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BACK TO BASICS

Quality management Part 2

Contract analysis

Vol.11 No.2 July 2012

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gmp review
ISSN 1476-4547

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Annual subscription rate:
£175

Editorial comment

It has been 4 years now since I wrote an editorial for GMP Review and looking back over this period I have been surprised at how much change has occurred in the pharmaceutical industry, which I had always considered to be stable and well regulated and which, on the whole, made good quality medicines available when needed.

Increased rates of change in both business practices (globalisation and the drive for cost management) and the regulations (building upon ICH guidelines) have contributed to this.

This month's fines and operational restrictions imposed upon GlaxoSmithKline in the USA[1] and the corporate Warning Letter issued to Novartis International AG late last year[2] clearly illustrate that the way businesses are run impacts upon their manufacturing operations. I have travelled extensively in the last few years visiting numerous manufacturing sites and below are some of my concerns about how multinationals in the industry can behave.

One of the biggest challenges for manufacturing sites appears to be the multitude of corporate initiatives as either a reaction to a problem on one site or as a management "way of working". You sometimes wonder how many of the executives issuing these have experience of pharmaceutical manufacture and related regulations as they try to impose them on different types of manufacturing operations. Many of the more common business principles, such as Six Sigma, have been successfully applied to the pharmaceutical industry, but they must be implemented in a way that recognises the regulations and the expectations of the inspectors. It looks as if businesses take the benefits without first ensuring that the required processes are in place to sustain a compliant operation. Then another incident occurs, or the management team changes, and another initiative is started before those ongoing are bedded in.

Removing a layer (or more) of management and empowering staff reduces headcount but this can also take out a vast amount of undocumented knowledge. Do the existing staff want to be empowered, are they sufficiently experienced to take on the responsibility and have they been trained? Sometimes the answer is no, no and no and you find a significant variation in individuals across a team.

On top of a flat structure sits the common and accepted practice of using temporary staff to manage fluctuations in workload. The extent of this has become too great in some organisations where I have seen up to 50 percent of temps, with a relatively high turnover rate, on nightshift in an "empowered organisation" with no supervision or QA presence to offer guidance. The training system invariably struggles to cope, communication is difficult and extensive use of the deviation system becomes the norm. There has been a beneficial shift of QA personnel from remote offices back into the production areas recently in some companies.

Reduced stock holding has resulted in a significant increase in both the use of purchased materials prior to completion of testing and the release of finished stock "under quarantine". As well as the "month end" rush to release material, some sites now have daily or weekly "back order" meetings where product required urgently is expedited. This is not a robust GMP system and is resource consumptive. It also illustrates something that has not changed; some senior management do not yet understand the role of the Qualified Person, whom they target at approving deviations so that stock can be released.

Businesses need metrics to monitor performance and drive improvement. There seems to be a proliferation of metrics being collected these days to satisfy the corporate need to demonstrate control. Sites have better things to do than collect data to provide information whose use they do not understand or fear it may be used against them. One of the most dangerous examples of this is the "league table" of unit cost across international manufacture. How can a simple figure be used to compare the value of a flagship site in the UK or USA, for example, with one in China or India?

Another example of poor use of metrics links to the increased focus on risk management by the inspectors[3]. Many sites have been criticised for poor metrics related to the management of deviations, for example, the simple percentage of deviations still open past their closure date. Companies have issued stringent internal targets for these without understanding the process and resource required to close them correctly. The consequence being that in-depth root cause investigations are not conducted and repeat deviations occur, this may be the next observation at inspection. The problem of managing deviations is compounded by the fact that many companies have become risk averse and have directed that "every event is a deviation"; it would be more helpful to provide guidance on identifying what should be included in the deviation system and so subsequently target resource to conducting thorough investigations which should contribute to reducing patient risk.

I am certain that some of you will have experienced at least some of the above. We are in a difficult business environment but there are currently ways of working that are compliant with GMP. Any help that you can provide in how you have successfully managed similar challenges to the above will be welcomed by our readership. After all, "Back-to-Basics" has to start at the most senior level in the company.

Although it has been around a long time now, QRM is not yet fully implemented in all companies. The PIC/S is continuing to provide good intelligence for the industry and you should use their excellent March 2012 Aide-Memoire "Assessment of Quality Risk Management Implementation"[4] to assess your own operation, before your inspector does.

