gmp review

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Quality by Design

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Editorial comment

If you haven't already seen it I recommend that you take a look at the European Medicines Agency website and a News and Press Release issued on 26/11/12. The title of the press release is " European Medicines Agency provides plan to help deal with manufacturing-related medicine shortages".

This is an interesting title and is sure to grab the attention of most us who read or contribute to GMP Review. However, the recommendation to read it comes with a health warning to anyone who works in the industry and suffers from high blood pressure. I know that I am not alone in thinking that the EMA's paper is rather condescending, even verging on insulting, to our industry.

The full title is "Reflection paper on medicinal product supply shortages caused by manufacturing/Good Manufacturing Practice Compliance problems". It consists of two documents. The first summarises the lessons that the Agency has learned from previous crises where it played a supporting or coordinating role and is supported by a second document that outlines the Implementation Plan 2012-2015. This second document contains Short Term and Medium Term Actions that are intended to help the European medicines regulatory network prevent, mitigate and manage shortages of important medicines.

As the rationale for the paper the EMA website states that the occurrence of shortages of medicines has increased over the last few years. The paper identifies the globalisation of manufacturing and supply chains as a major contributing factor to the occurrence of supply shortages. However, its first shortcoming is that it stops at this point and doesn't identify or address any of the other major contributing factors. If you want an insight into some of these just take a look at Hedley Rees' second paper on Supply Chain Management in this issue. Hedley provides a very timely analysis of the problems and a common sense approach to what governments, regulators and industry should do.

The EMA's narrow focus on manufacturing/GMP compliance problems becomes an even narrower view of the problem as the industry's approaches to risk management and business continuity planning come in for significant criticism.

The fact that the reflection paper was developed by the Agency in collaboration with the European medicines regulatory network, including the European Commission and regulatory authorities in the European Union (EU) Member States makes it even more worrying as the wording of the paper appears to deliberately place the regulators as a victim of the situation. For example, Section 3.1 is titled "The regulators' dilemma" as they struggle with restricted ability to take action against a manufacturing site in order to avoid product shortages and the very difficult risk-benefit judgements to be made between poor quality processes or product, or no product at all. Whereas section 3.3 is titled "The industry's approach" and immediately alleges that industry's risk management is reactive rather than proactive and how sustained pressure is needed to bring about a change in a manufacturer's approach to quality risk management and supply chain security.

To be told that our industry needs to be put under sustained pressure and educating in the impact of product shortages and the need for business continuity planning shows either massive ignorance or supreme arrogance, or even both, from the EMA.

This attempt to position the regulators as the good guys and manufacturers as the bad guys is inflammatory. It clearly shows an unhelpful culture and undesirable behaviours from a key stakeholder in the supply of medicines to the public.

There is one ray of hope offered in the paper and that is the proposal for a workshop in Q2 2013 at which industry "should be invited to propose solutions to the problems encountered". A critical factor in the success of that workshop will be the attitude and behaviours of the EMA Secretariat towards the industry. They need to accept their responsibilities for assuring continuity of supply and partner with industry to take a proactive, strategic approach to risk management and supply chain security, rather than just focus on the crisis management aspects.

EMA need to recognise the shortcomings in their own operations and work collaboratively with industry. Accordingly, the industry needs to see itself as an equal partner with the regulators in the secure supply of medicines and behave in that manner.

One further note of interest this month is the revisions to Eudralex Volume 4 GMP Guidelines. Unlike the EMA paper the Eudralex revisions make a lot of sense. Chapter 1 is revised to align with the concepts and terminology described in the ICH Q10 tripartite guideline on Pharmaceutical Quality System. In view of this, Chapter 7 has also been revised in order to provide updated guidance on outsourced GMP regulated activities beyond the current scope of contract manufacture and analysis operations. The revisions finally come into effect on 31st January 2013.

Finally, from everyone at GMP Review and Euromed Communications we wish you a happy and prosperous 2013!

Peter Savin

Regaining supply-chain control: Is Pharma missing the target?

by Hedley Rees

Will regulations reverse the decline?

In the last four or so years, we have seen patients dying from adulterated materials (eg Heparin, 2008), shortages of life saving medicines, a catalogue of drug recalls and warning letters on manufacturing and supply issues, and a plethora of counterfeit products sold and consumed as the genuine article, risking the safety and well being of unsuspecting patients.

Given the above, it has become increasingly clear to all that there is inadequate control over the Pharma supply-chain. In an attempt to establish higher levels of supply chain integrity, governments and regulators have been swift to respond. Legislation has been enacted both in Europe and in the US. The EU has passed the Falsified Medicines Directive, leading to major revisions to Good Distribution Practice (GDP) and some revisions to Good Manufacturing Practice (GMP). In the US, the FDA Safety and Innovation Act (FDASIA) has been enacted into law, again with the intention of cracking down on illicit activities in the supply-chain, as well as encouraging better working practices. Mandatory ePedigree is now also actively under consultation at congressional committee level.

The vast majority of these measures are targeting finished product supply-chains making the journey from the final stage of production, through pre-wholesales, wholesalers, pharmacies, clinics and online ordering sites, into the hands of healthcare professionals and patients. Serialisation and authentication activity is now reaching fever pitch, as the various actors in the finished product supply-chain grapple with the associated cost, coordination and technology issues that must be solved in the next year or two.

All this pain of increased regulation will be worth it as we see an end to our supply-chain woes, won't it? Sadly no, and in fact there is a danger it will make matters worse, as the various actors in the supply-chain focus on interpretation of regulations that may make sense in theory but have not been tested in practice in the 'real world'.

It is not even as if the current regulations are deficient in any material way; the issue has always been one of adherence. For example, expectations on a third party logistics provider (3PL) for handling and storage *should* be clearly outlined in the Quality & Technical Agreement (QTA) between the licence holder and the 3PL and proper due diligence carried out in determining fitness for purpose of the 3PL's services. Any licensing of 3PL's, a possibility suggested in the EU GDP consultation, would appear to be duplication and undermine that basic duty of the licence holder. The massive inspection resource requirement would surely also be unsustainable.

This is not the end of it. There is also one glaring oversight that renders much of this effort useless. Most of what has gone wrong in the past has its roots in the manufacturing supply chain. The misbranded Heparin started life in the supply chain with an adulterated component material that was fully incorporated into the Baxter finished product. Authentication would have confirmed that lethal product as genuine. So too for the J&J/McNeil recalls – the issues were at supplier level and the risks to consumer well-being were incorporated into the finished product; and so too the many shortages associated with supplier quality issues such as glass vial delamination; and so too it goes on.

In a nutshell, stakeholders appear to be homing in, with laser-like precision, on that part of the supply chain where the problems present themselves. As any good physician would point out however, it is always necessary to look beyond the presenting symptoms into the underlying cause(s). So far, we do not appear to have completed the root cause diagnosis.

What are the root cause issues?

Let us first look at the symptoms – product integrity issues in the distribution channel. Why have issues presented here? Because this was the first area Pharma started the dis-connection process, as it abandoned direct links with its customers to the wholesaler network. That disconnection has been complete for decades and licence holders now have virtually no control over their products once they leave the site of finished production or their pre-wholesaler. The resulting no-mans land is a happy hunting ground for those wishing to make money from illicit dealings. There is so much movement of products between disconnected parties in the distribution channel, dark spaces are easy to find and capitalise on. Will more regulation remove the dark spaces? We will have to wait and see – personally, I'm extremely doubtful.

There are of course impending changes within GMP that aim to drive greater visibility of the supply-chain upstream of the finished product, and these are very welcome. However, in the same way strengthening the Highway Code would not automatically lead to better drivers, so more stringent regulations do not automatically improve supply-chain practices. The 'dark spaces' also need to be eradicated and this is where the issue lay. Pharma companies have been playing the same dis-connection game that it played with wholesalers – by outsourcing and off-shoring on a massive scale; and this game hasn't just been taking place in commercial manufacture, it has also been a favourite of Pharma R & D for quite some years now.

Drug developers seem to go all over the world for sources of supply and contract manufacture, creating complex, multi-stage supply chains that have no basis in common sense. Why would anyone buy raw materials in China, ship them to India

to make intermediates, on-ship them to Italy for API production, from where it goes to a Belgian drug product contract manufacturer to make a bulk dosage form, who then ships it to a third party in the UK for packaging? Pharma does though.

This is where the REAL issue lay. As readers will know full well, Pharma supply chains have to be registered as part of the drug development process. This starts with the initial application to administer drug to humans – the Clinical Trial Application (CTA) or Investigational New Drug application (IND). From this point on, change to any aspect of the supply-chain is hard to come by, since regulators will rightly demand justification. Rather than risk delay or possible rejection, the status quo will prevail; and the status quo will normally involve the round the world scenario above – multiple hand-over's and interfacing Quality Systems, arms length contractor relationships…and of course, the 'dark spaces'.

This supply-chain is eventually handed over to the commercial manufacturing teams after the NDA or MAA has been submitted. Some of the more forward looking companies try to engage their commercial manufacturing folks at an earlier stage, but normally the best that can be achieved is involvement from phase II; and often many of the critical supply-chain issues cannot be remediated to the timescale available for planned launch.

The conclusion from this is that the only sustainable way to build robust, fit for purpose supply-chains is to use supply-chain thinking from the very inception of a new molecular entity – when a compound emerges from discovery research. This should not involve extra cash, just a re-structuring of the process, and rather than delay progress to the clinic, it should speed things as failure rates tumble and the basic principles of strategic supply chain management are applied.

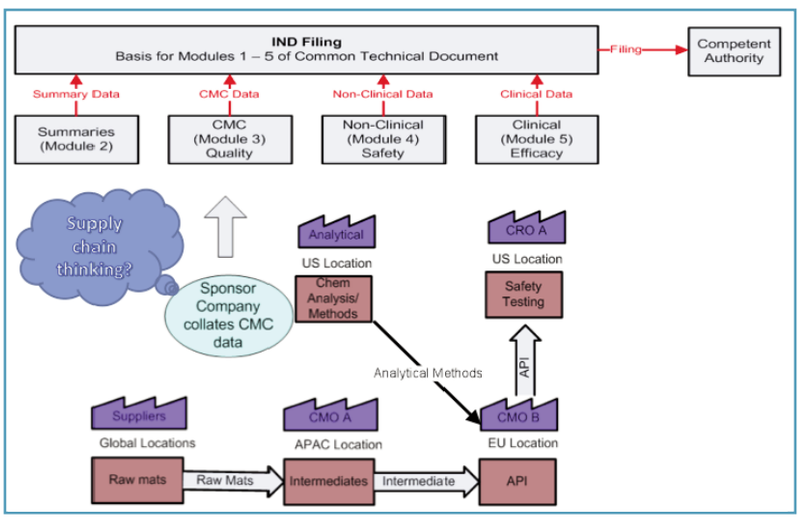

Figure 1: *Regulatory filing and the supply-chain*

The major requirement would be to move away from the race to the clinic with imperfectly characterised molecules, towards a prototype of a drug product that is designed with manufacture for patient use in mind. This is a fundamental principle that permeates exemplar sectors producing products for customer markets.

