficiency of microbiology and bioequivalence reviews.

Conclusions

In early 2006, OGD posted two example QOSs and the QbR questions (Appendix A) on their Web site.[5] As an additional aid to sponsors preparing a QOS for a QbR application, a Frequently Asked Question (FAQ) document was added to the OGD Web site on 7 June 2007. OGD expects the model examples and FAQ to help ANDA sponsors prepare a succinct and useful QOS for their applications. To further guide individuals and industry in understanding the expectations and trends with QbR, OGD gave three workshops on how to prepare an effective QOS between October and December 2006, and an additional QbR training at the GPhA ANDA Basics Course in May 2007. On 11 April 2007, OGD and GPhA held a Web cast meeting to discuss the progress of QbR and to further explain OGD's expectations for submitting Quality by Design ANDAs.

As OGD fully implements QbR in 2007, there remain the following challenges:

- How much more information and knowledge on development activities is needed for filing?
- The FDA's need is to provide more clarity on their expectation of the QOS and PDR.
- OGD is developing a risk-based approach to reduce CMC supplements.
  - Develop metrics beyond the preliminary risk assessment strategy proposed by OGD.
  - Can post-approval data be evaluated upon review or inspection and used for regulatory relief?
- For some sponsors, additional development work (e.g., process) will be needed to fully address QbR prior to submission.

Participants of the breakout session recommended the following:

- Further clarify Quality by Design and elements for inclusion in the QOS.
- Develop Question-based Review for drug substance, DMF.
- Capture all the reviewer experiences.
- Communicate OGD's QbR initiative and expectations.
- Work with stakeholders to develop a model example for design space.

The breakout session allowed all participants to understand how QbR has changed R&D and manufacturing practices, share experiences, and identify remaining concerns. With more than 360 QbR ANDAs received between January and July 2007 (Figure 1) and the majority of them in queue to be reviewed, OGD will be able to provide more comprehensive data on how sponsors are implementing QbD in the future.

The opinions expressed by the authors do not necessarily reflect the views or policies of the US Food and Drug Administration (FDA).

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About the Authors

Dr. LaiMing Lee is a Pharmacologist and Special Assistant in the Office of Generic Drugs, FDA. At the FDA, she had been actively involved with incorporating product development and process understanding concepts into the chemistry review, preparing bioequivalence studies recommendations, and is the Chair of the OGD Education Committee. Lee received her undergraduate degree in pharmaceutical sciences and PhD in pharmaceutics from the University of Michigan. She can be contacted by e-mail at: laiming.lee@fda.hhs.gov.

Dr. Robert Lionberger is a Chemical Engineer in the Office of Generic Drugs, FDA. He received his undergraduate degree from Stanford University in chemical engineering, and a PhD from Princeton University in chemical engineering. Prior to joining the FDA, Lionberger was an Assistant Professor of chemical engineering at the University of Michigan. At the FDA, his activities include development of bioequivalence methods for locally acting drugs, mathematical modeling of drug dissolution and absorption, and incorporation of product and process development information into the CMC review process. He can be contacted by e-mail at: robert.lionberger@fda.hhs.gov.

FDA, Office of Generic Drugs, 7519 Standish Pl., Rockville, Maryland 20855, USA.

Dr. Lawrence X. Yu is Director for Science in the Office of Generic Drugs, FDA. He also is adjunct Professor of Pharmaceutical Engineering at the University of Michigan and an adjunct Associate Professor of Pharmaceutical Sciences at the University of Maryland. Prior to joining the FDA, Yu had worked at both Pfizer (Upjohn) and GlaxoWellcome for eight years. He received his BS and MS in chemical engineering from Zhejiang University, his MS in pharmaceutics from the University of Cincinnati, and his PhD in pharmaceutics from the University of Michigan. A fellow of the American Association of Pharmaceutical Scientists (AAPS), Yu has authored or co-authored more than 200 papers, patent, book chapters, abstracts, and invited presentations. He can be contacted by telephone at: +1-240-276-9309 and by e-mail at: lawrence.yu@fda.hhs.gov.

Christine Mundkur is the Senior Vice President at Barr Pharmaceuticals. She joined Barr in 1993 as Associate Counsel. In September 1997, Mundkur became Director of Regulatory Affairs and Regulatory Counsel. In September 1998, she became Vice President, Quality and Regulatory Counsel and in August 2001 was promoted to Senior Vice President, Quality and Regulatory Counsel. She can be contacted by e-mail at: cmundkur@barrlabs.com.

Barr Laboratories, 400 Chestnut Ridge Rd., Woodcliff Lake, New Jersey 07677, USA.

Dr. Gordon Munro is the Senior Vice President, Quality Assurance for Watson Pharmaceuticals. He is responsible for all quality programs, ensuring a coordinated and integrated approach to quality at all of Watson's facilities. Most recently, he was Director of Inspection and Enforcement, and Acting Head of Medicines at the Medicines and Healthcare products Regulatory Agency (MHRA). Prior to the MHRA, Munro was with GlaxoSmithKline for more than 25 years. He started his career in research before holding QA/QC positions of growing responsibility for numerous divisions, including Glaxo Wellcome Operations, Glaxo Manufacturing Services, as well as several years in Glaxo's International Quality Assurance Division. In his last role, he was Director of Quality and Compliance, Glaxo Wellcome Operations in the UK. Munro has a BS in pharmacy and a Masters in analytical chemistry from the University of Strathclyde, Scotland; and a PhD in analytical chemistry from the Council for National Academic Awards. He can be contacted by e-mail at: Gordon.Munro@watson.com.

Watson Pharmaceuticals Inc., 311 Bonnie Circle, Corona, California 92880, USA.

Gordon Johnston is currently the Vice President of Regulatory Sciences for the Generic Pharmaceutical Association (GPhA). Johnston joined GPhA in 2003. Prior to joining GPhA, he served as a consultant to the pharmaceutical industry from 1999 to 2003. Johnston joined the Office of Generic Drugs, FDA, in 1987 and served as the Deputy Director from 1994 until his retirement in 1999. Before joining FDA, he served as a pharmacist in US Public Health Service facilities. He holds a BS in pharmacy and MS in healthcare administration. He can be contacted by e-mail at: GJohnston@gphaonline.org.

Generic Pharmaceutical Association (GPhA), 2300 Clarendon Blvd., Suite 400, Arlington, Virginia 22201, USA.

Joseph C. Famulare is the Deputy Director in the Office of Compliance at CDER FDA. He is responsible for a number of Drug Quality program areas, including addressing public health risks associated with legal violations; developing and overseeing drug compliance programs designed to reduce consumer exposure to risks of unsafe and ineffective drugs; monitoring the quality of human drugs through inspectional coverage, product testing, and other pre- and post-market surveillance activities. i.e., developing policies and compliance strategies to ensure that over-the-counter and prescription drugs are of high quality, properly labeled, safe, pure, and meet applicable drug approval requirements; developing policy and standards to achieve high product quality through application of current Good Manufacturing Practice requirements.) Famulare began his career as an investigator in the Newark District in 1977. He subsequently worked as a resident in charge investigator in the Buffalo district and a supervisory investigator in the New York district. Much of his fieldwork has been in the drug cGMP area. He can be contacted by e-mail at: joseph.famulare@fda.hhs.gov.

FDA - Office of Compliance, 11919 Rockville Pike, Rockville, Maryland 20852, USA.

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Programming of Quality Laboratories Using Work Flow Analysis

by Dr. William E. Ferguson

This article presents the application of workflow analysis to create a laboratory design program. Two case studies involving quality laboratories demonstrate the applicability of this technique. The benefits to both management and staff are discussed.

The focus of laboratory programming is the identification of those elements of a laboratory operation that will enable the staff to optimally fulfill the vision and mission of their organization. The subsequent design creates an environment that well supports the departmental mission.

Programming:

- Identifies the activities and the best practices employed by the scientific staff to accomplish their activities
- Determines how these activities might change in the future so that the new or renovated facility appropriately responds to change
- Arranges appropriate adjacencies of operations within the laboratory building
- Creates a layout that fosters community and connectivity among the staff

More recently, the author has been involved with the design of quality laboratories. One project in particular (first case study), required the activities and work flow be mapped so that space types and functions could be identified and the subsequent impact on the organization be determined. This project became a prime example of the benefits of workflow analysis.

This article presupposes that a properly designed laboratory optimally supports the scientific activities that scientists and technicians undertake every day. Thus, the degree to which a renovated or new facility supports, and in fact, makes more efficient these activities, is a measure of the effectiveness of the design.

First Case Study: Expanded and Renovated Quality Control Laboratories

The first case study involved a renovation of and addition to a small quality control operation in a pharmaceutical company. This operation was responsible only for materials produced in the adjacent manufacturing plant. Their laboratory organization was structured along sample types, each with responsibility for everything from sample receipt to data logging. Figure 1 provides a schematic view of the operation.

