Global Regulatory Viewpoint
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Self Inspection and its Potential Benefits Via ICH Q9—An Interview with Kevin O’Donnell, Ph.D., Irish Medicines Board

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This issue of “Global Regulatory Viewpoint” discusses self-inspection programs in the pharmaceutical industry and associated considerations with Kevin O’Donnell of the Irish Medicines Board. This article was previously published in the Summer 2008 issue of the Journal of GXP Compliance.

Note: The views expressed in this paper are the personal views of Dr. O’Donnell and are not necessarily the views of the Irish Medicines Board.

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Kevin obtained his Chemistry Degree from University College Galway, his Masters Degree from the Dublin Institute of Technology, and his Ph.D. from the Dublin Institute of Technology. His Ph.D. research related to the development of a practical quality risk management solution designed for use within GMP-regulated environments as an aid in facilitating compliance with the risk-based qualification, validation, and change control GMP requirements of the European Union (EU). That work resulted in several peer-reviewed research papers, and one which was awarded the 2007 “Article of the Year” award by the Journal of Validation Technology.

Q. There has been significant change occurring in the GMP-regulated environment in EU in recent years. One of the most recent and significant of those changes has been the formal addition of quality risk management provisions into the EU GMPs. Are we near the end of this current period of change, or is there more change yet to come?

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The last few years have seen significant change within the EU good manufacturing practice guidelines (GMPs), and much of this change is still ongoing. In 2005, the European Commission (EC)’s GMP guide was restructured into one document containing two main parts and a series of annexes. Part 1 of the guide provides guidance applicable to medicinal product manufacturing, and Part II applies to active substance manufacturing (1). The annexes offer guidance in areas that have been deemed to require specific and additional guidance. Annex 3, for example, provides guidance for manufacturers of radiopharmaceuticals. Sampling of starting and packaging materials is covered in Annex 8, and Annex 15 offers relatively detailed guidance in the areas of qualification and validation.

Some individual chapters of the EC GMP guide have either been recently revised or are under active review and modernization at this time. Chapter 1, for example, on quality management, was revised in October 2005 to bring in product quality review requirements, was revised again in July 2008 to formally incorporate quality risk management activities into the overall quality assurance program that is required in GMP environments. Annex 1, on the manufacture of sterile medicinal products, has been under review since 2005, and the new version of this annex became effective in March 2009. The new Annex 1 provides updated guidance on the EU requirements in the areas of media simulations, classification and monitoring of controlled environments, bio-burden monitoring, and capping of freeze-dried vials (1). It should be noted that the provisions on the capping of freeze-dried vials became effective on March 1st, 2010.

But there is more change yet to come, and ICH Q9 (2) has been an important enabling factor in driving forward this change program. Parts of chapters three and five of the EC GMP Guide, for example, which deal with premises and equipment and production, are undergoing review at this time, with a view to improving the existing guidance in the areas of cross contamination and the use of dedicated facilities. Overall, GMP in the EU today is based on an evolving set of guidelines, which are beginning to reflect the use of new and improved technologies, the better use of science and risk-based approaches. Hence, it is likely that the GMPs will continue to develop and change into the future, and we must all be willing to embrace this changing environment in the interests of public and animal health.

Q. Does the EU requirement for a formal risk assessment mandate that all decisions have to have documented failure mode and effect analysis (FMEA) or other risk assessment tools associated with the decision-making process?

A. No, this is not currently required, nor will it be, even with the coming into effect of the new version of Chapter 1 of the EC GMP Guide, which will incorporate quality risk management provisions. The EU GMPs do not require the use of any specific formal risk assessment or quality risk management tool. Explicit GMP requirements for risk analysis and risk assessment are stated in Annex 15 on qualification and validation (and also in Annex 17, on parametric release), but the use of FMEA or other formal tools is not mandated. This is within the spirit of ICH Q9, which describes potential uses of the various tools but does not promote or require the use of one tool over another.

I think what is important is that the company demonstrates a focus on risk, and the quality risk management methodology or approach that a company chooses to use, whether it is a formal tool or a more informal approach, should be suited to the process or activity that is being subjected to quality risk management activity, and it should be in line with the two main ICH Q9 principles:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

Q. The topic of quality risk management has received great attention in the past few years. Are there other GMP areas that, in your experience, have not received adequate attention from Industry?