Figure 1 shows a typical supply chain for pre-clinical assessment of a compound that will be used as a basis for the eventual CTA/IND CMC submission to regulators. In the trade, this is called a 'dirty batch', to provide maximum cover for potential toxicology issues. If this API batch passes muster with the regulators, all subsequent ones can only get easier to register. The issue with this of course is that once the regulators accept it, there is very little incentive to improve beyond the minimum standard; and that is what typically happens – potential future manufacturing and supply chain issues are carried forward into the dosage form at phase I and then into phase II. By the time commercial manufacture is on the cards, it is all too late. Quality, cost and delivery performance issues are locked in for life.

Could there be a better way?

Very definitely – YES, but it requires a complete overhaul of the industry mind-set. The drug commercialisation process must be turned on its head. The historical way of finding a compound and selling it to a mass market (the Model T Ford approach) must be replaced by a holistic process whereby patients and healthcare professionals (customers) are at the centre of the drug development effort (the Toyota approach). Then manufacture must be aligned to deliver on their needs. Then R & D must develop prototypes that provide proof of concept in the dosage form intended for the specific indication that manufacturers can take forward, or reject if commercial manufacturability is not proven.

Figure 2 overleaf shows a schematic of an approach to prototyping. Note that what is tested for safety, efficacy and quality is the drug product in the intended dosage form, with all the input materials included. Development candidates will have far higher hurdles to jump here, but it does put the emphasis on solving issues at the point where they can be addressed, or in the worst case, compounds abandoned and replacements found. The huge supply-chain advantage to this is that the architecture can be designed so that there are minimum hand-overs, supplier/contractor relationships can be deepened and shared working practices can be exchanged. The main principles would be:

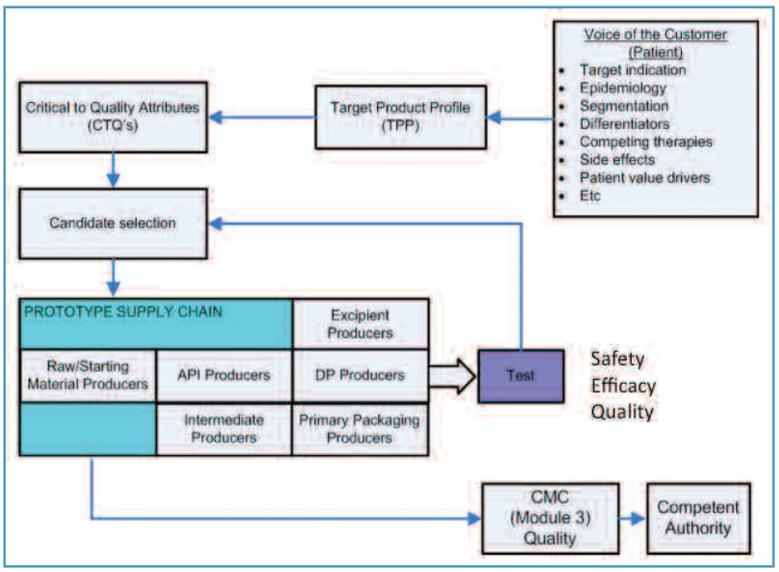

Figure 2: *Overview of a prototyping process*

- Design prototype based on full stakeholder involvement, including marketing, manufacturing, procurement, key suppliers
- Allocate overall management responsibility for the programme
- Discovery research stays with prototype testing – iterative
- Focus on *predicting* performance and manufacturability of compounds
- Build a deep understanding of material and process capability
- Institutionalise risk management into development programmes
- Build a fit for purpose outline of the end-to-end supply chain.

The benefits of this approach would be immense, not least in its impact on attribution rates, which Tuft's recently inform us, have increased from a previously horrifying rate 4 out 5 failing to make it through the clinic, up to 5 in every 6 falling over. We should all remember, by far the biggest contributor to the cost of drugs is the cost of these failures, so the prime opportunity for reducing the cost of drugs is based on failure reduction. The greatest benefit of all however, would be to the patients whose lives are not blighted or ended by toxic materials finding a way to their door through the maze that is today's Pharma supply chain.

What should stakeholders be doing next?

The only possible conclusion to make from the above is that Pharma as an industry is missing the target by spectacular proportions at the moment. Legislation and regulation will help in part, but the real solution is for the industry (those companies holding product licenses and sponsoring clinical trials) to step up to the plate and take responsibility for managing their own supply chains in professional ways. Governments and regulators can facilitate that by pulling the levers to drive the right behaviours, as companies increasingly focus on proper supply-chain management processes. Below are some further thoughts that may seem rather radical, but if not the complete answer and possibly unrealistic in parts, could drive a healthy dialogue between governments, regulators and the industry itself:

- Turn the development process on its head – put patient-use first
- Don't award patents for molecules until they are working prototypes
- Supply chain for clinic and the market should be under one responsibility – with strong SCM competencies
- Teach SCM principles at University to our chemists, pharmacists etc.
- The IND/CTA CMC review process should require a higher level of understanding of the compound and it's manufacturability
- Companies intent on making a financial exit before commercialisation should prove the supply chain foundation is sound
- Big Pharma should demand supply chain integrity from the companies they do licensing deals with
- Regulations won't solve the issues, and in EU they are likely to make matters worse
- Big Pharma CEO's must step up to the plate and make change happen – learn from Toyota's handling of the 'foot pedal' incident (scientists eventually found no defects in Toyota vehicles and put it down to driver error).

Readers may well have their own personal items to add to this list. The important thing is that all stakeholders realise this is not a quick fix as no complex systemic issue ever is – there is possibly a generation of change required to get to where things need to be.

Hedley Rees is Managing Consultant at Biotech PharmaFlow. As an expert in Lean Thinking and Production Systems, he is a zealous advocate of FDAs 21st Century Modernization and ICH Q8 – Q11. He is an Advisory Board Member of the International Institute for Advanced Purchasing & Supply (IIPS) and global chain specialists, Marken. Hedley Rees is author of "Supply Chain Management in the Drug Industry", published by John Wiley & Sons. Email: h.rees@pharmaflowltd.co.uk

Good relationships – the key to good manufacturing practices

by John Faulkes

As he scans his email messages this morning, Kerry sees the preview of a note from the client-side project lead, Sam, and his heart sinks. He sighs and takes a deep breath before opening it, but already he knows that it's not going to be a good day.

Kerry is a project manager at Biosolve, a specialist CMO. He looks after three clients, the biggest of which is ABC Pharma. Last week he'd had to guarantee to Sam, their CMC contact in ABC, that delivery of the latest batch of processed solution was going to be made next Tuesday. The client has just heard directly from someone in the Biosolve's downstream suite, that won't now be possible.

Reluctantly he notes to go down to the suite later this morning. Even more reluctantly he emails his boss with the news.

How do we respond to situations like this?

This kind of issue happens somewhere every day. Even if we have the best planning and organisation in the world, stuff happens, things go wrong. Unfortunately, Kerry feels that things go wrong at Biosolve all too often.

Sam, the Pharma client, is feeling let down. He wishes that Biosolve understood his own timelines. He also wishes he could work things out with Kerry and Pat, the downstream suite manager. Unfortunately, Sam's CMC head will undoubtedly get involved by firing angry messages to Biosolve management, blaming Sam for choosing them in the first place.

At a hastily convened meeting of the Biosolve SMT, the Finance Director reports that ABC has done exactly that. They are talking about penalty payments. The Ops manager says that in the last week, ABC management has already suggested establishing daily updates until the next delivery, even stationing a rep from their CMC function in Biosolve's facility.

Kerry himself is, as ever, in a difficult position. He has very little control over the production guys; things go wrong and the SMT get immediately involved without reference to him. Eventually things will likely get back on an even keel, but it's an unsatisfactory situation.

Build a trusting relationship

Let's pause for thought. Although Pat and his colleagues in the Downstream Unit appreciate the efforts of the sales guys, they're exasperated by being given project timelines that they know at the outset are impossible to meet. They are encouraged to work faster, but get increasingly demotivated. Micro-management from above or from clients will probably make things even worse. And after a while, Biosolve may build a reputation that it doesn't want.

This article describes an all-too-familiar situation – a requirement for increased performance without any more available resources. But without much time to think – in the face of urgent delivery issues and an embryonic CMO-Client partnership that is struggling to work. What can we do to grasp these issues? Read more to find out.

What we will suggest in a situation like this is something that may well feel 'unnatural' and a leap into the dark: *build a proper team and let it manage the work; let them build a trusting relationship with their opposite numbers.*

Why do something different?

Any conversation about meeting challenging deadlines runs, sooner or later, into questions of available resource (i.e. there isn't enough). It sounds nonsensical but in reality we often pretend that there is. Companies often 'oversell' to clients. But pulling back from this isn't always an option. We're in a competitive world, and somehow we have to get more done with available time and money.

Generally the latter means motivating people. *Getting everyone to work as hard as possible, to be as focused as possible*, to help us achieve our company goals.

This sort of attitude is often referred to as 'engagement'. This is the responsibility of companies' managers. But in addition, there is some 'free' motivational energy out there that can be used – and it has benefits for the individuals AND can improve productivity.

To bring these up to the present day, validated research by US economists showed that there are three things that really do increase engagement with work. *Autonomy* – self direction is good; *Mastery* – people love to do what they are good at, and can get better at, plus *Purpose* – people benefit by being connected to an overall, longer term goal. These three things generally occupy the top level of the Maslow model, and the right-hand end of the Herzberg.