This QC operation could be considered "decentralized" since each laboratory has full responsibility for all aspects of testing for their respective sample types. There is redundancy of activities among these laboratories. This operational model often works well for smaller

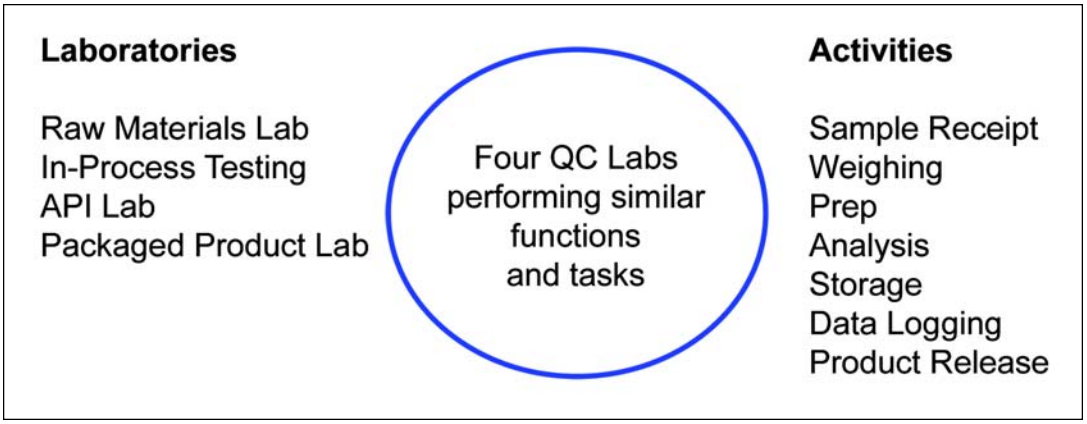

Figure 1. Client operations for the first case study.

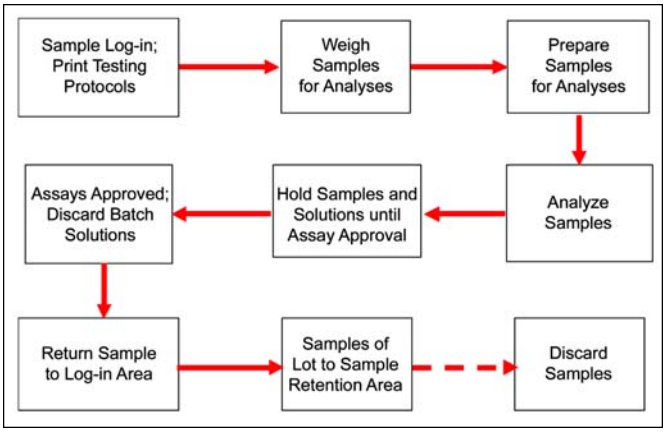

Figure 2. Flow chart of QC operation.

QC operations.

Throughout the project interview process and on into the first project planning session, the client group seemed focused on maintaining their operations in this mode. However, as we began the first programming session, this proved to not be the case.

Typically for a programming effort, we seek to determine what drives the operation, how it works and what changes if any, the client group or its management would like to instill. Thus, we identified and discussed each of the activities and sought from them their ideas on how each might be conducted more efficiently and hence how a different laboratory layout might evolve. So, for the sample receipt and handling activity, we asked if a common point of entry for all samples might be helpful. The response from the client group was unanimous and positive. This triggered closer scrutiny of the rest of their operations by our design team.

We asked if they would like to consider an alternative approach to their laboratory operation. If sample handling could be centralized, why not centralize their entire operation? This would mean designing spaces that are activity specific. For example, sample prep would have its own space and sample analysis might be accommodated by having one or more laboratories focus on specific testing methods.

Meetings with those responsible for each of the individual laboratory operations were focused on how centralization would affect their responsibilities. Generally, each was positive about the potential change, as was the area director. Staff must be reorganized so that responsibilities among those presently in charge could be redistributed to properly administer the new organization.

Continuing through the evolution of this design, there were discussions with the client representatives concerning the organizational impact of the changes expected as a consequence of this new proposal. From these discussions, there were some immediately beneficial results foreseen for the new operation.

1. Homogenization of testing types within a dedicated laboratory offered a new type of community for those performing the tests. For example, technicians performing chromatographic analyses and co-located in the same laboratory could assist each other, thereby increasing their competence.
2. Equipment suddenly needing repair might not influence workflow significantly when other such instruments were present.
3. Equipment repairs may be made more quickly, due to the increased collaboration and group problem solving.
4. Troubleshooting assay performance could be done collaboratively as well.
5. Staffing allocations would be easier to optimize over the three-shift per day operation.

The next step was to adapt the information presented in Figure 1 to the now larger venue, that of the entire department. Fortunately, many quality laboratory operations have relatively routine procedures that run on a reasonably consistent schedule. This allows easy identification of activities and the spaces to support them. From Figure 1, we can identify the steps that a sample takes as it wends its way through

Flow Chart Step	Corresponding Activities/Space Type(s)
Sample Log-in	Sample receiving; log-in; gather samples for analysis
Sample Weighing	Weigh room with balances in weigh enclosures
Sample Preparation	Prepare samples for analysis
Sample Analysis	Various analytical labs: HPLC and GC; spectroscopy, dissolution testing; microbiology; physical measurements
Sample Solution Holding	Cart marshaling area for sample solutions
Discard Batch Sample Solutions	Space for discarding materials
Sample Return to Log-in Area	Sample receiving; log-out
Samples to Storage	Sample retention area
Sample Discard	Sample discard holding room

Table A. Identification of QC space types.

Space Identification	Space Activities
Sample Handling	Sample receiving; log-in; dispensing
Materials Weighing	Weigh room with balances in weigh enclosures
Sample Preparation	Fume hoods for sample solution and analytical solutions prep
Sample Analysis	General testing: physical properties
Sample Analysis	Chromatography: GC, HPLC
Sample Analysis	Spectroscopy: AA, UV/Vis, NMR
Sample Analysis	Microbiology: prep lab, incubator room, microbiology lab
Sample Solution Storage	Cart marshalling area in lab
Sample Solution Discard	Alcove in physical properties lab
Sample Storage	Stability storage in stability chambers
Sample Storage	Sample retention

Table B. QC space list and attendant activities.

testing and ultimately to approval or rejection. This is presented in the flowchart depicted in Figure 2. After some discussion, the flowchart was determined to be representative of the present and future operation by the client group.

Initial scrutiny of this flow chart fosters identification of some of the space types. These are listed in Table A.

The next step in the process was to compile the project space list. The spaces were identified according to the activities they were to house. Considering that the area that was slated for renovation and the additional space adjacent were not overly generous, some of the activities were combined in a single laboratory. Table B presents the space list with the activities for each of the spaces.

From the space list, a rough adjacency diagram was created. This diagram approximated the arrangement of these spaces in the renovated facility. The sample storage area identified in Figure 3 was located away from the QC activities, due to the lack of available space nearby.

Without coming to an understanding of laboratory operations and subsequently creating a work flow diagram, it is likely that this quality laboratory organization would have maintained the same operating mode. The client group would have received renovated laboratories that would have supported their present operation very well. However, the workflow exercise called attention to the potential benefits of reorganization with its expected increase in productivity. This became important to the client.

Second Case Study: New Facilities for a Large Stability Operation

The second case study involved design of a new facility for a large stability organization at a pharmaceutical company. The new facility also was slated to coalesce other operations as well. However, the majority of the space was dedicated to the stability function that was to become a regional hub for the corporation.

The existing stability operations were located on a nearby manufacturing site and were fitted into available space within the main building. Thus, it was no surprise that they were not optimized in terms of space and adjacencies. The first project activity was to understand these operations and then determine the optimal workflow and the proper adjacencies of the component groups that were to be moved to the new building.

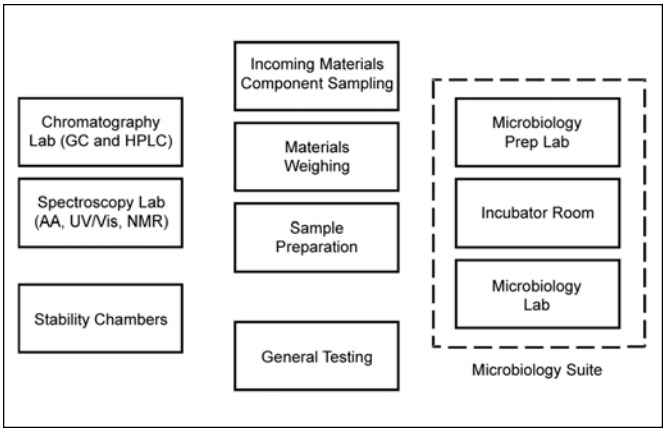

Figure 3. QC laboratories adjacency diagram.