A. As a GMP inspector in the EU, if I were to choose one area within the EU GMP environment that warrants immediate attention, it would be the area of self inspection. I feel that the current self-inspection programs and activities in place at some pharmaceutical product manufacturers are probably not operating correctly, are not delivering the value they should, and require a major redesign and overhaul. Regulators have a role to play here too.
Q. Self inspection has been a component of the EU GMPs for many years. What do you see are the problems in this area at this time?

O’Donnell: I am often surprised during inspections that the major and critical deficiencies that we sometimes identify were not previously identified and corrected by the companies themselves, via their own self-inspection programs. I am talking here about obvious deficiency issues that we would expect to have been identified internally.

For example, we sometimes see poorly executed deviation investigations that do not adequately address the potential impact of the deviation on product quality, and which are not in line with company deviation procedures. We see equipment cleaning practices that are not sufficiently detailed or which do not follow the validated cleaning procedures, and sometimes, manual cleaning procedures do not specify simple things such as what cleaning agents to use for cleaning equipment. When inspecting quality control (QC) labs, and also during independent market surveillance activities, we sometimes find that the analytical methods that are in use do not reflect the methods that were validated or those that were registered in the marketing authorization dossier.

Another emerging area that is of intense interest at this time, with the heparin contamination issue, and which casts doubt on the adequacy of current self-inspection activities is the qualification of critical material suppliers (and of contract manufacturers of intermediates and products).

With regard to suppliers, we sometimes see during inspections that only minimal qualification work is performed to approve a key supplier before reduced QC testing is implemented in-house on the material. With regard to the use of contract manufacturers, sometimes, the scope and extent of the audits performed by the contract giver do not address the key activities that are to be contracted out to the company. This can occur when an external QA auditing group has already performed an audit at the same contract manufacturer for a different product or service, and where that audit report is then used as the basis for the approval of future contract manufacturing activities performed at that company, even when the new products and services provided are significantly different.

Perhaps better self-inspection programs will pick up on these types of issues, and ensure that they are corrected. In this way, self inspection might help to determine whether the company’s supplier approval program is operating correctly. Despite the advances made within many GMP areas over recent years (e.g., the standard of premises and processing equipment, laboratory instrumentation, computer system validation, etc.), I feel that the area of self inspection has probably not developed in the way it should have. This is leading to non-compliances and manufacturing problems, such as deviations and quality defects, and recalls continue to occur, and actually may be increasing in some areas.

All of the above issues could probably have been identified by the companies themselves, if adequate self-inspection programs had been in operation. A former GMP inspector who is currently heavily involved in helping companies improve their self-inspection programs recently made the point to me that, sometimes, those who conduct self inspections may not be sufficiently experienced to be able to interpret what they are seeing during such inspections, or to think laterally in order to make connections between an observation in one part of an operation and the effect it might have in another area.

While it is, of course, good that companies are sending their staff on auditing courses, self inspections still sometimes comprise little more than a review of compliance with current standard operating procedures (SOPs), and they do not always serve to challenge the scope and content of those procedures. As we move into the future, I think it will be important for self inspections to look at the bigger picture, in terms of process design and control, and this might lead to better risk identification in those areas.

Q. What do you think are the main factors that have led to inadequate self-inspection programs?

O’Donnell: The factors are numerous and interconnected, and I probably do not know all of them. The fact that most GMP inspectorates do not routinely inspect company self-inspection reports has probably been a factor. While the reasons for this were well founded and positive, this policy has probably led to some negative outcomes. One is that the level of resources, the amount of time, and the commitment that senior management in companies have traditionally allocated to self-inspection activities have probably been too low, and the resulting self-inspection programs have not been as effective as perhaps they should have been.

While most companies probably do wish to have effective self-inspection programs in place, self inspection appears to be regarded as an area that, while it must be
addressed, is lower on the scale of priorities, given the many other important things that have to be addressed in GMP environments.

In recent times, dialogue between GMP inspectors and Industry has tended to focus on more exciting topics such as process analytical technology and quality risk management, and issues such as self-inspection seem to me to have attracted little discussion, and this may also be a contributory factor and has not helped the situation.

The ISO 9001:2000 Quality Management Systems Standard (3) is relatively strong in the area of self-inspection, and I think that GMP manufacturers could benefit from applying some of those ISO provisions. But ICH Q10, on Pharmaceutical Quality Systems (4) will hopefully help in this area. This document brings in several ISO quality management-type features that are relevant here, such as management reviews and an increased focus on self-inspection.