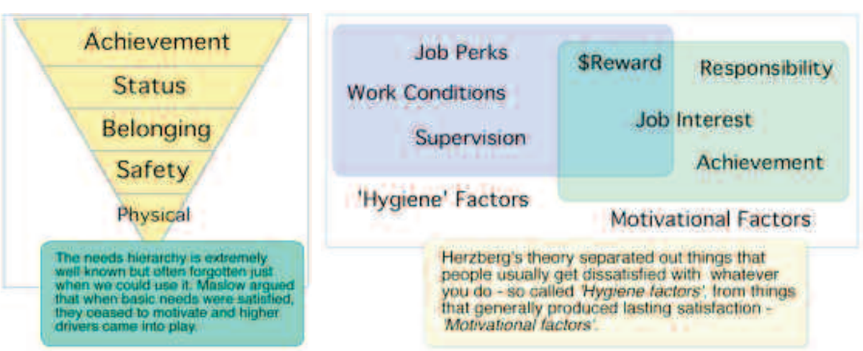

***Figure 1** shows two motivational models that are as old as the hills but still very relevant. Left, the Maslow and right, the Herzberg motivational models.*

Why are they important? It's **because all of these motivators are within the remit of a project team**. This could well be an inter-company team that spans two companies in a business relationship. **The more authority and responsibility invested in this team, the more motivated they will be to make things work.**

To trust or not?

This means trust, and trust has the potential to transform performance. The clearest, best planned, strategies can be fatally compromised by a low-trust environment.

Everyone has horror stories about this. These may be based on *gullibility*, too much trust, where we've believed enthusiastic promises, failed to check facts and been disappointed. Or on *suspicion*, too little trust, where we've been over-cautious and missed an opportunity.

In the ABC Pharma-Biosolve relationship, we may get either Sam or Kerry to lead a joint team. We would make sure all the players were represented on it. And we would charge it to manage the work, calling on senior management only when necessary.

It can be difficult to make a case to operate in this way. It certainly cannot be achieved if there low trust internally. But when companies have worked hard on their internal culture, there is another, arguably more difficult step required to build a trusting relationship across two organisations. Over-supervision is the default and is difficult to step back from (see **Figure 2**). However, there are some really helpful things you can do that will generate a more enthusiastic attitude across the business.

Build the internal cross-function teams

In the case of Biosolve, it would mean talking to the SMT, and other key players and highlighting where are the logjams of responsiveness and dissatisfaction internally. Remember that job descriptions, objectives, appraisals and roles/expectations are very often defined for line functions, whereas cross-functional structures are left to 'fend for themselves'. They need clarity, especially a defined role for the project manager and the teams' role with senior management.

These things apply to the internal teams, but also pay real dividends across a client-partner relationship:

- **Discuss the goals in depth.** Not just the CMO deliverables, but take time out to make everyone understand the overall Sponsor business objective. It's the sponsor's uncertainties and product development contingency plans that typically suppliers 'don't need to know' (until something goes wrong).
- **Set expectations in advance about when alerts and reports will be sent.** When 'things happen' – who alerts whom? Plan in advance. Trusting people never means that they don't let you know what's going on. The CMO is likely to be motivated to help a Sponsor – so why not let them drive some of the communication. Why not let them prepare agendas for meetings in advance?
- **Complete a thorough stakeholder analysis, together.** Sure there are difficult characters in the senior teams on both sides. Treat them like customers. Help people to understand what their position is, what their personality is and how best to influence them.
- **Complete a risk assessment together.** A project team can use this as a powerful influencing and communication mechanism. Not only can you flag up what horrible losses might occur, but you can also have a plan ready. In the real situation that inspired this case study, the project team's ongoing risk monitoring was actually built so that part of the SMT weekly meeting agenda was set automatically.
- **Talk about the relationship.** Take time to ask what's going well and why. What hasn't worked well, why, and what are we going to do about it.
- **Assess the relationship.** There are ways and means of assessing the health of a relationship. It's a great idea to get an outside pair of eyes to observe your team in action, and/or you can use an online assessment.

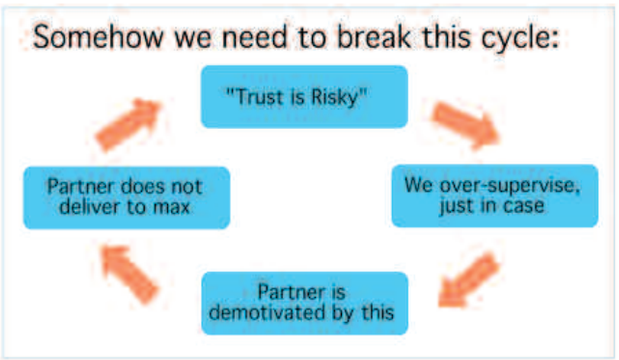

Figure 2

Get someone in to help you with the above!

Starting out to change some of these things can quickly become lost in detail, bias and distraction. And let's face it, you're there to resolve why molecules don't do what they are supposed to, not human beings! It really helps to get someone experienced (and neutral) to help you out.

Further reading: www.wimp.com/surprisingmotivation/
Stephen M R Covey 'The Speed of Trust' Simon & Schuster

John Faulkes helps companies to develop ways to work in effective business relationships, coaches and facilitates teams and team leaders. The case study in this article is based on a real project to improve CMO-Pharma relationship management, which John led in the last few years.
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New guidance for environmental monitoring in cleanrooms:

by Tim Sandle

an overview of the revised USP <1116> chapter

In May 2012, with the publication of the 35th edition of the United States Pharmacopoeia (USP), the chapter pertaining to the environmental monitoring of cleanrooms was updated[1]. Chapter <1116> "Microbiological control and monitoring of aseptic processing environments" is one of the few points of reference for the environmental monitoring programme. For the establishment of the environmental monitoring programme for sterile manufacturing, the microbiologist has few sources of 'official' guidance. The main sources are Annexe 1 to the EU GMP Guide[2], the FDA Guide to Aseptic Manufacturing[3], and the USP. In addition, the PDA has published a balanced guideline (Technical Report 13, last revised in 2001)[4]. In addition, there is the little used two-part ISO biocontamination control standard (ISO 15698)[5].

Although the USP is not mandatory it is taken as an important reference source and it is invariably drawn upon by U.S. Food and Drug Administration (FDA) inspectors for guidance and to enable comparison with the site undergoing inspection.

The need for a well thought out environmental monitoring programme is essential in order to assess the frequency of monitoring, the locations for monitoring, and types of culture media and incubation conditions. It is also important to consider upfront how the data will be collected, analysed and reported.

Revision

The revision process with the USP chapter has taken place over several years. The last update to the chapter was in 2007, and this was relatively minor in comparison to the 2012 review. According to Dr James Akers, a member of the USP Microbiology Committee, the review was triggered by change: "as contamination control technologies and analytical methodologies continue to evolve so must guidance and standards."[6]

In undertaking a revamp of the chapter, the USP committee had three key objectives:

- To focus the chapter on environmental monitoring only, by removing information relating to aseptic process validation and to the physical aspects of cleanroom operations.
- To focus the document exclusively on the monitoring of aseptic environments, by removing references to the monitoring of non-sterile environments.
- To reconsider the alert and action level (limit) concept.

Each of the key changes is examined below.

Chapter scope

The scope of the <1116> chapter has narrowed and focuses on aseptic manufacturing only, covering the following areas:

- Pharmaceutical sterile products,
- Bulk sterile drug substances,
- Sterile intermediates,
- Excipients.

Furthermore, its concern is limited to the following environments:

- Conventional cleanroom with a unidirectional airflow (UDAF) device,
- Blow-fill-seal,
- Rapid Access Barrier Systems (RABS),
- Isolators.

The chapter does not make any reference to the environments within which terminally sterilised products are prepared.

Acceptance of ISO 14644

A notable change with the new edition of the chapter is the final acceptance of ISO 14644 as the de facto global cleanroom standard[7]. All of the previous USP cleanroom descriptions have been removed together with any reference to former FS 209 standard. This brings the USP chapter in line with the 204 FDA aseptic filling guide.

Cleanroom measurement

The chapter makes reference to some aspects for the verification that cleanrooms are functioning to an acceptable standard. Reference is made to air-change rates, air velocity and air movement.

With cleanroom air changes the chapter states the expected standards of a modern cleanroom. These are:

- ISO class 8 = 20 air changes per hours.
- ISO class 7 = 50 air changes per hour.
- ISO class 5 = 100 air changes per hour.

The chapter also reiterates the need to have an airflow speed at ISO class 5 of 0.45 m/s (±20%) for a UDAF device in a cleanroom However, in acknowledging the differences between cleanrooms and isolators; it allows the use of isolators to be user defined.

The chapter also discusses the importance of conducting airflow visualisation (smoke) patterns at ISO class 5 in the 'operational' state. Importantly, the chapter recommends that an environmental monitoring programme should only be devised once airflow mapping has been completed.

Environmental monitoring

In relation to the methods for environmental monitoring the chapter makes no changes. For viable monitoring the use of the standard techniques is outlined: settle plates, active air samplers, contact plates, swabs and finger dabs. The recommended agar for viable monitoring is soyabean casein digest medium (equivalent to TSA) with an incubation regime between 20-35ºC for not less than 72 hours. Whether a selective fungal agar is used is left to the discretion of the microbiologist.

In discussing environmental monitoring, the chapter recommends due caution. This is because:

- No monitoring programme can prove sterility and should not seek to do so,
- Environmental control is more important than monitoring (in that any perceived risks should be addressed rather than simply monitored),
- Control should foremost be demonstrated by media simulations.

Furthermore, the chapter notes that environmental monitoring is often used for the wrong purposes as requirements have evolved in a manner that have not fully considered the analytical capability of the methods. This is a key point for the chapter and one pertinent to the discussion of action levels below.

The chapter does acknowledge rapid microbiological methods and reference is made to the technologies which allow real time particle counting and which are capable, through the use of fluorescent technologies, of differentiating between viable and non-viable particulates.

Contamination rates

With the focus upon aseptic filling, the chapter is not unrealistic in its exception of occasional, low-level microbial contamination events. The chapter states:

"An expectation of zero contamination at all locations during every aseptic processing operation is technically not possible and thus is unrealistic."

The chapter argues that many contamination events are due to so-termed 'false positives', by which they mean personnel intervention into the critical zone.

In relation to contamination levels, the USP chapter discusses the differences in relative risk between cleanrooms, RABS and isolators. These differences are based on the degree of personnel interaction and the strength of the aseptic barrier. More frequent contamination events are expected with cleanrooms than with a RABS, and, in turn, more frequent contamination events are expected with a RABS than with an isolator system.

The discussion of contamination is broken down into air-borne particles and viable counts.

Particle counts

With particle counts, the chapter notes that there will be occasional fluctuations with UDAF devices in cleanrooms. However, for isolators particle fluctuations should be less frequent and excursions above the class limit should a matter of greater concern.