Peter Willis

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Placing excipients at the heart of safe medicines

by Iain Moore and Flavia Arce

The humble excipients which go into the formulation of a medicinal product rarely capture the attention commanded by active pharmaceutical ingredients, but are critical and essential components of drugs.

Their functions are many. Some excipients help to transport the API to the site in the body where it is supposed to exert its activity, protecting it so it can exert the optimal therapeutic effect. Others make sure the API is released at the right time or place, thereby avoiding potential side effects. Some help to identify a product if its authenticity is in question, while others aid patient compliance by improving the taste or appearance of a medicine.

A good and consistent quality

Despite being inactive, excipients generally make up the bulk of a medicine in terms of weight and generally have well-defined functions in a drug product. Clearly, that makes it important that they are of good and consistent quality, as even minor deviations in an excipient can have a significant impact on its pharmaceutical functionality and performance.

Patients rightly expect that any medicine they take has been manufactured to the highest standards and, while this is true most of the time, recent manufacturing problems affecting even the largest drugmakers are evidence that this is not necessarily assured. Moreover, there have been several cases in recent years where serious adverse reactions have been attributed to the excipients used in a drug product.

For example, in Nigeria in 2008, at least 84 children aged between 2 months and seven years died as a result of deliberate substitution of the widely-used excipient glycerine with diethylene glycol in a teething mixture. An incident in Panama the previous year led to the deaths of 21 people who died after taking a cough syrup made with diethylene glycol that had again been mislabelled as glycerine. Another 38 people were affected by side effects including disorientation and kidney failure.

These are all thought to be cases of economically-motivated adulteration (EMA), a phrase defined by the US Food and Drug Administration as the "fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production, i.e., for economic gain."

There are plenty of examples of EMA outside the excipient arena, notably the case involving contaminated the active pharmaceutical ingredient heparin in 2008 which led to over a hundred deaths in the USA. In this case, a toxic adulterant was added to heparin in order to boost its apparent activity.

EGMP for excipients

Ensuring that the excipients used in medicines are of appropriate quality is the responsibility of the medicines manufacturer under European law. However, the increasingly complex supply chains in the pharmaceutical industry caused by globalisation in raw materials sourcing illustrate the difficulties faced by companies sourcing excipients and other raw materials. In the Panama case above, the glycerine/diethylene glycol passed from a supplier in China not registered to supply pharmaceutical-grade products through the hands of several companies and traders before being bought by the pharmaceutical manufacturer.

The European Commission has been looking at remedying this situation for several years. In 2005 it published a series of amendments to Directive 2001/83/EC on medicinal products for human use[1-3] to mandate the development of a Good Manufacturing Practice (GMP) system for excipients in order to bring them into line with other constituents of medicinal products.

Although some of the intended steps in the 2005 amendments were rescinded in 2010, others have been included in the publication of the Falsified Medicines Directive[4], most notably the legal definition of an excipient and the requirement for the Marketing Authorisation Holder to confirm that a suitable standard of GMP has been implemented by the excipient supplier.

Overall there are more than 1,200 excipients in use in medicinal products – not including colours and flavours – but only about 300-400 have monographs in recognised pharmacopoeia. This range of excipients – from simple sugars to complex polymers – means that 'pharmaceutical' GMP standards, i.e. those enshrined in Eudralex vol IV Part 2 for active pharmaceutical ingredients, are unlikely to be implemented for any but a handful of excipients.

Other standards needed

A significant barrier to developing effective legislation has been the diffuse nature of the excipient market and the lack of a defined excipient industry, with players in the sector spanning commodity food ingredient manufacturers through to companies that specialise in functional ingredients for pharmaceuticals.

Fears have been voiced that overly stringent GMP requirements – for example at the same level as those applied to APIs – could levy a disproportionate cost burden for excipient suppliers which only provide a small proportion of

their overall output to the pharmaceutical industry. It has also been suggested that the cost of compliance for these companies could rise to unbearable levels, so they may choose to stop supplying their products to the industry at all and lead to shortages.

Meanwhile other standards such as ISO 9001, widely used in other industries such as food, do not go far enough in their present form, so pharmaceutical manufacturers and excipient suppliers alike have been forced to rely on self-regulatory measures such as auditing, quality agreements and other business approaches to help ensure excipient quality.