Another important factor is probably the low level of official regulation and guidance that is currently available in the area of self-inspection. In the US, for example, self-inspection is not specifically addressed in the FDA’s GMPs via 21CFR 210/211 (5). In the EU, while the main GMP Directives, 2003/94/ELI (6) and 91/412/EEC (7), do explicitly require repeated self-inspections to be carried out, the resulting guidance offered in this area via Chapter 9 of Part I of the EC guide to GMP (1) and via Section 2.4 of Part II is quite minimal.

This is not to say that the existing guidance is not useful. Chapter 9 is very important, as it clearly states as a general principle that self-inspections should be conducted in order to monitor the implementation and compliance with GMP principles and to propose necessary corrective measures. It lists areas that should be examined via self-inspection activities, and it states that self-inspections should be conducted in an independent and detailed way, by designated competent person(s) from the company. Lastly, it makes provision for the use of independent audits by external experts, and it discusses recordkeeping requirements. But Chapter 9 could probably be improved, by making direct and explicit reference to key areas that should, in my opinion, be subjected to self-inspection activities, such as change control, deviation management, qualification, validation, batch release, and other high-level components of the quality management system.

Q. You have described some of the problems in the area of self inspection and the factors leading to the current situation. Where does the way forward lie in your opinion?

A. O’Donnell: I personally feel that an increased and more transparent focus on self inspection will deliver significant benefits and opportunities to companies, especially now that quality risk management is becoming a fundamental component of the GMPs. This should not only result in improved levels of compliance and in better inspection outcomes, it may also help deliver real and tangible opportunities for reduced regulatory oversight for those companies who elect to go this route.

Q. Can you expand on this?

A. O’Donnell: A number of GMP inspectorates are presently working on ways to apply the guidance of ICH Q9 to their inspection planning and scheduling processes. As we know, Q9 introduced the concept of reduced regulatory oversight, stating that effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company’s ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight.

In the inspections area, reduced regulatory oversight might take the form of less frequent inspections, or less intensive inspections, or perhaps inspections in which some areas are not inspected or are less thoroughly reviewed based on risk considerations. But this is not a simple area in which to develop policies and procedures, and characterizing (or ranking) manufacturing sites on the basis of risk is not an easy task.

One interesting idea that is currently under discussion among GMP inspectors at an international level is that, rather than attempting to rate sites on the basis of the level of risk that they may present, it may be more beneficial (and indeed practical) to identify characteristics of a site that render it to be considered low risk. This approach is useful, as it recognizes that all manufacturing sites have the potential to present significant risks to patients/animals and users of medicines, regardless of the type and number of products that they manufacture. The idea that sites involved in aseptic processing carry a greater level of risk than sites producing non-sterile products is probably too simplistic an approach, and the type of serious recalls that have occurred in recent years is probably a demonstration of this.

This approach is also in line with the thinking put forward in the current ICH Q10, and this is important in the context of this interview. Q10 gives potential sce-
narios that present opportunities for risk-based regulatory approaches, including risk-based inspections. The requirement here will likely be that sites will move away from just complying with the GMPs, and work towards demonstrating that an effective pharmaceutical quality system is in place, which includes an effective use of quality risk-management principles.

This is an interesting part of ICH Q10, and when one considers what this may mean at a practical level, it becomes clear that an effective pharmaceutical quality system cannot probably be demonstrated without an explicit demonstration of an effective self-inspection program being in place. Indeed, when identifying characteristics of a site that may render it to be of low risk, self inspection in my opinion is an area that needs to be formally assessed in this regard.

As a GMP inspector, I do support the concept of reduced regulatory oversight, where justified, for example, where there is an effective quality management system in place, coupled with a good level of process understanding and an appropriate application of quality risk management. In this regard, I feel that self inspection could play an important role. If designed and resourced correctly, it could provide GMP inspectors with assurance of the company’s ability to deal with potential risks. It is an area that has the potential to identify, address, and prevent non-compliances and risks before they become problem issues, and it has the potential to drive continual improvements at the site. This is what inspectors are looking for! Self inspection should really be regarded as an integral part and vital of a site’s quality management system, but I am not sure that this is presently the case in some companies.

I personally would not be comfortable offering reduced regulatory oversight in the inspections area to a site whose self-inspection program was one that I did not thoroughly understand, or was one in which I did not have confidence. I believe that if we are to have real and tangible applications of the idea of reduced regulatory oversight that is envisaged in ICH Q9, the current approach to self inspection has to change.