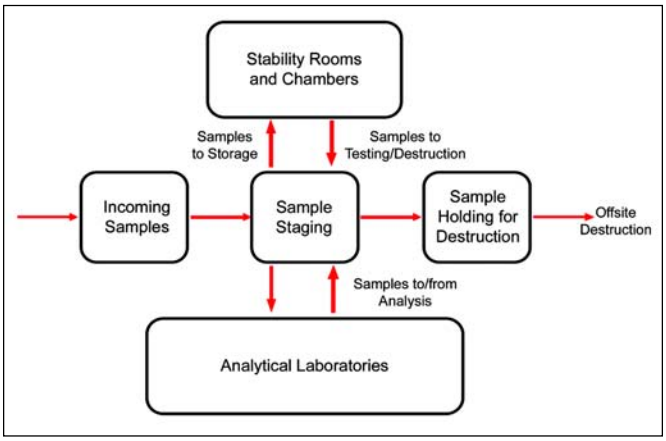

Figure 4. Flow diagram for stability organization.

After discussions with the client team and some discernment of how each of the component functions was to evolve, we compiled the following workflow diagram - *Figure 4*.

The incoming sample and sample staging rooms were small and their activities fitted into very small spaces. There was too little marshalling space for samples and their associated paperwork. In contrast, storage of stability samples in environmental rooms and chambers was reason-

Space	Space Type	Space Activities
Incoming samples	Large receiving office with hood for opening boxes	Confirm paperwork, tear down pallets, open boxes arrange and label samples
Sample Staging	Large office area with bins for organizing samples with their paperwork	Data logging, labeling, assemble kit of parts for analysis, receive kit of parts from analysis, create analysis report for stability data file
Stability Rooms and Chambers	Environmental rooms, chamber room	Storage of samples in modular environmental rooms or in stability chambers
Analytical Laboratories	Chromatography	GC and HPLC testing
	Spectroscopy	AA, IR and NIR, NMR, and UV/Vis
	Dissolution testing	Dissolution testing
	Methods Development	Development and validation of new test methods, troubleshooting of existing methods, specialty testing for off-specification samples
Sample holding for destruction	Storage room	Storage and preparation of samples for offsite destruction

Table C. Stability organization space list and activities.

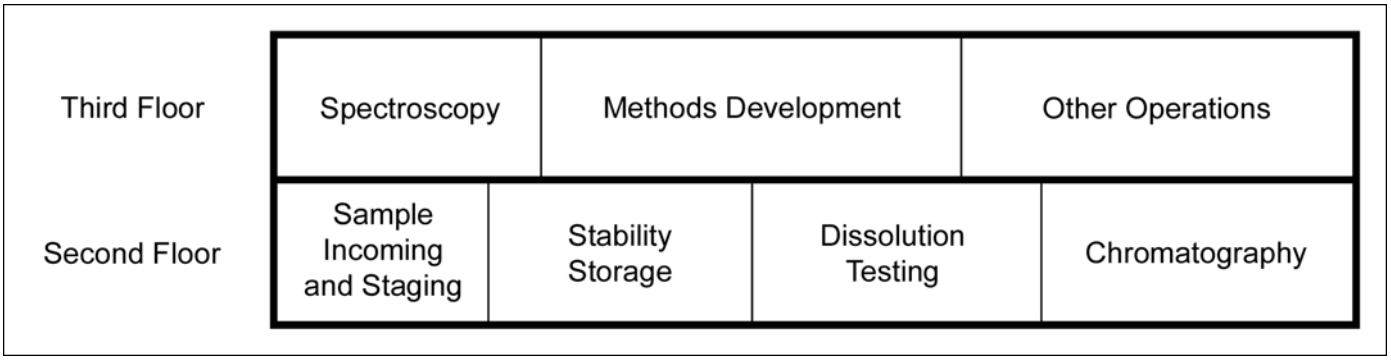

Figure 5. Stability organization stacking diagram.

ably sized for present operations, but not for the future responsibilities expressed by the company. The analytical laboratories were of good size, but the layout of furniture and storage did not adequately support the activities. Finally, the sample discard room was adequate for its use, but configured inefficiently.

Each of the blocks in the flow diagram represents a space or spaces that house activities. To assure the correctness of the flow diagram, we compiled the activities that each of these spaces was to support. The client group reviewed the list and approved it - *Table C*.

In the evolving building structure, the stability operation was to occupy the second floor and a majority of the third floor. Arranging these spaces proved to be challenging, due to the wide disparity in size of the various space types. The layout evolved by placing the incoming sample, sample staging, and stability storage rooms central to the laboratories and closest to those labs whose analytical techniques were most frequently used, namely the chromatography and dissolution testing labs. The rest of the operation was housed on the third floor. A stacking schematic is presented in Figure 5.

One of the interesting aspects of the project was the extent of discussion with the stability staff and their management. While they all had an intuitive sense of the workflow in their department, no one had ever seen it presented as a workflow diagram. Predictably, this provoked some introspection on how they might make the operation more effective and efficient to the ultimate benefit of the project and their new facility.

Summary

The use of workflow analysis to characterize operations involved the following sequence of activities for each project:

- Understand the vision and mission of the organization(s).
- Prepare a work flow analysis of the operation as it exists and ratify its accuracy with the client.
- Determine, with the client, if the work flow analysis adequately represents future operations for the department(s). Modify if necessary.
- Identify space types for each of the activities in the workflow diagram.
- Compile a space list from these space types.
- Determine optimal adjacencies for the activities.
- Review at each stage with the client group.

These project activities were followed by completion of each of the lab programs by:

- Determining individual laboratory layouts that will optimally serve the activities to be housed within
- Providing capacity consistent with the growth plan(s) for the department(s)
- Defining utility needs and the locations of these utilities in the program spaces
- Monitoring the evolution of the construction drawings to assure the functionality of the program spaces

Perhaps the most interesting aspect of this method of programming is the use of design to optimize operations. The design that resulted in the first case study was expected to substantially change the operation within the quality labs, evolving from a decentralized model with all labs performing all activities, to a centralized model with labs defined according to the activities they support. The latter could be considered an "assembly line" approach to analytical laboratory operations from which distinct benefits may accrue:

- Centralization of activities fosters collaboration among staff performing similar functions, potentially increasing competence.
- The ability to change or evolve analytical techniques is made easier and faster.
- Staff allocation and scheduling over a multi-shift operation is simpler.
- Also, it is likely that the individual laboratories are larger, and are open labs. This also fosters collaboration.

The use of workflow analysis during the programming of scientific facilities can provide management and staff a better understanding of their operations and the ability to modify operations through the use of design. This means that design can be a tool to change business practices. The consequences thereof are threefold:

- Optimized operations
- Increased productivity
- A greater competitive advantage

About the Author

Dr. William (Bill) E. Ferguson is Principal of Ferguson Consulting LLC, focusing on scientific processes and the facilities that support them. Formerly, he was director of laboratory planning and design at CUH2A, where he was responsible for managing the laboratory planning discipline, evolving best practices at CUH2A, and assisting with business development efforts. Prior to CUH2A, Bill was director of facilities planning for the Pharmaceutical Research Institute (PRI) of the Bristol-Myers Squibb Company. His responsibilities there involved the funding and creation of all facilities consistent with corporate and PRI visions. His experience includes strategic planning, design and construction/renovation of facilities, and the assessment of the impact of technology on laboratory and pilot plant layout and function. His educational background includes degrees in chemical engineering (BS and MS) and chemistry (PhD). He has experience in process chemistry and engineering, including pilot plant and manufacturing start-up of new bulk manufacturing processes. He has also taught college chemistry. He can be contacted by e-mail at: weferguson@verizon.net.

Ferguson Consulting LLC., 311 Glenn Ave., Lawrenceville, New Jersey 08648, USA.

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Drug Pedigrees: Your Supply Chain Needs Them. Are You Ready?

by Norm Howe, Stephen Goldner, and Chris Fennig

This article describes the challenges represented by counterfeit drugs and the consequences for companies that fail to recognize the threat to their value chain. It outlines the technical solutions that are available, assesses the merits of those solutions, and shows which solution fits best in different situations.

The Problem

The diversion of legitimate drugs and sale of counterfeit drugs is a significant drug industry problem, a law enforcement problem, and a health hazard to the world population. Dr. Scott Gottlieb, Deputy Commissioner for Medical and Scientific Affairs, US Food and Drug Administration, said in speech on 20 September 2005, "In 2000, the FDA opened six counterfeit drug cases, in 2003, we opened 30, and last year, we opened 58... Just this past month, on 31 August, we busted up a Lipitor counterfeiting and smuggling operation that was trafficking almost $50 million worth of the drug."

Studies by the World Health Organization estimate that counterfeit drugs are a $32 billion-a-year business. Counterfeit drugs have found their way into developed and developing countries alike. On 3 March 2006, Dr. Gottlieb spoke again on drug counterfeiting, "It has been estimated in the press that eight to 10 percent of the global medicine supply chain is counterfeit - a figure that rises to 25 percent or higher in some countries. Quantifying the problem is difficult because the counterfeiters do such a good job copying the genuine product and hiding their tracks, that it is hard to identify what is real and what is fake." Companies are faced with a growing threat to their brand value, the safety of their products, and to their bottom line. The industry is already paying the price of counterfeit drugs, but no one really knows what that cost is.