Viable counts

Due to concerns about the imprecision of monitoring methods, the USP regards all types of viable environmental monitoring as semi-quantitative, since:

- The methods are inaccurate,
- Variation exists between methods (for example, models of active air sampler vary in collection efficiency up to a factor of 10),
- Recovery of microorganisms can be low, with swabs and contact plate recovering less than 50% of the microbial population found on a surface,
- People can contaminate any sample through the act of taking the sample,
- The methods are poor at recovering damaged or stressed microorganisms (like those found in aseptic filling environments).

Considerable emphasis is placed upon the trending of data and linking data fluctuations to events, as part of corrective action investigations. Such events may include:

- Maintenance e.g. HVAC, equipment,
- Disinfection,
- Unusual events and activities,
- Physical changes e.g. temperature and humidity,
- Staff training.

Action levels for viable monitoring

The section on action levels for viable environmental monitoring represents the biggest change to the chapter. The USP has a concern with the use of alert and action levels as numerical values and notes that alert and action levels evolved without sufficient consideration given to the metrology of environmental monitoring. This represents a significant departure from EU GMP.

The chapter argues that treating a result of 4 colony forming units (CFU) as significantly different from one of 2 CFU is not scientifically justifiable based on method limitations. The chapter notes that the limit of quantitation of environmental monitoring methods, that is the number of CFU that can be reported accurately, is 15.

Instead the USP chapter proposes basing action around the frequency of detection of microbial contamination rather than with the actual count detected. For this the chapter recommends that non-zero events are counted and compared to a contamination recovery rate metric. These incident rates are based on the premise that areas with more advanced contamination control technology should record fewer incidents of microorganisms. For example, lower incidents should be seen for an isolator compared with a conventional cleanroom. These incident rates are:

Whether these rates are achievable is a matter of debate and this will relate to the user's own facility.

In relation to actual counts, the USP chapter recommends that counts above 15 CFU are investigated. From this it could be assumed that it is perfectly acceptable to have counts detected on plates of up to 14 CFU in an aseptic manufacturing area without any investigation should the incident rate trend be

acceptable. This is not, when compared with EU GMP, likely to be something acceptable to the European regulatory inspectors.

Monitoring frequencies

The USP also provides guidance about frequencies of sampling. For isolators this runs:

- Active Air Sampling-once/day
- Surface sampling-at end of each campaign
- Glove sampling-left to the user's discretion

In relation to RABS, the revised <1116> states that 'open RABS' and 'closed RABS', where an open RABS should be monitored at the same frequency as conventional cleanrooms, reflecting the occasional need for direct operator intervention; whereas closed RABS should be monitored to the same as isolators, based on the low expectation of personnel intervention into the critical zone.

For conventional cleanrooms the recommended frequencies of monitoring are unchanged from the previous version of the chapter. These are:

- ISO class 5 = Each operating shift,
- ISO class 7 = Each operating shift,
- ISO class 8 = Twice per week,
- Other areas = Once per week.

With these there are differences to EU GMP. Given that EU GMP requires continuous monitoring in relation to aseptic filling, the USP recommended frequencies could be read as requiring a level of a lesser frequency than those specified by EU GMP.

Sampling locations

For the locations for viable environmental monitoring, the USP chapter considers the adoption of the ISO 14644 grid approach for particle counts but discounts this approach and instead argues that:

"Microbiological sampling sites are best selected with consideration of human activity during manufacturing operations."

The chapter goes on to recommend that such sites are to be selected from careful observation and mapping of the cleanroom, noting that the most likely route of contamination is airborne.

Other changes

The revised USP chapter contains some other, more minor changes. These are:

- An emphasis upon staff training, including those who take microbiological samples,
- Need for a qualified site microbiologist,
- The importance of staff health checks and control of entry to critical areas,
- Importance of correct gowning,
- Importance of risk assessment and risk mitigation.

Future developments

With the removal of all references to non-sterile facility environmental monitoring, the USP is considering the development of a chapter on "Microbiological Control & Monitoring of Non-Aseptic Processing Environments", for which the indicative chapter number <1111> has been assigned. Whether such a chapter will come to pass is uncertain given that operational intentions vary much more widely than with aseptic processing.

Conclusion

The USP chapter, as revised, raises some valuable points in terms of guidance for writing an environmental monitoring programme; in accepting the limitations of methods; and emphasising the importance of trend analysis. However, the near disregard of low level counts detected within the most critical zone creates a schism with EU GMP and the approach is likely to lead to disagreement amongst regulators. Whilst the incident counting approach is a useful addition to investigating EU GMP Grade A counts it cannot, and arguably should not, wholly replace it.

There are some further differences with EU GMP. For example, EU GMP Annex 1 presents the averaging of microbiological data, whereas the USP does not mention this. There is also no mention of microbial resistance to sanitisers or any indication of acceptance criteria for media simulation trials despite the reference to their importance.

Thus the USP chapter does not provide a complete solution to the intricacies of the environmental monitoring programme and is best used as a reference point to help shape and to benchmark individual monitoring programmes.

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Practical implications of Process Validation Guidance

by Siegfried Schmitt

For around a decade the concept of process validation remained unchanged in the respective regulations. This concept had been under review though and in 2008 the United States Food and Drug Administration (FDA) published a draft guidance document on process validation, which was superseded by the final Guidance for Industry, Process Validation: General Principles and Practices in January 2011. The European Medicines Agency (EMA) is somewhat lagging behind and published their draft Guideline on Process Validation on 29 March 2012 for public comment. Whereas the US document is written as a guidance document for use in inspections, the European one serves as guidance document for assessors of regulatory submissions (drug applications).

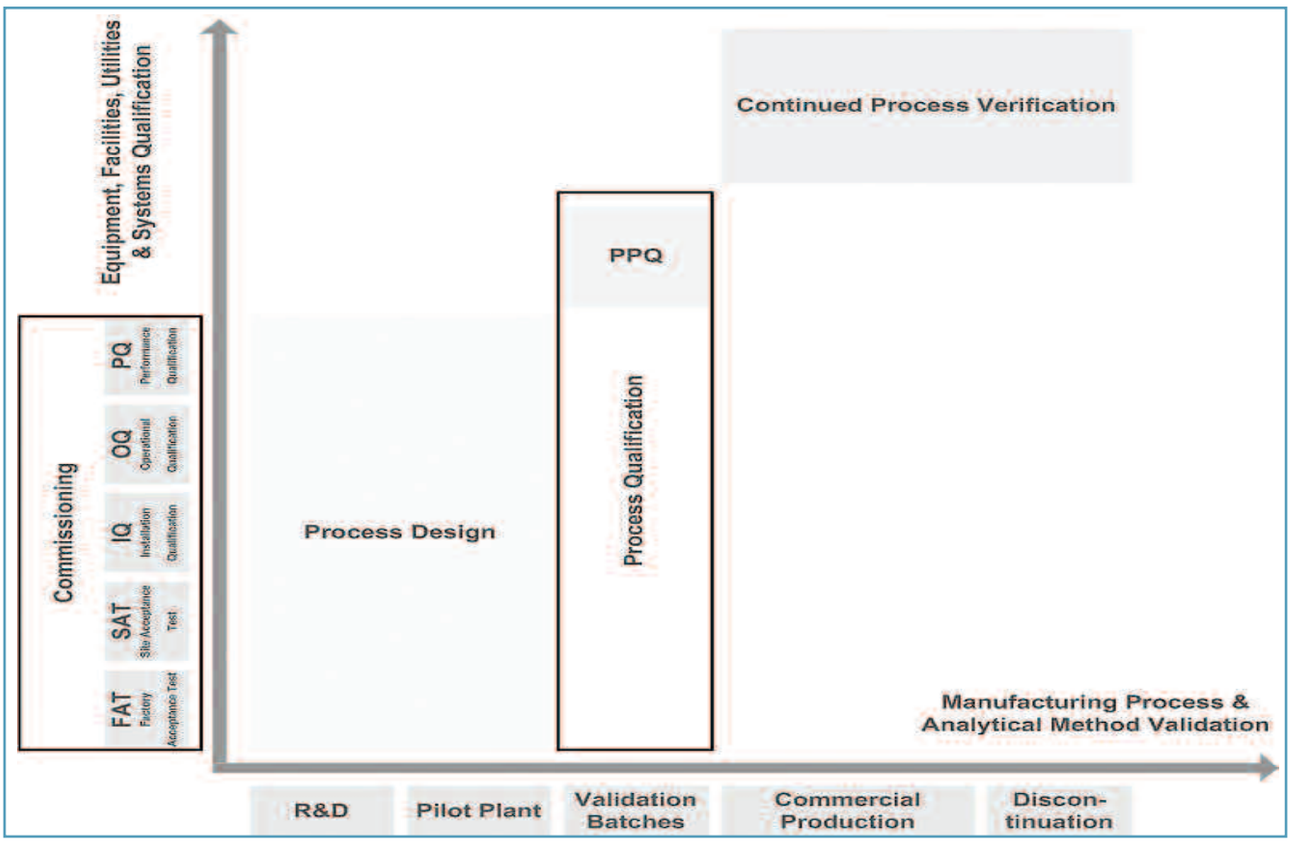
With the new guidance new terminology was introduced, such as Continued Process Verification or Process Performance Qualification (PPQ). It can be confusing when trying to understand how the traditional and the new approach and terminology correlate. Graphic 1 provides this information for the product lifecycle.

- Process Validation is now a true lifecycle approach
- There is new terminology for old concepts
- Knowledge management is fundamental for success

Changes to the traditional approach

Apart from an obvious change in terminology, the major new requirement is that of Continued Process Verification. Whereas in the past the regulators expected industry to maintain a process in a validated state and verify this in intervals, the new approach is one of continuous verification. That means that with every batch produced the validity of the process is being challenged. This is by no means a trivial requirement. In the traditional approach, companies would analyse their production batches once yearly retrospectively and report the outcome in the Annual Quality Report. At worst one would be a year late in realising that something was amiss.

It is now necessary to perform real-time (statistical) process trend analysis of the product, process and control parameters.



Graphic 1: *Correlation between traditional and new validation guidance terminology.*
Key to Graphic 1: FAT = Factory Acceptance Test, SAT = Site Acceptance Test = IQ - Installation Qualification, OQ = Operational Qualification, PQ = Performance Qualification, PPQ = Process Performance Qualification, R&D = Research & Development.

Again, in the past, most companies would merely verify and report if the values were within specifications, but not if there was any trending observed. Typical examples seen by the author were clear trends (e.g. yield or % impurities) towards upper or lower limits. However, no action was ever taken unless the limits were exceeded. These trend data would only be assembled at year end, far too late for any intervention.