These considerations have been recognised by the European Commission, whose early efforts to develop a Directive on GMP for excipients focused initially on a limited list of certain high-risk excipients, such as those derived from human or animal material, intended for use in sterile preparations or known to be associated with criminal activity, such as glycerine or propylene glycol.

After reviewing an Impact Assessment report on the proposed directive[5] – which concluded that the risk posed to patients in Europe from excipients was very small, and that the cost of implementing formalised GMP would far outweigh any public health benefit – the European Commission decided to abandon the plan in 2009[6].

Instead, it said it planned to develop an alternative GMP strategy for excipients based on the reform of existing legal requirements on manufacturing and quality control.

EXCiPACT system

Faced once again with a regulatory vacuum, industry groups such as IPEC Europe, IPEC-Americas, the European Fine Chemicals Group (EFCG) and European Association of Chemical Distributors (FECC) have taken matters into their own hands and have developed a universally-applicable scheme based on appropriate levels of not only GMP but also Good Distribution Practice (GDP).

The aim is not only to help ensure medicine quality, but also alleviate the burden of inspections and audits on manufacturers, excipient suppliers and regulatory authorities.

The system – called EXCiPACT[7] – is based on the concept of third-party certification of suppliers to a consistent and well-thought-out set of standards covering not only GMP but also other important elements such as Good Distribution Practice (GDP).

The overall aim is to develop GMP and GDP principles for excipients as an annex to the widely-used ISO 9001 Quality System, allowing excipient manufacturer and distributor companies to include certification as part of their ISO 9001 registration audits.

Critically, the idea is to develop a network of approved third-party auditing companies who will certify excipients suppliers and distributors to the EXCiPACT™ Standards, taking that task out of the hands of the pharmaceutical manufacturer or indeed the regulatory authorities, which are already struggling to meet the inspection demands of drug products and APIs, let alone excipients.

If the audit is successful and certification is awarded, a drug maker can then purchase excipients from that supplier with a degree of assurance that the firm was providing quality materials.

The EXCiPACT™ Certification scheme was launched earlier this year in Barcelona at an event attended by over 150 people. Currently the scheme is undergoing sign up from 3rd party certification bodies and registration of auditors who have to meet EXCiPACT's strict competency requirements. Pilot audits are scheduled for later in 2012. After that the scheme will be fully available for all suppliers and users of excipient to use.

Since the initial draft of the European Directive on Falsified Medicinal Products in 2008, revisions by members of the European Parliament and Council of the European Union have extended the scope of the Directive to include excipients, and introduced the concept of a list of higher risk excipients subject to tighter controls by the Marketing Authorisation Holder, most notably the requirement to determine that an appropriate degree of GMP was applied in the manufacture of these excipients.

To comply with this requirement it is expected that physical audits of the excipient supplier will be performed so that the excipient user can then judge if the GMP applied in the manufacture of the excipient is suitable for their application. Such a pragmatic approach has been warmly welcomed, as it permits all parties to judge what is and what is not suitable in their particular set of circumstances. In this regard it seems to have been acknowledged that one size does not fit all when it comes to excipients.

Tragically though, the European authorities have done nothing concerning the distribution of excipients and it will remain up to industry-led initiatives like the IPEC Good Distribution Practices Guide to fill this particular vacuum on a voluntary basis. After all, the deaths associated with glycerine we not so much about failures in manufacture as in the supply chain.

IPEC Europe believes that a certification scheme such as EXCiPACT has the ability to contribute to safer medicinal products by setting minimum manufacturing standards, and minimum distribution standards which can be independently verified. This will raise standards across the industry, but without creating unmanageable administrative bottlenecks.

If the three main players on the stage – excipient suppliers,

pharmaceutical manufacturers and regulators – can work together to develop and agree a practical and useful approach to GMP and GDP for excipients, it can only serve to enhance supply chain security and patient safety.

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BACK TO BASICS: Quality management Part 2: Embedding a quality culture

by Paul Spencer

Introduction

In the Back to Basics article on Quality Management (April 2012), the emphasis was on what regulatory authorities expect to be in place for a pharmaceutical quality system to be effective. The ICH Q10 pharmaceutical quality system was adopted as the model of best practice as it addresses broader aspects of quality than just GMP compliance through the differing stages of the product lifecycle. This second article focuses on how things can go wrong even when a quality system is in place, and highlights steps that are required to change the culture to one genuinely focused on quality.