Q. With respect to reduced regulatory oversight, what practical changes would you propose are necessary?

A. O’Donnell: I feel that companies seeking some level of reduced regulatory oversight probably need to change the fundamental way that they view their self-inspection activities. Instead of regarding their self-inspection findings and reports as being off-limits to GMP inspectors, it would be useful if companies viewed their whole self-inspection program, including their self-inspection findings, as one which warrants review by GMP inspectors. But it is probably too early for such a leap forward at this time, and I would suggest that companies should start small.

One way to do this would be to begin critically examining their current self-inspection activities, so as to identify any necessary changes that are required to ensure that their self-inspection program is adding increased value in terms of the following items:

- Delivering more thorough self inspections
- Ensuring that self inspections are performed in the right areas, at the right intervals and by the right people
- Ensuring that the types of issues that are being identified in regulatory inspections can also be identified internally, if present, during self inspections
- Ensuring that opportunities for continuous improvement are identified during self inspection and are realised thereafter.

At some point thereafter, companies might begin to proactively and voluntarily invite GMP inspectors to formally inspect some (or all) of their self-inspection findings or reports, as well as other aspects of their self-inspection programs. Openly sharing with GMP inspectors how potential and confirmed non-compliance issues are identified and managed, and how the program drives continual improvement at the site, should serve to demonstrate to inspectors that an effective quality management system is in place. This demonstration of an effective quality management system is the intent of ICH Q10, as discussed above.

I realise that some may see these thoughts as being controversial, and I am not trying to be controversial, but I feel that the benefits envisaged by ICH Q9 cannot materialize without some changes in current practices.

I want to be clear that I am not in any way advocating that GMP inspectors should start to routinely review company self-inspection reports without good reason or prior invitation. In the real world, this probably would discourage companies from documenting the real findings of such inspections, or from performing thorough self-inspections. It is important, therefore, that we encourage companies to implement more value-adding self-

*It is important to recognise that inspectors in the EU are legally empowered to inspect all aspects of a company’s self-inspection program, including self-inspection reports.
inspection programs, regardless of whether the reports will be reviewed during regulatory inspections.

One way to do this might be to change the way we all view self-inspection—rather than viewing it as a stand-alone and isolated component of the site quality management system, it might more useful to view it (or maybe re-position it) as a formal quality risk management tool within the framework of the type of quality system envisaged by ICH Q10. After all, if designed correctly, self-inspection programs should be capable of identifying and managing risks, both current and potential, and of driving forward tangible and real continual improvements. Thus, in the future we might start to see self-inspection activities evolving into more formalized quality risk management activities, delivering an increased understanding of human factors and their impact on compliance, a better knowledge of production processes and their controls, and more risk-based critical control parameters.

The sharing of information in self-inspection reports may, as you say, be an area of concern in some companies. One could argue that companies should not be required to share their “dirty laundry” with investigators. There may be more open discussion and better problem solving during internal inspections when there is no fear of documentation of problem situations, publication in internal memos, and escalation to higher management within the company—people are fearful of “bad press.” More open discussion is helpful for better correction of problems. This perspective appears contrary to your approach to more open sharing of information with investigators. Please share your thoughts on this.

O’Donnell: I completely understand this perspective, and as I said, I am not advocating that GMP inspectors should start to routinely review company self-inspection reports without good reason or prior invitation. My thoughts in this area specifically relate to situations in which companies may be seeking some level of reduced regulatory oversight in the inspections area, as envisaged by ICH Q9 and Q10. There are probably many ways for companies to achieve this end goal. For example, as an alternative to openly sharing full self-inspection reports with inspectors, companies might develop detailed summary reports of the self-inspections that were performed, specifically for review by GMP inspectors. These summary reports could describe in detail the scope of the inspection, the areas that were inspected, the depth and length of the inspection, the individuals involved and any corrective measures that were implemented as result of the self inspection. Such an approach might add value, because it may help the inspector to better understand and assess the effectiveness of the company’s self-inspection program, rather than solely relying on the self-inspection SOP that is in place, the company’s annual plan for self-inspection, and the overall findings from his or her GMP inspection.

There most certainly could be other approaches too. The key point is that a more open approach to self-inspection, and better designed self-inspection programs should, in my opinion, help to demonstrate that an effective quality management system is in place at the site. This may then allow for some level of reduced regulatory oversight to be given, in line with ICH Q9 and Q10. This may also help demonstrate the commitment within the company to proactively address non-compliances when they are internally identified.