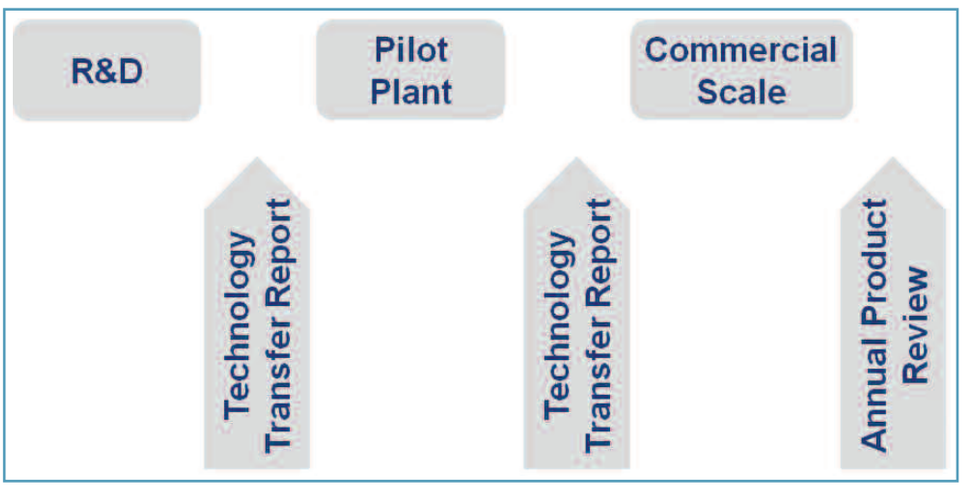
Where batch records are still paper-based, establishing such trend data can be difficult, if not impossible. Automation, at least for the recording of process parameters and analytical results is a necessity. This of course is a strong argument for considering the application for Process Analytical Technology (PAT).

Though the control strategy is not a new requirement, the way this should be developed and described however is different now. Traditionally, companies would file specific controls for their processes, without much or any discussion on the selection of these. Let us take the example of pH control for a neutralisation reaction. In the laboratory the acid in the round bottom flask may have been neutralised by the drop-wise addition of base, with the flask sitting in a dish of water and ice. The manual speed of addition of base would have been controlled by the temperature of the solution (visual check). In the pilot plant the addition may have been controlled by a pH meter and a control loop to the pump for the addition of the base. On a commercial scale an additional control factor may be added, fluid dynamics. Thus mixing speed, pH and temperature may be used as controls in commercial production. If this whole development and knowledge gained is correctly documented, one can file more than one control strategy for this one process, such as temperature and speed of addition (strategy 1), pH and speed of addition (strategy 2), mixing speed, temperature and pH (strategy 3), etc. The point is that despite the wealth of process understanding present, industry limits itself and prevents improvements and more importantly flexibility. In the case of multiple control strategies it can be possible to continue in a validated state even if one of the controls fails or is unavailable.

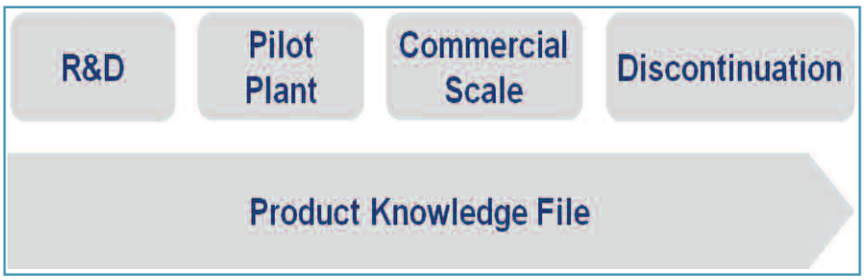
It is no surprise that industry is extremely reluctant to suddenly change the way process information is filed. For years the regulators have "conditioned" industry to describe precisely one single strategy, and industry has followed. Conditioned reflex is hard to overcome; for decades, the industry has been running from FDA (and EMA) inspectors like politicians from truth. The management isn't going to suddenly change their behaviour or outlook because the Agencies are now saying, "trust us." Does the (cartoon) picture of Charlie Brown attempting to kick a football (American) and Lucy pulling it away at the last moment sound familiar? After all this time, running and hiding from Agency representatives, managers aren't in a hurry to "kick the football" despite all the assurances that the Agencies will hold it still.

The regulators stress the need for process knowledge and understanding in these process validation guidelines. There is good reason for this as all too often this has been lost, be it because of "brain drain", i.e. the vast numbers of redundancies in the pharmaceutical industry, Research & Development being outsourced or acquired from third parties without adequate knowledge transfer, or simply because of inadequate documentation practices. The lifecycle approach calls for a rethink of the traditional way of documenting process knowledge and technology transfer. The traditional approach as shown in Graphic 2 is a step-wise approach where the information is captured in individual reports in intervals that can span many years. The downside of this is that only information deemed pertinent for the next step is typically included in the technology transfer reports and these documents are not normally written with the submission in mind, i.e. these do not tell the "story". These reports start gathering dust once issued, read and filed. They are rarely intended for continuous use and reference. Plus, these are only summaries with the raw data remaining in some archive, inaccessible to current process owners.

The way forward is to leverage modern technology, i.e. automated systems and to rethink knowledge management as



Graphic 2: *Traditional technology transfer documentation approach.*



Graphic 3: *Product Knowledge File*

a continuous process that sits along the product lifecycle – see Graphic 3. The information traditionally documented in the technology transfer reports and annual reports, would now be maintained in what could be named the Product Knowledge File. Such a file allows the generation of technology transfer documentation, annual product reports or any other report based on product and process knowledge for that point in time. Such a file could also contain the relevant raw data or at least link to it. Hopefully, such a file would also contain the information on the limitations and edges of failure for a process, plus the rationales for the control measures and specifications. This would be a major step forwards in many companies.

Outlook

The practical implications of the Process Validation Guidance from FDA and EMA are the need for establishing a process knowledge culture and documentation system that can and will support the validation lifecycle concept of continuous process verification. The width and breadth of knowledge gained can and should serve to achieve higher levels of control over the processes, resulting in fewer deviations and requiring fewer variations to Marketing Authorisations. Enhanced process understanding was always considered to aide process optimisation and is thus undoubtedly a commercial business benefit. Thus, compliance with these regulations makes perfect business sense. It will require however a change in mentality and the way knowledge is generated and maintained.

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Quality by Design: Perspectives on the current status of implementation

by Joanne Broadhead, Walkiria Schlindwein and David Potter

In terms of the current status of Quality by Design (QbD) implementation, the panel members from large pharmaceutical companies agreed that Quality by Design is now embedded within their development processes. 'Big pharma' typically adopted QbD methodologies at a very early stage of their rollout and have also contributed to the Food and Drug Administration (FDA) pilot schemes. The level of knowledge amongst employees is quite high and more often than not this knowledge level is achieved by 'in-house' rather than external training. These companies also apply QbD approaches to in-licensed projects where possible although this was noted to bring additional challenges.

The picture in small to medium size enterprises (SMEs) is, not surprisingly, very different. In this environment, cost is usually paramount and QbD is often perceived as adding another level of complexity and therefore expense. As members of the panel and audience pointed out, SMEs are often forced to strip out costs and are unable to take a long term view, even though they may wish to. Members of the audience from Contract Research Organisation (CRO) backgrounds also reflected this view in terms of their SME customers, with QbD sometimes being seen as something that can be 'bolted on' to satisfy regulatory demands.

One significant issue for CROs and SMEs is that they are required to shoulder many of the front-loaded costs (and therefore risk) of a QbD approach in the early stages of a product development process but are not the beneficiaries of the efficiencies and costs savings once a product is commercialised. Nevertheless, as Mike Hannay noted, understanding and adopting QbD approaches could create a significant competitive advantage for CROs with the right knowledge base. Mike also noted that whilst the first QbD projects within AstraZeneca consumed a huge amount of resource, now that processes have been streamlined the resource requirement is actually less than with conventional development methodologies.

The regulators' persepective

From the Medicine and Healthcare products Regulatory Agency (MHRA) perspective, the level of QbD implementation, as well as the content and size of QbD submissions, was also seen as highly variable. Brian Carlin noted that one factor in this was the lack of consistency between agencies and also between regulators within the same agency. Gustavo Marco acknowledged that there could sometimes be some variability in how different agencies interpreted the same guidelines but work is underway within Europe to standardize how the guidelines are applied. As

De Montfort University hosted a breakfast round table discussion event at the recent UKPHarmSci meeting in Nottingham, 12-14th September 2012. An invited panel of speakers from 'big pharma', SMEs, excipient companies, universities and the MHRA shared their views of the current status of QbD implementation and the obstacles to be overcome in advancing the QbD agenda. Members of the audience joined in a thought-provoking discussion around the status and future of QbD. This article reflects some of the key points of the discussion.

Gustavo pointed out, the regulators are on the same learning curve as the rest of the pharma community and this needs to be appreciated. Mike Hannay and Jo Craig both noted that the situation was even more complex when moving beyond ICH countries. Mike noted that this has added to the work that his R&D organisation needs to do in supporting submissions which may be QbD for some territories and non-QbD or 'QbD-lite' for others.

In general, the MHRA felt that the industry had been a little slow to embrace new approaches, including the concept of QbD. The panel (and audience) agreed that this is particularly the case in terms of manufacturing technology where the move to continuous processes has been slow. This undoubtedly reflects the fact that implementing the ICH Q8[1] approach to development is considerably easier than diverging from the traditional batch based approach for which there is much existing manufacturing capacity. It was noted that other industries such as food and tobacco manufacturers as well as pharmaceutical excipient manufacturers, are far more advanced than the pharma industry in terms of their adoption of modern technology and, as Steve Wicks commented, could even constitute a threat to traditional pharmaceutical manufacturers. Brian Carlin, from FMC Biopolymer, noted that the excipient industry has been using continuous manufacturing technologies for 50 years!