In 1987, Congress enacted the Prescription Drug Marketing Act (PDMA), which called for tracking and tracing of pharmaceuticals using paper pedigrees. The FDA, expecting that technical solutions such as Radio Frequency Identification (RFID) chips would progress more rapidly than has actually happened, has until now not enforced the legislation. In the absence of a Federal policy, it's been left to the states. Florida has taken the lead. Its law went into effect in July. California's law took effect 2 January 2007. Fourteen states have laws in the pipeline.

Drug manufacturers and distributors must now grapple with both an economic threat and regulatory chaos that will jeopardize their business. This article will define the problem, discuss the proposed solutions, and try to project the regulatory future.

Background

Although the pharmaceutical supply chain is simple in concept, the reality is far more complex. Drug containers must be traceable from the factory, through distribution, all the way to the end user. In addition, the drug must be traceable at the item or primary container level despite the fact that the primary package may get aggregated into cartons, pallets, and shipping containers. When the primary container is hidden inside a carton, line of sight trace technologies become impractical. Compounding this is the complexity of the real world supply chain - *Figure 2*.

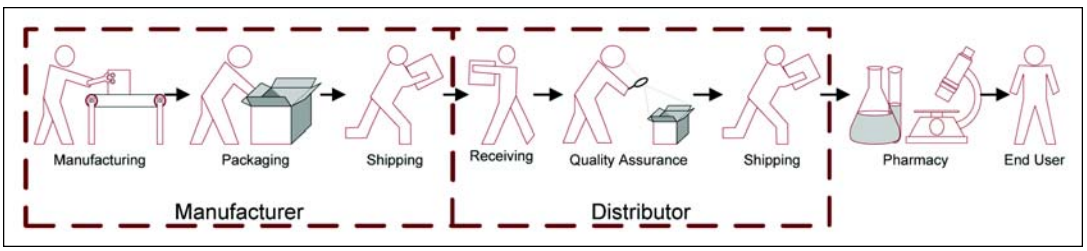

Figure 1. Conceptualized drug logistics flow.

"The significant advantage of all types of RFID systems is the noncontact, non-line-of-sight nature of the technology."

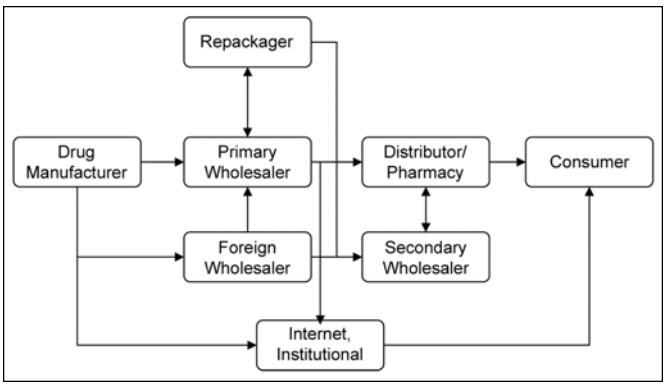

Figure 2. Actual drug logistics flow.

In 1999, the FDA published final regulations implementing the provisions of the PDMA. Both industry and Congress indicated a concern about the high cost of implementing these provisions and also raised a very real question of the seller's ability to obtain a transaction history from the prior distributors and the manufacturer. Consequently, the FDA decided to exercise enforcement discretion of the drug pedigree provisions, 21 CFR 203.3 and 203.50. In February 2004, the FDA again delayed the effective date of the drug pedigree provisions, this time until 1 December 2006, in part because it was informed by stakeholders in the US drug supply chain that the industry would voluntarily implement electronic track and trace technology by 2007. Although progress has been made, it is now clear that the use of electronic pedigree will not be widely adopted by 2007. As a result, in June 2006, the FDA announced that it did not intend to delay the effective date of sections 203.3 and 203.50 beyond 1 December 2006.

The Solutions

The three contenders vying to be the solution of choice for drug pedigrees are paper, bar codes, and Radio Frequency IDentification (RFID). RFID is the technology that the FDA envisioned when it delayed the effective date of the drug pedigree provisions of the PDMA in 2004. However, RFID is not the only technology which could potentially solve the impending drug pedigree crisis. Bar codes and old fashioned paper are in the game; especially bar code systems, which are currently used on all shipments. But neither paper nor one-dimensional bar codes meet the need when one adds up the monumental amount of data that needs to be manipulated if traceability down to the item level is required. Two-dimensional bar codes can carry substantial amounts of data, but they cannot carry enough information to identify the drug down to the item level. Plus, they can be counterfeited more easily than the drug itself. Any type of bar code still has the operationally inefficient requirement of line of sight data capture so the bar codes cannot be hidden on the inside carton on a pallet, for instance. Also, the amount of time that it takes to scan a bar code is significant since only one can be read at a time by a scanner.

RFID tags come in a wide variety of shapes and sizes. Paper-thin tags, pasted onto books and files, can be hidden between pages. Tags can be screw-shaped to identify trees or wooden items, or credit-card shaped for use in access applications. The anti-theft hard plastic tags attached to merchandise in stores are RFID tags. In addition, heavy-duty 5-by 4-by 2-inch rectangular transponders which are used to track intermodal containers or heavy machinery, trucks, and railroad cars are also RFID tags. The type that is most applicable to the pharmaceutical industry comes in the form of razor-thin tags that are applied to product and shipping containers for purposes of tracking and identification.

The information encoded on the RFID tag can be read by an antenna and reader mounted on a dock door or carried as a hand-held. The antenna transmits a signal to the tag and the tag transmits its information back to the antenna. Unlike a paper-based system, RFID follows products automatically. With each transaction, whether it's the original filling of the primary container, packing into a carton, palletizing, or shipping, the package is scanned and the transaction is recorded. Each package has a serial number and once the bottle or the smallest serial-numbered part of the chain is opened, the pharmacy electronically flags that number. From that point on, if that serial number were to come up again in the system, i.e., if a counterfeiter tried to reuse that radio-tagged bottle, it would be clear that something is wrong. The significant advantage of all types of RFID systems is the noncontact, non-line-of-sight nature of the technology. Tags can be read through a variety of substances such as paint, cardboard, and other visually and environmentally challenging conditions, where barcodes or other optically read technologies would be useless. RFID tags also can be read in challenging circumstances at remarkable speeds, in most cases, responding in less than 100 milliseconds.

There are two general types of RFID technology; Active RFID and Passive RFID. The distinction lies with the way the RFID chip is powered. Active RFID chips are powered by an internal power source, a battery. Passive RFID chips are powered by energy transferred from the reader. Passive RFID chips typically store about 128 bytes of information, whereas Active RFID chips can store a thousand times as much, but can be as big as a carton of cigarettes. Because of cost and size differences, only Passive RFID chips are used for large numbers of items so we will restrict our discussion from here on to Passive RFID chips.

The RFID story is complex because even within the Passive RFID chip types there are subtypes that are competing to become the de facto solution for the Drug Pedigree prob-

	PROS	CONS
High Frequency (HF)	- Maturity - Water insensitive - Global acceptance	- Short range - Low data transfer - Price
Ultra High Frequency (UHF)	- Long range - Rapid data transfer - Inexpensive	- Material dependent - Regionally dependent - Potentially harmful to drugs' structure
Near Field UHF (NF)	- Water insensitive - Air interface is global - Inexpensive	- Not in production - Numerous frequency bands - IP issues outstanding

Table A. Pros and Cons of the three RFID technologies.[1]

lem. Based on the Pharmaceutical Benchmark (the only objective, scientific study of RFID for use in the pharmaceutical supply chain of which the authors are aware[1]), the three RFID contenders, **High Frequency (HF), Ultra High Frequency (UHF), Near Field UHF (NF),** each have their pros and cons - *Table A*.

The study analyzes the RFID use cases that need to be deployed in order to track and trace drugs throughout the pharmaceutical supply chain with RFID technology. HF can be used in close proximity to water, such as a vaccine vial, while far field UHF cannot. But UHF has a much longer reach than HF. Beyond 12 inches HF does not function, whereas UHF is effective up to 36 inches as reflected in Figure 4. In addition, UHF is more sensitive to the orientation of the chip relative to the antenna - *Figure 4*. UHF is the most appropriate technology for capturing tag data from cartons arranged on a pallet. Therefore, the supplier/distributor must be careful to deploy technology appropriate to each use case. Near Field UHF may be the single solution for the future, but is not yet ready for prime time.

No matter which technology is chosen manufacturers and distributors will have to make sure that their installations conform to FDA regulations. Each drug will have to be stability tested to ensure the signals do not degrade their potency and each drug company will have to get FDA approval for revised labels that contain RFID chips and revised bar codes.

What Are Your Competitors Doing?