The second part of this paper examines the culture of Quality Management Systems and:

- how a common understanding of quality systems for the pharmaceutical industry has emerged with the publication of ICH Q10.
- why quality systems are needed.
- what elements of management are needed to establish an effective quality system.

The danger signs

Well before companies reach a crisis point, the warning signs are always there. Customer complaints are increasing, staff are demoralised, absenteeism rates are soaring, recruiting and retaining staff is becoming difficult, a 'them and us', low-trust, blame culture has developed. Such a toxic atmosphere is hardly conducive to the genuine quality culture expected in an ethical pharmaceutical company.

So how much longer can deviations, rejects, customer complaints, audit observations and identified but unmitigated risks pile up before drastic action is taken? Is it really necessary to head down a ruinous road where the root causes of quality problems are rarely found nor long term corrective actions implemented? At what point is the Corrective and Preventive Action (CAPA) system perceived by employees (and ultimately regulators) to be just a convenient parking place for problems that are difficult to resolve, rather than evidence that the quality assurance system is in a state of control? Does it really requirean adverse patient reaction, product recall or regulatory censure before the reputational damage and impact on the bottom line is fully appreciated?

When all the signs are there that regulators are getting tough and are looking for evidence that there is a genuine culture of quality within the company, focusing on presenting an 'illusion of compliance' during audits seems to be very short sighted. So why are some pharmaceutical companies seemingly drifting towards a culture more focused on cost reduction and profit maximisation, rather than one based on quality?

Avoiding the danger signs

Regulators[1] expect there to be mechanisms in place for the company to keep abreast of changes, trends and feedback from both the external and internal company environment. This is an integral part of the quality system and is essential for long term business success. Hence an effective quality system requires a regular management review process that responds rapidly to information vital to company performance.

When strategic decisions give priority to short-term shareholder expectations, over the needs of other stakeholders such as regulatory authorities, employees and ultimately customers, there is conflict with the ethics and values of most pharmaceutical companies. This undermines the effectiveness of quality systems with often far reaching consequences in the longer term.

Effective quality systems align organisational processes and systems with customer needs, providing a solid basis for both measuring and rewarding performance. By delivering consistent product quality as well as compliant regulatory performance, the quality system assures control, ultimately adding value to the bottom line through customer satisfaction that upholds the company reputation. Hence the quality system needs processes for identifying continuous improvements and ensuring that they are acted upon in a timely manner. After all, product manufacturing licences are given on the clear understanding that patient safety is paramount, requiring the commitment from senior management to ensure that all levels within all departments comply with quality policy[1].

Regulators are increasingly looking for evidence of a genuine quality culture, based more on trust, rather than purely GMP compliance, where all employees are empowered to take responsibility for quality. This requires adequate resource to thoroughly investigate, identify and correct the root causes of recurring problems, backed up by processes to escalate and address concerns when appropriate.

Building a quality culture based on trust and motivation

Establishing organisational goals

Responding positively to structural drivers of change is essential for business, hence establishing an effective quality system, aligned with strategic goals is crucial[2]. Staff feel motivated when they can associate with an organisational strategy that has been translated into achievable and

workable implementation plans aligned with organisational goals and ethical values[3].

Building a genuine quality culture is clearly essential but change management programmes often fail because senior management fail to recognise the need for wholesale, organisational cultural change, including their own behaviour[4].

Changing the culture

For a change management programme to succeed, senior management need a thorough understanding of the cultural issues that create a resistance to change, such as low trust, conflict with personal values and fear of failure[3]. Gaining employee commitment and motivation is possible when staff are kept fully involved and informed about how decisions will affect the quality of their work. In an ethical industry, employees expect the company to uphold its part of the 'psychological contract' ensuring that medicinal products are manufactured so that they are fit for intended use[1]. However, when senior management say one thing but do another, an environment of mistrust is created[4]. It is clear that for a genuine quality culture to take root, senior management need to lead by example as well as support employees to do their job properly[2].

Leadership style, commitment and behaviours

Research has shown that for senior managers to be effective, they need to demonstrate commitment to the company ethos, mission and organisational goals through their actions and behaviours. When they 'walk the talk' and proactively respond to internal and external cues that require intervention, senior managers gain the respect, trust and commitment of staff. This transformational leadership style of management is people orientated, encourages ethical behaviour, cooperation and team work and builds a sense of trust and empowerment that inspires people to take pride in their work[5].