What things might companies look for when critically examining their current self-inspection activities?

O’Donnell: I think there are several important areas that might be critically evaluated.

At a high level, one general area might be the design of the self-inspection program relative to the site in question.

For example, on inspection we sometimes see self-inspection programs that are relatively generic, in that they could be applied to almost any company that is manufacturing pharmaceutical products. The value of such an approach is questionable, as the specific characteristics of the site in question, as well as its specific processes, products, and general manufacturing arrangements are sometimes not adequately taken into account when the self-inspection program and its plans are being designed and drawn up. As production processes and manufacturing generally become more specialized and complex in the global environment that companies now operate within, it is important that self-inspection programs are customized to reflect the specific arrangements that are in place, such as the use of contract manufacturers and the reliance on corporate quality functions to assess contracted sites.

Sometimes also, the same amount of time and personnel resources are devoted to all of the inspections that are included in the annual self-inspection plan, regardless of the nature of the area being inspected or the level of complexity in the process or manufacturing activity of concern. Complexity in particular is an area worth looking at in greater detail.
Another area that might be looked at, and this is now at a more specific, practical level, is how the self-inspection program assesses the operation of the site-deviation and the complaints-management programs. Here, I am specifically speaking about the assigning of human error as a cause in deviation and complaint investigations, and the selection of retraining as a corrective measure for such incidents.

I feel that human error is often overused as a cause for many kinds of deviation and non-compliance issues, and re-training is sometimes misused as an appropriate preventative measure for such issues.

Also, the level of scientific rigor that is applied to deviation and complaint investigations can sometimes be relatively low, and this is a problem that needs to be corrected, especially when the incidents or complaints are of a recurring nature. In this regard, the support provided by senior management for thorough deviation investigations and for good root cause analysis is pivotal, but unfortunately, the pressures to get the batch out the door sometimes mean that staff may fail to conduct thorough investigations to get to the true root cause of problems. Such pressures can be amplified though the use of tight metrics and timelines for closing out deviation investigations, regardless of the nature or complexity of the deviation incident. Sometimes also, staff pay bonuses may be related to the close-out times that were achieved for deviations and other related investigations. Naturally, this can result in failures to deal with deviations in a thorough manner, and should be discouraged.

Q. We will return to the area of human error in a future interview, but before we finish this interview, perhaps you would expand on the issue of process and system complexity that you previously mentioned?

O’Donnell: Complexity issues come up time and again when one studies the application of risk management in other industries, but not so much in the pharmaceutical industry. I think that process and system complexity are important attributes to consider when trying to understand the reasons why non-compliances occur, why we have deviations within a quality management system, and how they may be prevented in the future. Indeed, ICH Q9, in suggesting some potential uses of quality risk management in the area of auditing and inspection, discusses the importance of taking complexity considerations into account. It states that quality risk management may be used to define the frequency and scope of audits, both internal and external, taking into account factors such as the complexity of the site, the complexity of the manufacturing process, and the complexity of the product and its therapeutic significance.

However, at a day-to-day level, such complexities are often not assessed or taken into account when designing a site’s self-inspection program, and I think that we can learn from the experiences of other industries in this regard as we seek to improve self-inspection programs in GMP-regulated environments.

In the aeronautics field, for example, much work has been carried out at NASA in an attempt to better understand the mechanisms by which failures and accidents occur. When describing the evolution of risk management activities at NASA, the Office of Safety and Mission Assurance at NASA has stated that, in the past, the theory that accidents can be prevented through good organizational design and management was prevalent (8). However, in the late 1990s, NASA recognised that this approach did not work with what it called complex and tightly-coupled systems. As suggested by a theory called Normal Accident Theory (9) (which is a useful theory on how accidents occur in complex systems), accidents and failures in such systems are inevitable.

NASA has made attempts to avoid such accidents and failures by reducing (or controlling) the extent of system complexity and system coupling. They have spoken about how, in complex and tightly-coupled systems, failures can be the result of many seemingly unconnected causative events, and that they can result from interactions that were not in the design intent of the overall system. The accident pathways that can occur are often complex and appear to have “an intelligence of their own,” exploiting circumstances that no engineer could reasonably plan (8). Importantly, NASA has stated that with complex systems, combinations of such events are “practically limitless,” and that these cascading failures can accelerate out of control, confounding human operators, and denying any chance of recovery (8).
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which are not visible or not immediately
• comprehensible
• Opportunities for failures to jump across subsystem boundaries.