California's drug-pedigree legislation took effect on 1 January 2007. Amphastar Pharmaceuticals, in conjunction with its distribution partners, is implementing e-pedigree software. It is working to institute a system for tracking its drugs in the supply chain and verifying their authenticity. Because it manufactures primarily low-margin generic drugs, the company decided to use two-dimensional serialized barcoded labels instead of RFID tags to identify and authenticate its products. Amphastar considered using RFID technology for its e-pedigree system, as it knows RFID tags can automatically be read and matched against the serial number in the e-pedigree document, eliminating the manual scanning needed with bar codes. However, for most of its drugs, RFID tags are too costly. But that may soon change. The International Standards Organization (ISO) has approved the EPC Gen 2 Class 1 UHF standard, ratifying it as an amendment to its 18000-6 standard. Passage of Gen 2 as a global standard could foster greater competition in the passive UHF RFID systems market, thereby lowering RFID hardware costs for pharmaceutical companies and other end users, in the last 12 months, both HF and UHF tags have dropped in price significantly.

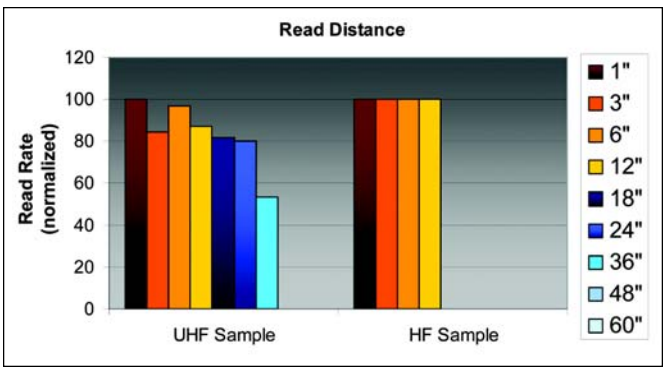

Figure 3. The effect of distance on read-rate for UHF and HF systems, courtesy ODIN labs.[1]

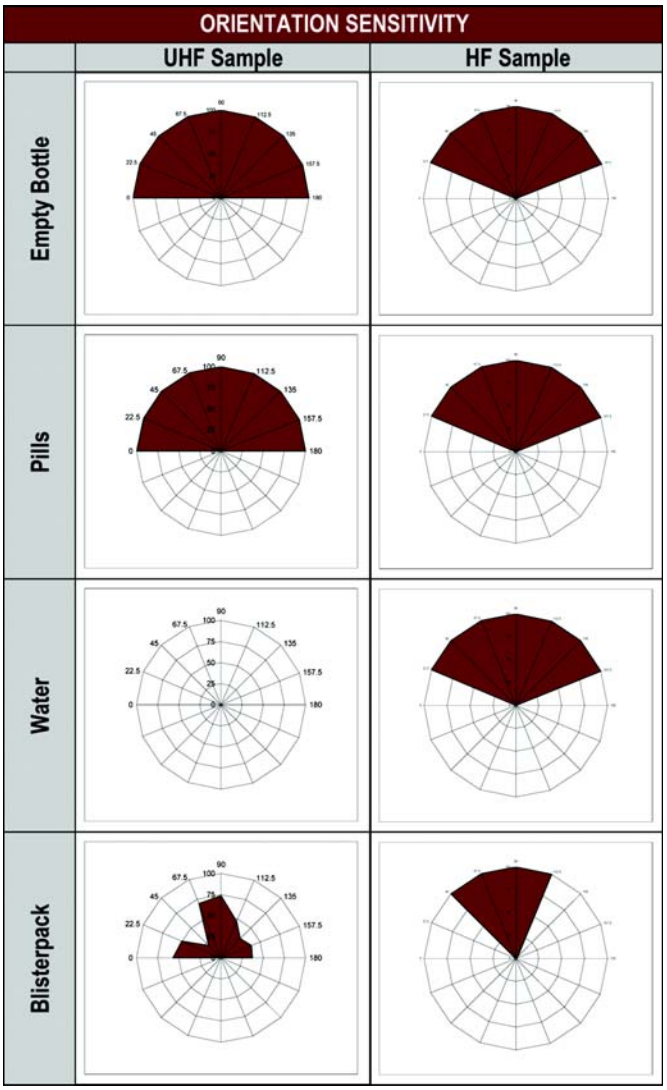

Figure 4. Orientation sensitivity of the RFID chip as a function of RFID technology and container type, courtesy ODIN labs.[1]

Considering a global drug (made in several countries and sold worldwide), Pfizer decided on HF technology for what is arguably the most famous public case of anti-counterfeiting. Their interest in RFID technology dates to a 2003 case involving bogus Lipitor. That very public case spurred Pfizer to participate in early FDA pilot programs. At a cost of approximately $5 million, Pfizer is putting HF RFID tags on bottles and cases, and UHF on pallets of another important brand, Viagra.

Where Do We Go from Here?

Pharmaceutical companies must now ask themselves how they will respond to the Drug Pedigree challenge. There are really three questions that need to be answered. What technology will we use? How will our technological response be regulated? And what will it cost? We have discussed the technology question and unfortunately we cannot give you a silver bullet solution that you can roll out tomorrow.

On the regulatory side, the FDA has said that it will phase in its enforcement activities following a risk-based approach driven by four factors:

Factor 1 – High Value in the US Market
Factor 2 – Prior Indicators
Factor 3 – Reasonable Probability
Factor 4 – Other Violations of Law[2]

Whichever technical solution you choose beyond pure paper will have to be proven to be highly reliable using scientifically valid techniques. Any records that are explicitly required by the regulations that you choose to keep in electronic form will be subject to Part 11.

The only thing we can really predict about the cost of Drug Pedigree solutions is that they will be significant. The cost of chips, readers, antennas, and incremental labor can be estimated. But while the cost of RFID chips and readers may influence the choice of technology, that cost issue might turn out to be trivial compared to the cost of dealing with all the data that will be generated if all drugs have to be tracked at the item level into all USA distribution systems. That data will have to be transmitted and stored somewhere. Someone will have to write the software to flag inconsistencies. More significantly, no process has stepped forward to serve as the platform for the billions of transactions and the myriad methods of data recovery and transmission. The system can not run without a way to reliably store and transmit the data to all stakeholders: drug companies, wholesalers, retailers, and the FDA. Whether there is a satisfactory economic return on that investment will probably never be known because the costs that the solutions prevent, such as lost revenue, lost brand value, and product safety, are so hard to measure.

Lastly, even the best technical solution will not work unless the inconsistencies that the system finds are solved. Someone will have to act upon those inconsistencies and enforce legal action where necessary. Otherwise, all the hardware and software will have been installed for nothing.

References

1. Summary findings from the *Pharmaceutical Item Level RFID Benchmark: Battle of the Frequencies* presented by Chris Fennig of ODIN technologies during his talk at *RFID for Pharmaceuticals* on 2 August. The full report is available at www.odintechnologies.com/store.
2. FDA "Draft Compliance Policy Guide 160.900 Prescription Drug Marketing Act – Pedigree Requirements under 21 CFR Part 203" June 2006.

About the Authors

Norm Howe got his BS in chemistry at UC, Berkeley, and a PhD in chemistry at UCLA. He has held many management positions in the pharmaceutical industry, most in production. He has led a number of cross functional cost reduction, product development, and business optimization teams. Howe is a Senior Partner at Validation and Compliance Institute, LLC, a consulting firm which helps companies to comply with FDA regulations, and supplies expert witnesses. He is a member of ISPE and the American Chemical Society. For recreation, he likes to play golf, which he finds to be very cost effective on a dollar per stroke basis. He can be reached by telephone at: +1-734-740-9924 or by e-mail at: howen@vcillc.com.

Validation and Compliance Institute, 1529 Boxford Rd., Trenton, Michigan 48183, USA.

Stephen Goldner is the Founder and Principal Officer of Regulatory Affairs Associates (RAA) - a national leader in getting medical devices and drugs successfully approved by the FDA. A chemist and an attorney by training, He has more than 30 years of experience as a regulatory professional. Prior to forming RAA, Goldner served as the vice president of Regulatory Affairs for Ferndale Labs in Ferndale, Michigan. He also served as the vice president of Regulatory Affairs for ICN Pharmaceuticals, now Valeant Pharmaceuticals, in Costa Mesa, California. Throughout his regulatory career, he has developed both a strong track record of success and strong working ties with the FDA. These interactions have included work on NDA/ANDA, 510(k), IND submissions, QA/QC validation, and insured GMP compliance. Goldner is noted for his professionalism, knowledge, and ability to navigate successfully in the complex regulatory world of medical device and drug approval. During his prolific career, he has generated more than half a billion dollars in revenue for his various employers and clients. He is an active member of the Regulatory Affairs Professionals Society (RAPS) and serves on the board of MichBio. In addition to his passion for getting new medical devices and drugs approved, he enjoys traveling, reading, music, good food, and conversation, and is active in his faith community. He can be contacted by telephone at: +1-248-855-5595 or by e-mail at: sgoldner@regaffairs.net.

Regulatory Affairs Associates, LLC., 30833 Northwestern

Hwy., Suite 121, Farmington Hills, Michigan 48334-2581, USA.