In the interests of cost cutting and "empowerment", many traditional departmental hierarchies have been replaced by leaner, process ways of working in the pharmaceutical industry. But leaner organisations and processes are only effective when systems are robust and employees can acquire the critical knowledge to do their jobs properly on an ongoing basis. The positive impact this has on employee motivation is key to embedding a genuine quality culture.

It requires strong leadership for quality policy to be focused on customer satisfaction, rather than just regulatory compliance, and for continual improvement to not only be advocated but visibly supported at all levels and in all departments[2]. With effective performance monitoring systems in place to identify trends, and if necessary escalate quality problems in a timely manner, the management review process can be highly effective. For a quality culture to be fostered, the commitment of appropriate financial, physical and human resources in the overall strategic interests of the business is essential[1,2] (see **Figure 1**)

Personal goals, roles and responsibilities

When people identify with organisational goals and values, have clearly defined roles, and achievable personal objectives with the right level of management support, they are more likely to be committed to the company and motivated in their work. Managers can demonstrate their support and commitment to their staff, and a quality culture, by ensuring that inter-departmental relationships, roles and responsibilities are clearly defined and that appropriate resources are provided[1&2].

Performance monitoring and feedback

Key performance indicators (KPIs) are essential for highlighting and addressing quality problems and for communicating progress to staff and management. Open displays of key performance data (through notice boards for example) are considered to be an indicator of a genuine quality culture. A combination of regular team briefings and one-to-one sessions are effective ways of demonstrating commitment to quality improvement, provided that they actually facilitate employee involvement. Employees are motivated when they feel genuinely empowered by managers who are able to communicate effectively, provide feedback and support, nurture team work and facilitate appropriate training[5].

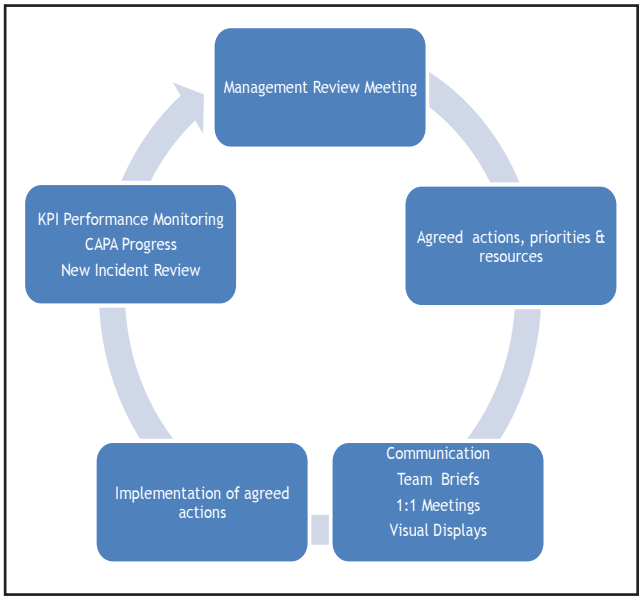

Figure 1: *The management review cycle.*

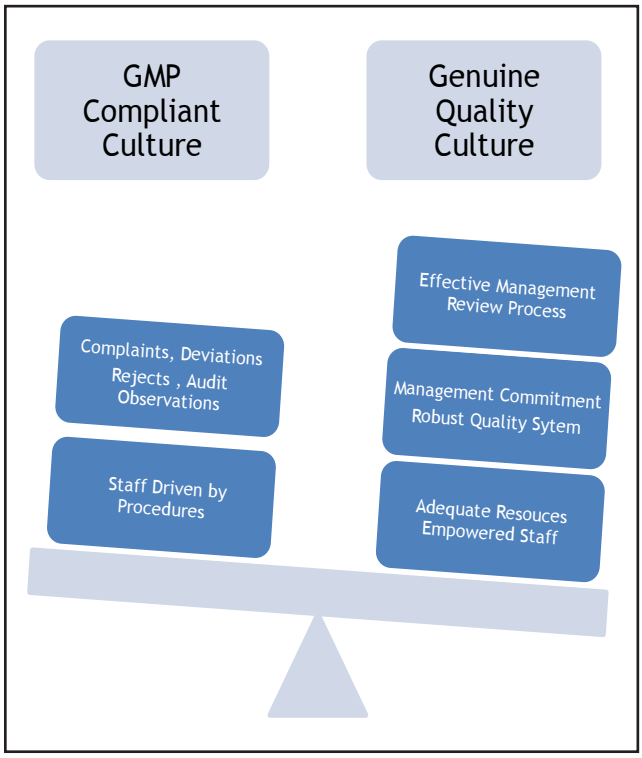

Figure 2: *Moving from GMP compliance to a genuine quality culture.*

Ultimately, this means that senior management communicate outcomes effectively and demonstrate commitment through the appropriate allocation of resources[1]. But what does this mean in practice?