They describe tightly-coupled systems as having:
• Time dependent processes that cannot wait
• Rigidly ordered processes, as in Sequence A must follow B
• Only one path with a successful outcome
• Very little slack in the system, as the system requires precise quantities of specific resources for successful operations (8).

As part of its risk management activities, in the late 1990s, NASA recognised that many of its own systems could be characterised as being complex and tightly coupled, and it began formal work to overcome the risks of accidents with such systems. Identifying, understanding, and reducing, where required, system complexity and coupling was a major part of that work.

NASA found that moving beyond the normal accident investigation pathways, which often only focused on operator error, inadequate training, faulty system design, mechanical failure, etc. and more towards investigations which give increased attention to near-miss events, close calls, incidents, and mishaps, was beneficial. This was because the closer scrutiny of those events allowed root causes of potential major accidents to be uncovered through careful analysis, and more meaningful and proper corrective actions for the prevention of future accidents could then be developed (8).

Q. How do you see this relating to the GMP environment?

A. O’Donnell: It is not likely that the GMP environment is any more immune to the adverse effects and problems posed by system complexity and coupling than NASA has been. For this reason, it will likely be beneficial to ensure that the self-inspection and quality-risk management methodologies that are used within the GMP-regulated environment are capable of identifying, and/or taking into account, the extent of system complexity and coupling that may be present in the process or item under study. Self-inspection programs could then be focussed on those processes and systems that are known to be complex and tightly coupled.

Q. Can you give a practical example here?

A. O’Donnell: Well, change control activities, for example, relating to medicinal product packaging and artwork can sometimes be highly complex. This is because they can require the input of several different groups and people for the coordination, assessment, review, approval, and implementation of the proposed change, not to mention the input of regulatory agencies and off-site printing companies as well.

In addition, such activities are often tightly coupled, as there can be strict timelines to be adhered to for each part of the process, and complex interactions may have to take place in a certain order to allow the packaging change to be implemented in a compliant but economically viable manner. Such interactions may include those between regulatory affairs and production personnel, and between regulatory affairs and marketing groups, in order to communicate and schedule manufacturing and marketing activities with the changed packaging or labeling component. This is an area that experience has shown to be high risk for companies; non-compliances at manufacturers have frequently come to light in the areas of product packaging and labeling, and many of those issues were attributed to the poor management of changes in printed packaging components.

The investigation of such issues revealed that, sometimes, the procedures and systems in place for packaging and artwork change control were highly convoluted, had many interdependencies, and were subjected to tight timelines. In hindsight, they could probably be described as being highly complex and tightly coupled. Also, there was sometimes a poor understanding of how the change control system within the company actually operated. For example, regulatory affairs staff involved in packaging and artwork-related, change control activities were not always aware of other key groups within the same company that were also highly involved in the implementation of such packaging and artwork-related changes.

It was clear that a reduction in system complexity and coupling would be of benefit.

While the above observations and strategies in relation to normal accident theory are interesting, in the general pharmaceutical manufacturing environment, I think there is often little attention given at this time to understanding (beyond a conceptual level at least) the theories behind how non-compliances occur. Thus, the potential existence of complex, tightly-coupled systems is not one that is generally focussed on (or probably well
understood) within the GMP environment, and opportunities for improvement and learning in this area are probably not being realized.

At the IMB, we have found that an understanding of system complexity and coupling can be achieved via the use of rigorous process mapping exercises. These exercises have allowed system complexities and couplings to be identified and documented in an easy-to-understand, visible manner, and the reasons for deviations from work plans could then be better understood.

During a 2006-2007 developmental study carried out with an external consulting company on the Market Compliance Section at the Irish Medicines Board (Market Compliance is a group within the IMB’s Compliance Department), some of the Section’s main work programs (namely, the sampling & analysis program and the quality defect & recall program) were rigorously analysed via formal process mapping studies. This was done to identity potential process improvements and opportunities for efficiency gains.