Chris Fennig is responsible for leading strategic client engagements and R&D activity at ODIN technologies. He has focused on the emerging RFID industry since its inception and has successfully engaged leaders in the industry through his professional consulting services. His experience includes direct interaction with Wal-Mart's top suppliers, leading Aerospace companies, and global pharmaceutical companies designing and implementing novel RFID solutions. Fennig received his MS in physics entrepreneurship from Case Western Reserve University, a program dedicated to empowering physicists as entrepreneurs and his BS in engineering/physics from Taylor University in Upland, Indiana. He can be contacted by telephone at: +1-703-822-3776 or by e-mail at: chris@odintechnologies.com.

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Introducing the New 2007-08 Board of Directors

ISPE is pleased to announce its new International Board of Directors for the 2007-2008 year. The Board was selected by Members this past September through an international ballot. They were formally introduced to our membership at the 2007 Annual Meeting. Each will serve the Society for a term beginning 6 November 2007.

Chairman of the Board

Bruce Davis
Global Capital Director at AstraZeneca in the United Kingdom, covering all business areas including operations, R&D, and commercial.

"The healthcare industry is changing rapidly in terms of patient and government demands, cost pressures, and product complexities. Research, development, and operations are increasingly working closely together to maximize product and process understanding. Technologies – both simple and complex – to support product development and manufacturing are key to this understanding. This has meant professionals within the industry need to develop skills embracing science and engineering, as well as being highly adept at managing business, technical, and global demands. ISPE has a significant role to play in supporting and helping such professionals. Our volunteer status, our international presence, and our links to the regulators enable ISPE to take a lead in providing the training and education that our industry wants – be it international events, local seminars, or publications. I would support the ever strengthening links between science and engineering and would encourage greater understanding and communication internationally. I would encourage ISPE to provide the tools and training that are needed to support the industry's professionals – whether individuals are from large or small companies, from small or large molecule background, from generics or new products, from manufacturing companies, suppliers, agencies or academia, or from different countries around the globe."

Vice Chairman

Charles P. Hoiberg, PhD,
Pfizer, Executive Director, Regulatory CMC - Policy and Regulatory Environment group, Maryland, U.S.

"For future membership growth and increased importance, ISPE faces several daunting challenges given the changing environment of the pharmaceutical industry and the regulatory agencies. Pressures are increasing on the global industry to develop new drugs, reduce manufacturing costs, and incorporate innovative approaches, such as process analytical technology, quality by design, and the "desired state." Similarly, the regulatory agencies are reassessing their approval processes and GMP practices and reengineering for the 21st century. Given ISPE's highly technical membership, its excellent conferences and training programs, and its good relations with the regulatory authorities, ISPE has a great opportunity to play an integral role to ensure success for itself and the pharmaceutical community through new initiatives, such as Product Quality Lifecycle Implementation (PQLI). As Vice Chairman of ISPE, I plan to play an important role in the implementation of change that will continue the success and engineering/scientific leadership that ISPE represents."

Treasurer

Alan Mac Neice
Project Director for Biologics, Elan's Biopharmaceutical Science, Athlone, Ireland

"The pharmaceutical industry is in the midst of a fundamental evolutionary change. In the past, business and regulatory paradigms acted as brakes to change in pharmaceutical manufacturing. That is no longer the case. Regulators are pushing the industry to catch up with other manufacturing industries in the application of science driven techniques to improve the quality, efficiency, and efficacy of manufacturing operations. The commercial environment is pushing in the same direction as the old business models are failing to deliver. The new pharmaceutical industry will be driven by technical people who are educated, trained, and well informed. They will need easy access to a vast body of knowledge that is current and evolving. They will also need access to networks of knowledgeable professionals. It is ISPE's role to meet the needs of these people. I believe my vision of the industry, its people, and ISPE will enable me to clearly see the correct path forward for our organization in a challenging and changing world."

Secretary

Andre Walker
Director of Manufacturing Engineering, Biogen Idec's Commercial and Clinical Operations, Massachusetts, U.S.

"Changes in regulatory philosophy create the opportunity for the pharmaceutical industry to leverage sound science and engineering practices in order to speed products to market and increase efficiencies. ISPE is in the forefront of this paradigm shift, and uniquely positioned to catalyze change across the broad spectrum of functions required to develop, manufacture, and distribute therapies. I feel my varied experience within the Society has provided a solid foundation for me to work alongside ISPE's fantastic volunteers and professional staff as we prepare the Society for the changes facing the membership and the industry."

Introducing the New 2007-08 Board of Directors

Continued.

New Directors

Nuala Calnan
Principal Consultant, Project Management Group, Dublin, Ireland
"Our industry is at a fulcrum point of unprecedented change. The cost of drugs continues to rise, while the political pressures to demonstrate value for money is increasing. This rising cost is largely driven by sharp increases in R&D funding, yet productivity is in decline. However, demand for safe and effective medicines continues to rise as the population ages and new medical needs emerge. In conjunction, the regulatory framework is transforming. Now we are being encouraged, even empowered, to promote innovation in how we develop, deliver and manufacture our products. The need for a dynamic new approach is clear and the time is now. I strongly believe that ISPE is well positioned to not only influence this transformation, but to play a leading role in defining and implementing this new approach. Building upon the ISPE's already unique relationship with the regulators, I want to see us expand our global reach by developing stronger ties with European and Asian regulatory bodies. I believe we must focus on knowledge creation and begin to truly leverage new technologies to facilitate worldwide collaboration and communication of this knowledge directly to our members. We must challenge ourselves by innovating the way the Society operates. Being part of the International Board, I wish to be an enthusiastic and determined voice to engage the Society in fulfilling our role in the transformation underway."

Charlotte Enghave, PhD
Senior Consultant, Finished Product Department, NNE Pharmaplan, Soeberg, Denmark
"ISPE has from the beginning of my career had a great influence and impact on my work life. I believe that it's important to continuously increase your own competencies. I would like to support ISPE to continuously improve the services that we provide, those being conferences, guidelines etc. If ISPE shall continue to be "the Society of choice," then we need to look at improving the benefits for the members both locally and internationally to secure new members, but for me even more important to retain members. I would like to ensure that members have a high influence on ISPE and the associated benefits. I believe that the networking opportunities in ISPE are a great asset for all of us and this should continue in the future. The forming of the Communities of Practice (COPs) is an important step to increase the possibilities to connect people within an area of interest. I think that there still is work to be done and would like to contribute to having the full benefit of the COPs."

Nigel Frost
Managing Director, Thermal Transfer Ltd., Derbyshire, United Kingdom
"ISPE is about people, nearly 25,000 of them from all four corners of the world, united by their vocation in life, the pharmaceutical industry. Their industry. Our industry. Having been fortunate enough to spend more than 20 years in this sector, my 'raison d'etre' for standing as a board candidate is to put something back into the industry for our future generations. I intend to challenge the status quo and avoid complacency, such that we can continuously innovate and push forward our preconceived boundaries. To survive, however, we must remain fit. Ever tightening financial constraints mean we have to not only be technically innovative, but also ensure that we are commercially aware; delivering value for money solutions to ensure that the medicines we ultimately produce can benefit as many individuals as possible. We need to learn from other industries, proudly copying their ideas, but adapting them to suit the specialist needs of our market. Unnecessary complication and bureaucracy must be challenged, not accepted. With such a wide variety of facets and disciplines, I believe the way forward is to provide a harmonious environment, such that like-minded people of diverse skill bases can come together for a common purpose. If successful in this nomination, l will serve you, my fellow ISPE members, with passion and vigour; but will not be frightened of taking a non-traditional approach if this achieves our common aim."

Damian Greene
Director / Team Leader, Pfizer Global Manufacturing (PGM), New York, U.S.
"ISPE must deliver value to its membership – to recruit new members, and more importantly, to retain our existing membership. We can do this by improving our systems for members to connect with other members. Recognizing that only a small fraction of our membership is able to regularly attend the large meetings and conferences, we must make better use of the communications tools now available. The tens of thousands of pharmaceutical industry professionals who make up the membership of ISPE are an unparalleled repository of specialized information and expertise. In today's competitive business environment, members need immediate access to this resource. The Communities of Practice are a step into this new future for ISPE. These communities will provide a forum for community members to help each other solve everyday work problems and engage in active networking; to develop and disseminate best practices, guidelines, and procedures for use by community members; and

Introducing the New 2007-08 Board of Directors

Continued.

will manage the ISPE knowledge-base."

David E. Petko, PE
Senior Director, Auxilium Pharmaceuticals, Inc., Pennsylvania, U.S.
"As new challenges develop for global industries, ISPE must continue to strengthen its position as the integrator for academia, government, and industry. We have identified many opportunities to work with industry and regulators worldwide, offering our technical assistance as they begin new risk-based initiatives. Recently, ISPE developed a new ASTM Standard for "risk-based commissioning and qualification," taking ISPE beyond the realm of Baseline® Guides. In addition to our increased role in the development of worldwide standards, we are also improving our ability to disseminate knowledge to our membership as well as regulators via our expanded educational platforms and joint training programs. The ability to influence regulatory bodies and transfer knowledge has certainly created a competitive advantage for our membership. I look forward to the interaction with colleagues from around the world as we move forward in this ever-evolving global environment."