"QbD not a binary tool"

The perception of QbD as an 'all or nothing' alternative to conventional pharmaceutical development may also be off putting to the SME sector. A member of the audience commented that 'QbD should not be viewed in a binary way'. This view was also echoed by Gustavo Marco; the regulator would rather see elements of QbD used in a development programme than none at all. A poor understanding of some of the tools and principles of QbD can also lead to the misconception that a QbD approach to development is significantly more front-loaded than conventional

development. This perception sometimes results from a poor understanding of what QbD tools can deliver; for example proper use of experimental design techniques can generate significantly more information from fewer experiments than traditional methods of experimentation. Similarly, as Steve Metcalf noted, the use of continuous processing technology can also enable DoE experiments to be conducted in a matter of hours rather than weeks. By correcting these misconceptions around what QbD is and isn't, it should be possible to achieve a greater buy into QbD among those outside the 'big pharma' community. As Steve Metcalf remarked, 'You don't need all the PAT technology to adopt a QbD approach'.

Whilst those present at the discussion seemed to agree that QbD is a 'good thing', there was almost certainly an element of 'preaching to the converted' given that the audience was drawn from attendees at the UKPharmSci meeting; a population who typically have a strong Pharmaceutical Sciences background. There certainly seemed to be a feeling that a significant number of 'QbD sceptics' remain, particularly amongst the SME community. Big pharma are clear in their belief that adopting a QbD approach is the right thing to do; it is about understanding the patient need, doing good science, adopting appropriate risk management techniques, gaining process understanding, etc., and is likely to result in a more robust product in the long term as well as some regulatory benefits. There may also ultimately be cost savings although this is not the key driver for big Pharma. They feel that they now have evidence to support the benefits of a QbD approach to development, having transferred processes to operations organisations with significantly better process capabilities than in the past. There was a consensus amongst the panel and audience that it would be very helpful if big pharma were able to share some of their successes[2].

Training and education were mentioned a number of times during the discussion and there are perhaps two significantly different target audiences for such training. Clearly the grass roots pharmaceutical scientists need to have a good understanding of the tools and principles of QbD and how this can be applied. There are a number of short courses available addressing this need and also the distance learning MSc programme at De Montfort University. It is also clear that the leaders of SME companies need a greater understanding of the potential benefits of adopting a QbD approach. The challenge for the pharmaceutical sciences community is to explain to the wider pharma world and to their customers that the key elements of a QbD approach will result in a more robust product in the long term as well as some regulatory benefits and potentially cost savings. These claims need to be supported by evidence.

In summary, QbD is now largely embedded by big pharma and they, as well as the regulators, are convinced of its benefits. This message needs to be disseminated more widely – ideally backed up by evidence from big pharma's experiences to date. In parallel, more needs to be done to train and educate both grass roots scientists and their leaders so that a 'tipping point' is reached at which QbD approaches to pharmaceutical development become the norm. This will be to the benefit of industry, the regulators and ultimately the patient.

We are very grateful to our panel members for leading this important discussion: Mike Hannay, Vice President, Medicines Development, AstraZeneca; Jo Craig, Vice President, UK Product Development, GlaxoSmithKline, Steve Metcalf, Director, SteM Solutions; Steve Wicks, Professor, University of Greenwich; Brain Carlin, Director of Open Innovation, FMC Bioplolymer; Gustavo Marco, Manager and Senior Assessor, MHRA.

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Joanne Broadhead currently works part time for DMU having spent most of the last 15 years working for AstraZeneca. Her main role on the QbD programme is to continue to strengthen the links with industry and the regulators so that we can continue to provide the most up to date learning material delivered by industry experts. In addition she is part of the QbD academic team.

Walkiria Schlindwein has worked in academia for more than 15 years. She is currently the programme leader of the Postgraduate courses in QbD (full time and distance learning) and a member of the academic teaching staff. She has a strong academic interest in the science underpinning QbD and has developed collaborations with numerous organisations that are active in this field.

David Potter supports the team by handling the communications, technology and events. His background is in applying innovative technologies within education.

by Malcolm Holmes

Introduction

Developments in the "regulation" of the pharmaceutical industry since our last review include:

Europe

EC/EMA

Swiss GMP and inspection standards for API considered equivalent to those of the EU

Switzerland has been listed as the first country with equivalent standards in the manufacture of active pharmaceutical ingredients (APIs) to those of the EU.

Based on the decision to include Switzerland to the listing of third countries, Switzerland will not have to issue a 'written confirmation' for each consignment of active substance for medicinal product for human use imported into the EU as of 2 July 2013. Other countries that have requested an assessment are Australia, Brazil, Israel and Singapore. Notably, India and China have not yet applied.

Guideline (for comment) on the use of bovine serum in the manufacture of human biological medicinal products

This revision of the original 2003 guideline (CPMP/BWP/1793/02) outlines the general principles that should be applied to the control of the quality and safety of bovine serum used during the manufacture of human biological medicinal products. This revision affects only Sections 7.3.3 and 7.3.4 where the testing requirements for Bovine Viral Diarrhoea Virus (BVDV) and anti-BVDV antibodies have been revised to be in accordance with the requirements applied for the production of immunological veterinary medicinal products (EMEA/CVMP/743/00-rev 2.). The revision was open for comment until 31 Dec 2012.

Guideline (for comment) on quality of oral modified release products

This guideline concerns quality aspects, especially pharmaceutical development and in vitro testing, of dosage forms in which the release of active substance is modified. It only covers delayed release oral dosage forms with the principle of gastro-resistance and prolonged release oral dosage forms. Pulsatile and accelerated release dosage forms are not covered. Delayed release dosage forms with other principles, including those designed to release in a specific area of the gastrointestinal tract in response to a specific trigger (e.g. enzymes) or at specific time(s) after ingestion are also not specifically addressed. However Many principles discussed under paragraph 2 with respect to prolonged release oral dosage forms will be relevant to other modified release dosage forms intended for oral administration or via other routes.

This guideline, together with the guideline on quality of transdermal patches, replaces the note for guidance on modified-release products: A: oral dosage forms B: transdermal dosage forms: part I (quality).

The document, is open for comment until 15 March 2013.

Changes to variation rules started to apply from 2 November 2012

The main purpose was to extend the application of the Variations Regulation to marketing authorisations granted at national level so that all marketing authorisations granted in the European Union (EU) are subject to the same rules, a number of changes affect centrally authorised medicines. These include:

- Changes to the decision-making process for variation procedures, so that changes that are critical for public health are reflected in marketing authorisations within two months, while other changes are reflected in periodic updates (within one year);
- The inclusion of compliance statements with the agreed, completed paediatric investigation plan in the marketing authorisation.

Information explaining how the new rules will affect pending variation procedures and applications submitted following a work-sharing procedure is available.

The Agency will be updating post authorisation procedural advice to reflect the changes.

Provisions governing purely nationally authorised medicines and applications submitted following a work-sharing procedure start to apply on 4 August 2013.

Reflection paper on medicinal product supply shortages caused by manufacturing/GMP Compliance problems

This Reflection Paper is concerned with public health crises that arise due to unforeseen disruptions within the manufacturing process, caused by manufacturing/GMP compliance problems and affecting medicinal products for human use, independent of their route of authorisation, where a need for co-ordination of the assessment and risk reducing actions at a Community level has been identified. The EU GMP Inspectors Working Party (GMP/GDP IWG) has adopted a concept paper for revising Chapter 8 of the GMP Guide "Complaints and Product Recall". The concept paper has identified that the management and minimisation of supply shortages that may arise as a result of quality defects should also be addressed in a revision of Chapter 8. The proposal, among other things, is to clarify reporting requirements relating to restriction of supply whether or not this relates to a quality defect.

While control and supervision of the national market remains a national responsibility, Member States may

experience difficulties in acting in a purely national way when faced with a pan-European crisis.

This Reflection Paper summarises the lessons learned from previous crises where the EMA had a supporting or co-ordinating role, and presents short and mid-term actions that may allow the Network to prevent, mitigate, and manage shortages of important medicinal products.

Draft Concept paper on revision of Annex 15 (Qualification & Validation) of the GMP guide

Annex 15 was originally published in September 2001 and since then there have been significant changes in the GMP environment with the incorporation of ICH Q9 and Q10. In addition, the Quality Working Party (QWP) is in the process of updating its guideline on process validation and there has been advancement in manufacturing technology through the introduction of process analytical technology (PAT) and the continuous manufacture concept. There have also been many changes to other chapters and annexes in the GMP guide, which may have an impact on annex 15.

Draft Concept paper on revision of Annex 17 of the GMP guide

This concept paper addresses the need to update annex 17 (parametric release) of the GMP guide. At the time the original guideline was adopted (January 2002), the main foreseen application area was sterility testing, with particular focus on the release of terminally sterilised medicinal products. Since then, there have been significant changes in GMP consequent to the adoption of the ICH Q8, Q9 Q10 and Q11 guidelines. Furthermore the Quality Working Party has recently published a guideline on real-time release testing.

UK Medicines and Healthcare Regulatory Agency (MHRA)

Public consultation (MLX 379): Transposition of Directive 2011/62/EU ("the Falsified Medicines Directive") into UK legislation

This consultation sets out, under sections that address the key topics addressed in the Falsified Medicines Directive, a brief summary of the way in which the Directive will change the current regime. It invites comments on the proposals for implementation.

The Falsified Medicines Directive substantially changes the European framework concerned with the supply of medicines, and may capture businesses that have traditionally not been directly regulated. An example of this would be internet platforms based in the UK offering medicines for wholesale or retail supply, which may be considered to be brokering or offering "sales-at-a-distance". The purpose of this consultation is to:

- Present draft transposition regulations and explain the MHRA approach in determining them;
- Test that the transposition regulations are full, accurate and workable legislative text;
- Ensure that the draft transposition regulations do not introduce any unintended changes;
- Seek further evidence of the impact of the transposition regulations and proposed policy changes.

MHRA wins High Court case on wholesaler dealing

MHRA has written to all those holding wholesaler dealer's licences reminding them of the regulations following a recent High Court case. The case concerned whether or not regulations allowed for those that operate both as registered pharmacies and licensed wholesale dealers to obtain medicinal products from pharmacies which do not hold a licence to distribute

The judge ruled that it is unlawful for the holder of a wholesale dealer's licence to obtain supplies from a person who does not have a licence to distribute medicinal products. He also said that it is no defence for the holder of the wholesale dealer's licence to claim he was acting as a pharmacy when he obtained the products from a person who does not have a licence to distribute.

The core of the judgment is that in order to comply with legislation, holders of wholesale dealer's licences (even if they also operate as a pharmacy) must only obtain medicines from another wholesale dealer licence holder or from a licensed manufacturer.

Public consultation on the revision of European legislation on medical devices

Medical device regulation continues to be a hot topic of debate following PIP breast implants and the recent safety concerns involving metal-on-metal hips.