The process-mapping work performed on the product sampling and analysis process showed that the process was highly complex and tightly coupled; there were many steps in the process, there were a large number of process hand-overs between staff, and there were several time-based interdependencies that had resulted in workflow problems. It became evident following our analysis of the process maps that certain delays and backlog problems which had been associated with the sampling and analysis program over preceding years could be directly attributed to the highly-complex and coupled design of the process. One delay or unforeseen event in one part of the process, such as a delay in obtaining registered analytical methods and specifications for a product, often had a significant impact on the whole program, and the testing of other samples often had to be rescheduled as a result.

So, work was carried out to redesign the process for the sampling and analysis program, to address the above issues. Through these efforts, some of the complexity of the process was removed, due to redesign and simplification efforts both in the process steps and in the procedures and other documentation that accompanied the process. In addition, key process couplings such as the time-dependent links between product sampling activities, the obtaining and review of analytical methods and laboratory capacity issues, were removed. This allowed for greater flexibility in carrying out these individual (decoupled) activities, and better planning and scheduling of sample analysis work was made possible.

The resulting redesigned process has proven to be much more efficient. Deviations from planned work activities and sample backlog issues do still occur, but their extent has been substantially reduced.

Getting back to pharmaceutical manufacturing, I believe that a critical understanding of system or process complexity and coupling could be similarly beneficial in the GMP environment, especially with respect to deviations and non-compliances. The time is probably right for this now as well, given the current drive towards the use of more formalised quality risk management methodologies in the GMP environment. This presents an opportune time for the industry to begin identifying which systems are complex and tightly coupled via process mapping or other techniques, and this work should then allow quality risk management efforts to be directed at the most highly complex and highly coupled systems and processes. Then, with respect to self inspection, the resulting quality risk management exercises could enable the company to target its self-inspection efforts at the areas where there is the greatest risk.

We have talked primarily about self inspection today. Let us summarize the key points of today’s discussion.

O’Donnell: The points discussed in this interview are summarized as follows:

1. **On the use of formal quality risk management tools such as FMEA in decision-making:**

   Quality risk management provisions are being incorporated into the EU GMPs at this time, but the use of specific formal risk assessment and quality risk management tools such as FMEA for decision-making is not an explicit requirement. Companies should choose the most appropriate approach they wish to take when performing risk assessments and quality risk management activities, in line with ICH Q9 principles.

2. **On self inspection and the use of quality risk management principles:**

   Self inspection is probably an area within the EU GMPs that could benefit from more rigorous attention within the overall regulatory environment, and improvements are probably required in this area if companies wish to benefit from the potential for reduced regulatory oversight as envisaged by ICH Q9. The current EU GMP guidance in the area of self inspection was reviewed, and some ideas were put forward for suggested improvements in this area, if and when this part of the EU GMP guide is revised.
There was discussion on how current self-inspection programs might be redesigned to provide increased value. The idea of repositioning self inspection beyond just being a stand-alone and isolated component of the company quality management system, towards viewing it as a formal quality risk management tool within the framework of the type of quality system envisaged by ICH Q10 was also put forward. The idea here was that well-designed self-inspection programs should be capable of identifying and managing risks, both current and potential, and of driving forward tangible and real continual improvements.

3. On the sharing of self-inspection findings with regulatory inspectors:

The potential benefits of a move toward an increased and more transparent focus on self inspection were discussed. This was specifically in terms of the potential to realise the provisions of reduced regulatory oversight as per ICH Q9, and the challenges in this area were reviewed.

The internal inspection program of an organization should be proactively shared with the investigator if companies are seeking some level of reduced regulatory oversight. The problems inherent with the open sharing of full self-inspection reports with regulatory inspectors were acknowledged, and ideas were put forward for how companies might demonstrate the effectiveness of their self-inspection program without voluntarily sharing full self-inspection reports.

4. On process complexity and coupling considerations, and how they may prove beneficial when designing self-inspection programs:

The benefits of taking into account system and process complexity when designing self-inspection programs were discussed. NASA’s work in the area of system complexity and coupling was briefly reviewed, and practical examples were given for how complexity and coupling considerations have been helpful in reducing problems with processes. When a process is identified as being highly complex or tightly-coupled, it follows that the self-inspection of such a process should have a scope, frequency, and intensity that are commensurate with the risk posed by that level of complexity and coupling.

Thank you, Kevin, for interesting and informative comments.

REFERENCES

ARTICLE ACRONYM LISTING
EU European Union
FMEA Failure Mode and Effects Analysis
GMPs Good Manufacturing Practice Guidelines
IMB Irish Medicines Board
QA Quality Assurance
QC Quality Control
SOPs Standard Operating Procedures