Re-Elected Directors

Arthur (Randy) Perez, PhD
Executive Expert, IT Quality Assurance, Novartis Pharmaceuticals Corp., New Jersey, U.S.
"Recent trends have presented ISPE with unusual challenges during my two years on the International Board of Directors. A combination of factors have adversely affected the Society's income, ranging from reduced spending by pharmaceutical companies to increased competition from for-profit organizations for attendance at our conferences and training programs. Nonetheless, through careful management of our resources during this difficult time, we have been able to continue to provide high value to the industry, launching important programs such as the Certified Pharmaceutical Industry Professional℠ and the *Journal of Pharmaceutical Innovation*. We continue to develop and publish work products that are hailed by both industry and regulators, such as the Baseline® Guides, the forthcoming GAMP® 5, and several Good Practice Guides. In addition to continuing to contribute to ISPE technical publications, I am working on several teams involved in tailoring ISPE's programs to the needs of today's membership, including new conference models with increased interaction with attendees, new technology-based options for training, and improving the overall experience for our volunteers, without whose hard work ISPE could not have grown to become an effective partner for both industry and regulators."

Stephanie Wilkins, PE
President, Pharma-Consult US, Inc., New Jersey, U.S.
"The past two years have been challenging for the pharmaceutical industry with increased demand for cost efficient operations without sacrificing quality and ISPE has certainly been impacted by this challenge. It is more important than ever that ISPE remain focused on its core business/mission to assist the industry in rising up to and meeting the challenges. By providing sound educational programs and technical documents that address harmonized scientific risk-based approaches to providing safe medicines to the public, ISPE is truly assisting the industry in lowering production costs, improving process efficiencies, increasing quality, and meeting regulatory compliance. If re-elected to the International Board of Directors, I will strive to make sure ISPE prepares these quality programs and documents as well communicate with the membership on how each member can be a voice to help meet the challenges ahead."

The following Directors were elected in 2006 to serve a two-year term:

Joan Gore is the Manager of the US Clinical Trial Planning and Packaging organization at Eli Lilly and Co. Gore, a registered pharmacist, has expertise in both oral and parenteral manufacturing, packaging, parenteral formulation development, CT material supply, GMPs, import/export regulations, supply chain management, global business process improvement, and third party management.

Tomiyasu Hirachi is Representative Director and President of Qualicaps Co., Ltd. He is one of the founders and the first Chairman of ISPE Japan Affiliate. He is contributing to ISPE Japan Affiliate as a Former Chairman. Hirachi is a member of ISPE Professional Certificate Commission and International Leadership Forum. For more than 35 years, he has been involved in engineering and the pharmaceutical industries.

John Nichols, an engineer with more than 30 years of experience in the Life Sciences industry, is currently Director of Pharmaceutical Technology at Foster Wheeler. In this role, he is responsible for global coordination of technology while providing consultancy for specific projects. Prior

Introducing the New 2007-08 Board of Directors

Continued.

to this, Nichols was Engineering Director for Extract Technology Ltd., and Manager of Pharmaceutical Engineering for Foster Wheeler Reading Office, where he was responsible for staff involved in the design of bulk pharmaceuticals, bio-chemicals, and secondary finishing facilities.

As immediate Past Chairman, Jane Brown will serve as a Director for one Year.

Jane R. Brown is Manager, GMP Compliance for GlaxoSmithKline in Research Triangle Park , North Carolina , USA . She has been involved in Quality Assurance/ Regulatory Compliance in the pharmaceutical and medical device industries for more than 20 years. Brown has been a member of ISPE since 1993, and has served on the Board of Directors for the Carolina-South Atlantic Chapter and as President of that Chapter.

Six CPIPs Conferred

ISPE-PCC Awards First CPIP℠ Credential for Industry Professionals

The first international Certified Pharmaceutical Industry Professional (CPIP℠) credential – made available through the ISPE Professional Certification Commission (ISPE-PCC) – has been awarded to four industry professionals. The first testing period was held this summer. So far, six ISPE Members have been conferred at CPIPs.

This new credential offers the first competency-based international certification for pharmaceutical professionals and is helpful to the pharmaceutical industry in general by qualifying professionals to a global competency standard through demonstrated education, experience, and a rigorous examination. The following individuals have been conferred the CPIP:

- **Mr. Anders Brummerstedt**, CPIP, Manager Computer Compliance, NNE Pharmaplan, Soeborg, Denmark
- **Mr. Chuck Clerecuzio,** CPIP, Vice President of AMEC E&C Services, Inc., Plymouth Meeting, Pennsylvania, U.S.
- **Mr. Damian Gerstner**, CPIP, President, sys-tek, Blue Springs, Missouri, U.S.
- **Mr. Andrew A. Signore**, P.E., CPIP, CEO of IPS, Lafayette Hill, Pennsylvania, U.S.
- **Ms. Tiffany G. Tomlinson**, CPIP, Manufacturing Manager, IDEXX Pharmaceuticals, Inc., Greensboro, North Carolina, U.S.
- **Mr. Andre Walker,** CPIP, Director of Manufacturing Engineering for Biogen's Commercial and Clinical Operations in Cambridge, Massachusetts, U.S.

"We are pleased to bring this credential to the industry," said Jerry Roth, P.E., Director of Professional Certification. "It supports the U.S. Food and Drug Administration's acknowledged need for change within the pharmaceutical industry to improve drug product safety and quality and consumer cost effectiveness. We are delighted that ISPE can continue to be a catalyst for change and help move the industry forward."

Already, the CPIP credential is hailed by industry leaders as beneficial to team leaders, allowing the ability to impact greater quality and efficiency in their specific roles; along with using the CPIP credential to qualify project teams and support ongoing professional development. To learn more about the credential and how to apply for eligibility, visit www.ispe-pcc.org.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

Mark Your Calendar with these ISPE Events

December 2007

3 - 6 2007 ISPE Tampa Training Courses, Skills and practical knowledge for water, auditing, risk, regulatory, and biotechnology professionals, Renaissance Tampa Hotel, Tampa, Florida, US

5 New Jersey Chapter, Holiday Dinner Cruise, Leave From Lincoln Harbor Marina, Weehawken, New Jersey, US

6 Central Canada Chapter, Toronto Christmas Dinner, Toronto, Ontario, Canada

6 Pacific Northwest Chapter, End of the Year Social with Networking and a Tour of Redhook Ale Brewery, Woodinville, Washington, US

6 Puerto Rico Chapter, Risk Management Track, Puerto Rico, US

7 Central Canada Chapter, Montreal Christmas Dinner, Montreal, Quebec, Canada

11 Italy Affiliate, Gamp Steering Committee Meeting and Christmas Night Event, Milan, Italy

11 Delaware Valley Chapter, Holiday Party, University of Pennsylvania Museum of Arch, and Anthr., Philadelphia, Pennsylvania, US

12 Italy Affiliate, GAMP Italia Forum, Milan, Italy

15 Puerto Rico Chapter, Christmas Activity, Puerto Rico, US

January 2008

15 Central Canada Chapter, Toronto Breakfast Seminar (Pharmaceutical Session), Toronto, Ontario, Canada

16 Central Canada Chapter, Montreal Breakfast Seminar (Pharmaceutical Session), Montreal, Quebec, Canada

17 Central Canada Chapter, Quebec City Breakfast Seminar (Pharmaceutical Session), Quebec City, Quebec, Canada

17 New Jersey Chapter, Commissioning Event, Holiday Inn, Somerset, New Jersey, US

24 New England Chapter, BioPharma 2008 with Keynote Speaker, Crowne Plaza Hotel, Warwick, Rhode Island, US

24 San Diego Chapter, Biosite Facility Tour, San Diego, California, US

February 2008

25 - 28 2008 ISPE Tampa Conference, In depth seminars on biotech processing, validation, aseptic processing, PAT, GAMP 5, advanced automation and process control, critical utilities, disposables, and operational excellence, Exhibits and Sponsorships available, Hyatt Regency Tampa, Tampa, Florida, US

21 New Jersey Chapter, Career Fair, Holiday Inn, Somerset, New Jersey, US

28 San Francisco/Bay Area Chapter, Vendor Night, South San Francisco Conference Center, South San Francisco, California, US

Dates and Topics are subject to change

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Architects, Engineers – Constructors

Austin AECOM, 303 E. Wacker Dr., Suite 900, Chicago, IL 60601. (312) 373-7700. See our ad in this issue.

CH2M Hill, PO Box 22508, Denver, CO 80222. www.ch2mhill.com. See our ad in this issue.

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

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

IPS – Integrated Project Services, 2001 Joshua Rd., Lafayette Hill, PA 19444. (610) 828-4090. See our ad in this issue.

Parsons, 150 Federal St., Boston, MA 02110. (617)-946-9400. See our ad in this issue.

Bioreactors/Fermenters

Cleanroom Products/Services

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

Employment Search Firms

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

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Millipore Corp., 290 Concord Rd., Billerica, MA 01822. (800) MILLIPORE. See our ad in this issue.