In September the European Commission published what it thinks the new legislation on medical devices should look like. The Member States of the European Union and the European Parliament will now negotiate and agree on the final legislation. This public consultation sets out what MHRA thinks about the different changes suggested by the European Commission.

The MHRA has been pressing the European Commission to strengthen the current European system of regulation for four years and has now launched a ten-week consultation so that healthcare professionals and the public could give their views on whether new draft legislation from the European Commission goes far enough in the following areas:

- Promoting the safety of medical devices and ensuring public confidence in the regulatory system
- Improving the organisations (notified bodies) which assess the safety of medical devices

- Ensuring transparency and ensure better collaboration between national regulators

The comment period ended 21 January 2013

Change of ownership applications (COA)

The change of ownership scheme is used when a company wishes to transfer a licence from one company (legal entity) to another. To ensure that the MHRA has sufficient time to close all applications on the old licence as much warning as possible should be given of any proposed changes of ownership. Where possible, variations should not be submitted once an application for change of ownership has been made.

A new Response Deadline Implementation on all COA submissions made after 7th December 2012 has been imposed. A failure to respond to Request for Information (RFI) within 14 calendar days from the date of the letter will result in the withdrawal of the application.

Manufacturers should also note that a letter from the manufacturer (if not the applicant) should be supplied confirming that they are prepared to manufacture on behalf of the new licence holder. If the manufacturer is not going to be used or no longer exists an assurance should be provided that a variation will be submitted to delete the manufacturer(s).

Request for active substance information

MHRA is contacting UK-based MA holders to request data on active substance imported into the UK for manufacture. The aim is to minimise the risk of potential shortages of human medicines by identifying high risk suppliers which may need to be inspected by an EU authority as they cannot meet the requirements for certification by competent authority of the exporting third country that the plant manufacturing active substances operates in compliance with EU GMP, or with equivalent rules or that the third country has been listed by the European Commission as a country with an equivalent system of supervision and inspection as in the EU. MHRA's intention is to prioritise and coordinate these inspections, together with those for centrally authorised products, on an EU-wide basis.

(Note: Manufacturers and regulators have only until July 2 July 2013 to ensure that such written confirmation of EU GMP compliance is available. As yet it seems likely that for many active substances supplied from major countries, particularly India and China such confirmations may not be possible by the deadline. If this actually is the case there could be serious consequences for medicines supply. This initiative by MHRA is a step in the right direction but with only 6 months to go it appears a little late to be starting to assess the scale of the problem, which on an EU scale could be very large indeed. MBH)

Q&As from the falsified medicines directive

MHRA has issued a 4 page 17 point Q&A concerning Active Substances in relation to the Falsified Medicines Directive. It also covers matters relating to brokers dealing with such substances and other general matters

USA

Guidance for Industry -Self-Identification of Generic Drug Facilities, Sites, and Organisations

Self-identification under Generic Drug User Fee Amendments (GDUFA) is required for two purposes. First, it is necessary to determine the universe of facilities required to pay user fees. Second, self-identification is a central component of an effort to promote global supply chain transparency.

The information provided through self-identification will enable quick, accurate, and reliable surveillance of generic drugs and facilitate inspections and compliance.

Under GDUFA, if a facility fails to self-identify, all Finished dosage form (FDF) or API products manufactured at the facility and all (FDF) human generic drugs containing APIs manufactured at the facility will be deemed misbranded.

FDA estimates that approx. 2,650 facilities will submit self-identification The requested information will include:

- Name
- Registrant D-U-N-S Number
- Registrant Contact Information
- Establishment (Facility) Information
- Establishment Facility D-U-N-S Number
- FDA Establishment Identifier (FEI)
- Physical address
- Type of Business Operations
- Establishment (Facility) Contact Information

Blood products – Exceptions and Alternative Procedures Approved Under 21 CFR 640.120

The Director, Center for Biologics Evaluation and Research, may approve an exception or alternative procedures to any requirement in subchapter F (Biologics) of Chapter I (Parts 600 – 680) of title 21 of the Code of Federal Regulations regarding blood, blood components or blood products.

Both licensed and unlicensed blood establishments must submit requests for an exception or alternative procedure. Such requests should ordinarily be made in writing, however, in limited circumstances, such requests may be made orally and permission may be given orally by the Director. Oral requests and approvals must be promptly followed by written requests and written approvals.

It should be noted that requests for exceptions or alternate procedures includes specific circumstances and may require submission of supporting data unique to the circumstance. Publication of these approvals for a specific exception or alternative procedure does not necessarily mean that they can be generally applied to other manufacturers.

A cumulative list of approved exceptions and alternative procedures is available.

Important change to heparin container labels to clearly state the total drug strength

This label change will require manufacturers of Heparin Lock Flush Solution, USP and Heparin Sodium Injection, USP to clearly state the strength of the entire container of the medication followed by how much of the medication is in 1 milliliter (ml).

Since 2009, concerns have arisen about the conflict in labeling requirements between the Heparin Sodium Injection and Heparin Lock Flush Solution monographs and the General Chapter <1> Injections section on "Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products." USP has proposed revising the labeling section of the heparin monographs to ensure that the heparin container labels comply with the USP General Chapter <1> Injections section.

International

Canada

Consultation Draft Guidance on GMP for APIs (GUI-0104)

This Guidance is part of the overall process to bring the proposed amended Food and Drug Regulations into force. Highlights are as follows:

- GUI-0104 interpretations are based on the ICH Q7 GMP for APIs and the current Canadian GMP – 2009 Edition, Version 2 (GUI-0001).
- Annex F of GUI-0104 provides a cross-walk between ICH Q7, GUI-0001 and GUI-0104 interpretations.

The consultation period ended January 5th, 2013

Risk Classification of Good Manufacturing Practices (GMP) Observations GUI-0023

Health Products and Food Branch Inspectorate has revised this document which came into force in September 2012. Its purpose is to

- Classify the observations noted during establishment inspections according to their risk
- To ensure uniformity among the inspectors of the Health Products and Food Branch Inspectorate (Inspectorate) in the attribution of the rating following establishment inspections.
- To inform the industry of the situations that the Inspectorate considers unacceptable and that will generate a Non-Compliant (NC) rating following an inspection.

ICH

ICH Q7 Q&As Final Concept Paper

It has become apparent, based on the approval and implementation of ICH Q8, Q9, Q10, Q11 principles into GMP of APIs that certain individual implementation approaches are leading to non harmonised interpretation and new expectations beyond the intention of ICH Q7.

Technical issues with regard to GMP of APIs and also in context with new ICH Guidelines – need to be addressed in order to harmonise expectations during inspections.

A document would be helpful in removing these ambiguities and uncertainties and also in harmonising the inspections of both small molecules and biotech APIs

The timeline proposed for development of this document is

- Concept paper approved at ICH Steering Committee teleconference, 3Q 2012.
- First meeting of the Q7 IWG in San Diego, November 2012.
- Step 2/4 expected in 2014.

India

Draft Guideline on Good Distribution Practices for Biological Products

India's Central Drugs Standard Control Organisation (CDSCO) has published a draft Guideline on Good Distribution Practice (GDP) for biological products. Such products can be particularly sensitive to issues such as power blackouts which are a relatively routine event in India. This is covered in section 10.8 which states "storage areas shall be equipped with backup power source or have alternate storage available in the event of power failure."

INTERPOL-

PANGEA V Coordinated operation against illegal internet sale of medicines

A global operation against illegal online trading of medicines has taken place. The operation was joined by more than 190 authorities from 100 countries all over the world.

Worldwide, the operation resulted in 80 arrests, inspection of more than 130,000 parcels and seizure of over 3.7 million units containing potentially life-threatening medicines worth around 10.5 million US Dollar. During the operation, almost 20,000 illegal medicines websites were identified of which more than 18,000 have been shut down or have had their payment option removed from the website.

PIC/S

Membership status

- New Zealand's Medicines and Medical Devices Safety Authority (Medsafe) and Chinese Taipei / Taiwan Food and Drug Administration (TFDA) will join the Scheme as from 1 January 2013, becoming PIC/S' 42nd and 43rd Participating Authorities.

- Rapporteur and Co-Rapporteurs in charge of pre-assessment were nominated in respect of Uganda's National Drug Authority (NDA),
- A pre-accession membership application was received on 17 October 2012 in respect of Belarus.
- Paper assessments in respect of Iran have been completed
- Paper assessments in respect of Japan and Korea have commenced

API inspection training

PIC/S has developed a threefold PIC/S International API Inspector Training Programme.

A new global training course programme, which is not limited to basic training as it will cover the whole of ICH Q7 and will be open to both inspectors and industry, is about to be launched in co-operation with PDA (Parenteral Drug Association).

Revised PIC/S GMP Guide

The revised PIC/S GMP Guide (PE 009-10) was adopted by the PIC/S Committee The revision concerns Chapter 4 (in relation to Computerised Systems) & Annexes 6 (Medicinal Gases), 7 (Herbal medicines), 11 (Computerised Systems) and 13 (Investigational Medicinal Products).

The revised PIC/S GMP Guide will enter into force on 1 January 2013, as will the corresponding changes to the EU GMP.

Seminar on "Qualification and Validation

The objectives were to give to GMP inspectors theoretical and practical knowledge of new approaches to qualification and validation (Q&V), the theory and practice of Process Analytical Technology (PAT), control strategy of Real Time Release Testing (RTRT) and other important issues.

WHO

Annex 2 WHO GMP: water for pharmaceutical use

This document is provided in the WHO Expert Committee on Specifications for Pharmaceutical Preparations Forty-sixth report, under WHO Technical Report Series No. 970, 2012. It is a revision of WHO good manufacturing practices: water for pharmaceutical use, previously published in WHO Technical Report Series, No. 929, Annex 3, 2005.

The guidance contained is intended to provide information about the available specifications for water for pharmaceutical use (WPU). Guidance about which quality of water to use for specific applications, such as the manufacture of active pharmaceutical ingredients (APIs) and dosage forms and to provide guidance on GMP regarding the design, installation and operation of pharmaceutical water systems.

This document refers to available specifications, such as the pharmacopoeias and industry guidance for the use, production, storage and distribution of water in bulk form. In order to avoid confusion it does not attempt to duplicate such material.

The guidance provided can be used in whole or in part as appropriate to the application under consideration. Where subtle points of difference exist between pharmacopoeial specifications, the manufacturer will be expected to decide which option to choose in accordance with the related marketing authorisation submitted to the national medicines regulatory authority.

Annex 5 Development of paediatric medicines: points to consider in formulation

Safe and effective pharmacotherapy for paediatric patients requires the timely development of medicines and information on their proper use appropriate to the age, physiological condition and body sise of the child.