MKS Instruments, 5330 Sterling Dr., Boulder, CO 80301. (800) 345-1967. See our ad in this issue.

Siemens Water Technologies, 10 Technology Dr., Lowell, MA 01851. (978) 934-9349. See our ad in this issue.

Instrumentation

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

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Hurst Corp., Box 737, Devon, PA 19333. (610) 687-2404. See our ad in this issue.

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The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
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PS Form 3526, October 1999 (See Instructions on Reverse)

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b. Paid and/or Requested Circulation (1) Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. (Include advertiser's proof and exchange copies)	13,072	13,229
(2) Paid In-County Subscriptions Stated on Form 3541 (Include advertiser's proof and exchange copies)	0	0
(3) Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	8,208	8,382
(4) Other Classes Mailed Through the USPS	0	0
c. Total Paid and/or Requested Circulation (Sum of 15b. (1), (2),(3),and (4))	21,280	21,611
d. Free Distribution by Mail (Samples, complimentary, and other free) (1) Outside-County as Stated on Form 3541	94	126
(2) In-County as Stated on Form 3541	0	0
(3) Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail (Carriers or other means)	3,516	2,992
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g. Total Distribution (Sum of 15c. and 15f)	24,890	24,729
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16. Publication of Statement of Ownership
☒ Publication required. Will be printed in the Nov/Dec 2007 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Gloria N. Hall Editor and Director of Publications — Date: 09/25/2007

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

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PS Form 3526, October 1999 (Reverse)

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Active Chemical Corp., 4520 Old Lincoln Hwy., Oakford, PA 19053. (215) 676-1111. See our ad in this issue.

Astro Pak Corp., 270 E. Baker St., Suite 100, Costa Mesa, CA 92626. (800) 743-5444. See our ad in this issue.

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

Oakley Specialized Services, Inc., 50 Hampton St., Metuchen, NJ 08840. (732) 549-8757. See our ad in this issue.

Process Equipment

A&B Process Equipment, 201 S. Wisconsin Ave., Stratford, WI 54484. www.abprocess.com. See our ad in this issue.

Cotter Brothers Corp., 8 Southside Rd., Danvers, MA 01923. (978) 777-5001. See our ad in this issue.

Pumps

Watson-Marlow Bredel, 220 Ballardvale St., Wilmington, MA 01887. (978) 658-6168. See our ad in this issue.

Spray Dryers

Anhydro, 7024 Troy Hill Dr., Elkridge, MD 21075. (443) 878-4691. See our ad in this issue.

GEA Niro Pharma Systems, 9165 Rumsey Rd., Columbia, MD 21045. See our ad in this issue.

Heinen Drying Inc., 1504 Grundy's Ln., Bristol, PA 19007. (215) 788-8196. See our ad in this issue.

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Tanks/Vessels

Eagle Stainless, 816 Nina Way, Warminster, PA 18974. (215) 957-9333. See our ad in this issue.

Used Machinery

Validation Services

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

ProPharma Group, 10975 Benson Dr., Suite 330, Overland Park, KS 66210; 5235 Westview Dr., Suite 100, Frederick, MD 21703. (888) 242-0559. See our ad in this issue.

Valves

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

Washers

Miele, Inc., 9 Independence Way, Princeton, NJ 08540. (800) 991-9380. See our ad in this issue.

Water Treatment

Christ Pharma & Life Science AG, Haupstrasse 192, 4147 Aesch, Switzerland. +41 617558111. See our ad in this issue.

Siemens Water Technologies, 10 Technology Dr., Lowell, MA 01851. (978) 934-9349. See our ad in this issue.

Veolia Water Solutions & Technologies, Marlow International, Park Way, Marlow, Buckinghamshire SL7 1YL, United Kingdom. +44 1628897200. See our ad in this issue.

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International

The PIC/S[1] have made minor amendments to their April 2007 Guide to GMP for Medicinal Products. Footnotes to Chapter 6 and Annex 13 have been deleted.

Australia/ New Zealand

In July 2007, the New Zealand Government[2] announced the postponement of the ANZTPA establishment project on the grounds that they were unable to proceed with enabling legislation. The Australian Government has agreed to suspend negotiations on formation of the joint authority. Until such time as the process is resumed, stakeholders are advised to refer to the national authorities.

In August 2007, TGA[3] reminded sponsors via their Web site that the transition period to meet child-resistant packaging requirements ended at the end of June 2007. Sponsors were reminded that the Order requires sponsors to hold evidence that the specified performance requirements are met and may be called in for evaluation or review at any time.

Also in August 2007, TGA issued revised guidance on the GMP clearance of overseas medicine manufacturers. A sponsor applying for registration or listing of a therapeutic good manufactured outside Australia must provide evidence to show that the manufacture of the goods is of an acceptable standard. The guidance provides information on the acceptable forms of evidence of GMP compliance for overseas manufacturers, and how to submit such evidence to the TGA.

Europe

In July 2007, the European Medicines Agency (EMEA)[4] provided via their Web site an updated guideline on Excipients in the Dossier for Application for Marketing Authorization of a Medicinal Product. This guideline describes the information to be submitted on excipients (including antioxidants and antimicrobial preservatives) in marketing authorization applications or variations. It is applicable to all excipients in medicinal products for human use but not those in products in clinical research stages.

In August 2007, the EMEA also advised via their Web site that Annex 6 of the restructured GMP guide had been revised to make it more applicable to medicinal gases. This version reflects the need to define more clearly what should be considered as a starting material as opposed to a bulk pharmaceutical product. The existing annex states that bulk gases could be regarded as active substances used as starting materials or bulk medicinal products as decided by national competent authorities. The revised text includes a general rule to provide for a harmonized approach.

Within the same timeframe, a revision of Annex 2 of the GMP Guide to increase of breadth of biological products is proposed. In addition, specific GMP guidelines for advanced therapy medicinal products, including gene therapy, somatic cell therapy medicinal products and tissue engineered products are to be drafted. The deadline for comments on these proposals is 31 December 2007.

The **CHMP**[5] (Committee for Medicinal Products for Human Use) has published the monthly report from the July meeting held 16 to 19 July.

The July month report reminds holders of Marketing Authorizations Holders (MAHs) for biological products planning to introduce major variations in the manufacturing process o contact the EMEA Product Team Leader well in advance of submitting application to discuss their filing strategy and strategy for managing the transition to the new manufacturing process, including anticipated transitional timeframes and pharmacovigilance monitoring.

MAHs also are reminded to contact the EMEA Product Team Leader well in advance of submitting variations to introduce the use of process analytical technology (PAT).

The following relevant guidelines have been prepared or adopted by the Quality Working Party:

- Guideline on Excipients in the Dossier for Application for Marketing Authorization of a Medicinal Product (CHMP/CVMP/QWP/ 396951/ 2006).

- Question and Answer document on the harmonization of PhEur Chapters 2.6.12 Microbiological harmonization of non-sterile products – Microbial enumeration tests and 2.6.13 "Microbiological harmonization of non-sterile products – Tests for specified microorganisms"

The following relevant guideline has been prepared or adopted by the Working Party on Similar Biological (Biosimilar) Medicinal Products (BMWP):

- Draft Guideline on Comparability of Biotechnology-Derived Medicinal Products after a change in the manufacturing process – non clinical and clinical issues, (EMEA/CHMP/ BMWP/101695/2006)

The Committee on Herbal Medicinal Products (HMPC)[6] has published their monthly meeting report for the meeting held 4 to 5 July 2007.

In August 2007, the HMPC[7] adopted for public consultation the guideline on Quality of Combination Herbal Medicinal Products/Traditional Herbal Medicinal Products (EMEA/HMPC/ CHMP/CVMP/214869/2006). The deadline for comments is 31 October 2007.

The Pediatric Committee (PDCO[8,9]) has published their monthly meeting report[8] for the meetings held 1 to 2 August 2007 and 29 to 31 August 2007.

The Committee for Orphan Medicinal Products (COMP)[10] has published their monthly meeting report[9] for the meeting held 11 to 12 September 2007.

The Committee for Veterinary Medicinal Products (CVMP)[11] has published their Monthly Report of Application Procedures, Guidelines and Related Documents for July 2007 and includes a summary of the opinions issued by the CVMP in the current year and a list of adopted Guidelines and other public documents.

Ireland

In August 2007, the Irish Medicines Board (IMB)[12] announced via their Web site that the national regulations required to implement the Traditional Herbal Medicinal Products Directive [2004/24/EC] came into force on the 23 July 2007 and that a Traditional Herbal Medicinal Products Registration Scheme is now available to apply for certificates of traditional-use for relevant herbal medicinal products.

References

1. PIC/S - http://www.picscheme.org/index.php
2. ANZTPA - http://www.anztpa.org/index.htm
3. TGA - http://www.tga.gov.au/media/index.htm
4. EMEA - http://www.emea.eu.int/PressOffice/presshome.htm
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This information was provided by Ian Morland, MRPharmS, PhD, Pharmaceutical Research Associates (UK).