In December 2007 WHO launched its initiative "Make medicines child size" in order to raise awareness of and accelerate action to meet the need for improved availability and access to child-specific medicines. Among actions to support this initiative is the present "Points to consider" document on the formulation of paediatric medicines. The objective is to inform regulatory authorities and manufacturers on issues that require special attention in pharmaceutical formulation. Its focus is on the conditions and needs in developing countries. The guidance does not provide exhaustive information and does not exclude the possibility that other aspects may be relevant to the development of paediatric medicines.

Products

Contaminated steroid injections –Multistate (USA)Fungal Meningitis Outbreak

The Centers for Disease Control and Prevention (CDC), in collaboration with state and local health departments and the FDA is investigating a multistate fungal meningitis outbreak among patients who received contaminated steroid injections. Several patients suffered strokes that are believed to have resulted from their infections. The investigation also includes fungal infections associated with injections in a peripheral joint, such as a knee, shoulder or ankle.

FDA has informed the drug regulatory authorities in Europe, that the medication has not been exported to any EU country.

Further information on these and other topics can be found in recent versions of the "GMP Review News" circulated to subscribers by Euromed Publications and on the websites of the relevant regulatory bodies and international organisations. In addition a list of useful websites can be obtained from: info@euromed.com.

Book Review

A Road Map to GMP Compliance

In two parts, 'A Road Map to GMP Compliance' provides a summary of stand-alone articles originally published in 'The Journal of Validation Technology'. Interestingly, my review started on the return flight from visiting a company in the middle of a Warning Letter. Now I don't know about you, but a book title matters. A title must deliver what it promises. So, if my client had read 'A Road Map to GMP Compliance' and executed the recommendations contained within, would they have prevented their non-compliance 'woes'? Unfortunately, NO. However, some of individual articles are better than others. Let's start with the 'lows' and end with the 'highs'

The Lows

Although some of Torbecks recommendations in 'Implementing the Tools of Process Quality – A Policy Statement' are laudable the opening paragraph killed it for me. 'This feature discusses the various tools and techniques used by quality and compliance professionals in their daily work responsibilities'. This view is outdated and just plain wrong. Over 30 years in the industry have taught me that quality and compliance professionals have very little real influence on product quality. The quality of any medicine is actually down to the quality of those actually making it. In companies where high standards of GMP have become a habit you find that manufacturing personnel are the custodians of quality and compliance, not 'QA'

The section on 'Upsizing Compliance in a Downsizing Environment' (Henson) wrestles with the problem of seemingly opposing objectives. Namely increasing regulation and the need for companies to cut costs. In positioning FDAs view on downsizing and cost cutting the author starts by saying that 'FDA's primary concern is compliance'. I profoundly disagree. So did the many regulators I shared this statement with. The primary job of every regulatory agency is not 'compliance', it is patient safety. This includes bringing lifesaving medicines to the market place as soon as possible. If FDA's primary job is compliance why are they taking such a strong lead in ICH Q8, 9 and 10? The comment that 'a high percentage of warning letters issued by FDA refer to a failure of the QC unit to fulfil its responsibilities' will leave many committed QA folk speechless. In my experience every QA professional does the best with what they have. Failure in QC? No. Failure in company leadership? YES.

I found Jones's insight into the 'Review of Batch Production Records outdated for a number of reasons. It implies that a detailed BPR and a robust review process are the foundation of a reliable 'pass or reject' decision. As every experienced Qualified Person knows, a perfect BPR does not mean a perfect batch. Product cannot be released without having confidence in the entire Quality Management System. This section would have benefited from helping readers understand how this can be achieved rather than putting too great an emphasis on the BPR alone.

The Highs

Anisfeld's contribution, 'GMP Failures: Ignorance or Arrogance' chronicles GSKs $750 million fall from grace following its failure to manufacture drugs in accordance with GMPs at its Cidra facility, Puerto Rico. Although only those involved can vouch as to its accuracy, its serves as a very potent reminder to all. GMP compliance is not rocket science. It's about doing the basics very well. This requires leadership and intelligent investment. When one fails you pay a very heavy price indeed. What a shame most company CEOs will be too ignorant, arrogant or just plain 'busy' to read this article and learn from the mistakes of others.

Torbeck's articles on 'Data Culture' should be read by all. The pharmaceutical industry is most definitely guilty of being data rich but information hungry. In short, we generate lots of data and do nothing meaningful with it. Anything that encourages people to make better use of the data they generate is to be applauded.

Eldon's commentary on 'GxP Excellence by Design' is a gem. The pharma' s typical approach to GMP compliance has historically been very simple and very wrong. 'These are the rules…just follow them'. Eldon's 'eight key principles of excellence' emphasises what really matters. The importance of attitude, discipline and sustainability throughout the organisation, from top to bottom with no mention of blind, 'follow the rules', compliance. Hallelujah!

If you do decide to purchase this special edition, Part Two will probably make it worthwhile. It focuses on the importance of education and training. Starbucks Coffee invests approximately $10,000 dollars for each of its coffee 'baristas' per annum. In their first year all employees spend a minimum of 50 hours in Starbucks classrooms and dozens more at home with Starbucks workbooks and talking to the Starbucks mentors assigned to them. How does this compare with your companies training budget and commitment? Most pharma companies still see training and education as a cost not an investment. Something they have to do to tick the compliance 'box'. Anything that attempts to change this attitude should be celebrated!! As the old saying goes, if you think education is expensive, try ignorance.

Reviewed by Martin Lush, Senior Partner at NSF-DBA, Kirkbymoorside, Yorkshire, UK.

Published by Advanstar Pharmaceutical.
Part 1: 88 pages, Part 2: 84 pages
Price starts at $295 (Members only)

Events

February 2013

18-19 February 2013 – London, UK
Advances and progress in drug design
www.drug-design.co.uk

19-20 February 2013 – London, UK
Real world outcomes strategy for pharmaceutical products
www.healthnetworkcommunications.com/evidence

19-20 February – Brussels, Belgium
Disposable Solutions for Biomanufacturing
www.pharma-iq.com

26-27 February 2013 – Barnard Castle, UK
Cleaning validation
www.honeyman.co.uk

26 February-1 March 2013 – London, UK
The business strategy of affordable medicines
www.healthnetworkcommunications.com/generic

26 February-1 March 2013 – London, UK
Innovations in development for the biosimilar industry
www.healthnetworkcommunications.com/biosimilarseu

26 February-1 March 2013 – London, UK
World Generic Medicines Congress
www.healthnetworkcommunications.com

26 February-1 March 2013 – Berlin, Germany
Pharmaceutical Microbiology
www.europe.pda.org/Micobio2013

26 Feb-1 March 2013 – London, UK
Biosimilar Drug Development World Europe
www.healthnetworkcommunications.com

28 February 2013 – London, UK
6th Annual MHRA Paediatric Seminar
www.mhra.gov.uk

28 February 2013 – London, UK
The Pharma Summit 2013
Back to Basics: The Real Business of Pharma
www.economistconferences.co.uk

March

3-7 March 2013 – Sorrento, Italy
3rd International Conference on Multifuncational, Hybrid and Nanomaterials
www.hybridmaterialsconference.com

4-6 March 2013 – Copenhagen, Denmark
7th Annual FEI EMEA Front End for Innovation
www.IIRUSA.com/FEIeurope

12-14 March 2013 – Barnard Castle, UK
Cleanrooms: Principles in Practice
www.honeyman.co.uk

13-14 March 2013 – Bologna, Italy
Bio-contamination Control and Developments
www.ima-pharma.com

19 March 2013 – London, UK
16th Annual Discussion Meeting with the MHRA for QPs, QA Managers and their colleagues
www.pqg.org/pharma/events

20-21 March 2013 – London, UK
Stability Testing for Pharmaceuticals
www.informa-ls.com/filter/manufacturing

21 March 2013 – London, UK
Progress and challenges in pharmaceutical harmonisation
www.jpag.org

31 March-3 April 2013 – Lisbon, Portugal
9th World meeting on pharmaceuticals, biopharmaceutics and pharmaceutical Technology
www.apv-mainz.de

April

23 April 2013 – London, UK
The 13th Joint QP Symposium – Falsified Medicines and the EU Directive.
www.rpharms.com

May

14-15 May 2013 – Budapest, Hungary
Bioavailability, Bioequivalence, Dissolution and Biowaivers
www.informa-ls.com/filter/manufacturing

14-15 May 2013 – Brussels, Belgium
Filing Variations
www.informa-ls.com/filter/manufacturing

16-17 May 2013 – Edinburgh, Scotland
Problem Solving in process R&D
www.scientificupdate.co.uk

21-23 May 2013 – St Petersburg, Russia
Russian Pharmaceutical Forum
www.adamsmithconferences.com/sector/pharmaceuticals

Useful website addresses

European Medicines Agency (EMEA):	http://www.EMEA.europa.eu/
European Medicines Agency Inspections Sector:	http://www.EMEA.eu.int/Inspections/index.html
European Guide to GMP:	http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev4.htm
European Guide to GMP – updates etc:	http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/gmp_doc.htm
The European Commission DG Enterprise:	http://europa.eu.int/comm/enterprise/pharmaceuticals/index_en.htm
European Compilation of Procedures for GMP Inspections:	http://www.emea.europa.eu/Inspections/GMPCompproc.html
European Federation of Pharmaceutical Industries and Federations (EFPIA):	http://www.efpia.org/
European Guidelines on Quality, Safety, and Efficacy for Human Use Products:	http://www.emea.eu.int/htms/human/humanguidelines/background.htm
European Guidelines on Quality, Safety, and Efficacy for Veterinary Products:	http://www.emea.eu.int/htms/vet/vetguidelines/background.htm
European Pharmacopoeia (Ph Eur):	http://www.pheur.org/
FDA "Portal" providing access to the different parts of their website:	http://www.fda.gov/oc/industry/default.htm
Japanese Ministry of Health, Labor and Welfare (MHW):	http://www.mhlw.go.jp/english/
International Conference on Harmonisation (ICH):	http://www.ich.org/UrlGrpServer.jser?@_ID=276&@_TEMPLATE=254
Pharmaceutical and Research Manufacturers of America (PhRMA):	http://www.phrma.org/
The UK Medicines and Health Care Products Regulatory Agency (MHRA):	http://www.mhra.gov.uk/
United States Pharmacopoeia (USP):	http://www.usp.org/
World Health Organisation IMPACT Initiative:	http://www.who.int/impact