Provision of adequate resources

Meeting both customer and regulatory expectations are key business requirements hence it makes little business sense to provide insufficient resources to support the quality system. When employees are overloaded with recurring investigations into the root causes of quality problems in addition to their routine work, they soon become demotivated if they believe they are not adequately supported by senior management.

However, when the corrective and preventive (CAPA) system is functioning as intended for example, it has a positive impact on employee commitment as recurring problems highlighted by deviations, complaints, rejects, audit observations and ultimately product recalls are seen to be addressed effectively.

Hence it is critical that the management review process is seen to be an effective means of informing senior management about the need for, and progress of, CAPA projects so that the level of resource provision can be assessed objectively against trends being monitored across the business. As business sustainability is undermined when the focus is biased towards short-term profit maximisation, it is surely in the interests of the business as a whole that a genuine quality culture becomes embedded (see **Figure 2**)

Conclusion

The ICHQ 10 model for a pharmaceutical quality system was selected as an example of best practice because it addresses broader aspects of quality management than just GMP compliance. However, actually embedding a quality culture is essential for any quality system to be effective, and this means building trust that the company is genuinely committed to quality.

Establishing clear personal roles and goals aligned with organisational aims is essential to build this trust, as is the need for senior management to demonstrate strong leadership and commitment to the quality system. The development of meaningful key performance indicators helps to identify quality problems, and effectively monitors their resolution, but the management review process needs to be effective in providing adequate resources to resolve recurring problems.

When senior management are perceived to be taking quality seriously, clearly communicating progress, developing and empowering their staff and involving them in decisions that affect the quality of their work, the basis for a genuine quality culture has been established. Ultimately however, it is consistently behaving in ways that support the quality system that is key to building the trust that embeds a quality culture.

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The role and structure of pharmacopoeias Part 5: The Japanese pharmacopoeia

by Dr. Rodney L. Horder

This final article in the series had previously been held pending publication of the English version of the 16th Edition of the Japanese Pharmacopoeia.

In this series of articles, the author provides answers to the following questions:

- What are the major pharmacopoeias?
- What is their legal status and relationship to their local regulatory agency?
- What are key compliance requirements and features?
- How frequently do they publish, and how can revisions be tracked?
- What is the current status of pharmacopoeial harmonization within ICH?

Japanese Pharmacopoeia (JP)

The Japanese Pharmacopoeia (JP) is produced by the Pharmaceuticals and Medical Devices Agency (PMDA), part of the Ministry of Health Labour and Welfare (MHLW) in Japan. The official version is in Japanese, but an English Version is published to meet the needs of the non-Japanese speaking people. When and if any discrepancy arises between the Japanese original and its English translation, the Japanese version is definitive. The publications and general information on JP are available on-line at the PMDA JP English Website: http://www.pmda.go.jp/english/pharmacopoeia/index.html. The JP can be downloaded as a .pdf file for off-line use, but note that it is 51mb.

JP is established and published to regulate the properties and quality of drugs in Japan. Items are selected for inclusion based on significant use in Japan.

Following publication of the 15th edition of JP in 2006, the PMDA Committee responsible for the JP undertook a major review of philosophy to ensure that the JP is used more effectively in the fields of health care and medical treatment by taking appropriate measures, including getting the understanding and cooperation of other parties concerned. Five basic principles of JP were established as follows:

1) Including all drugs which are important from the viewpoint of health care and medical treatment;
2) Making qualitative improvement by introducing the latest science and technology
3) Promoting internationalization
4) Making prompt partial revision as necessary and facilitating smooth administrative operation;
5) Ensuring transparency regarding the revision, and disseminating the JP to the public.

Consequently, the 16th edition has been amended significantly compared with the 15th edition.

Legal status and relationship to regulatory agencies "Japanese Pharmacopoeia: legal status"

Japanese Pharmaceutical Affairs law requires compliance with JP for medicinal products and their constituents that are marketed in Japan where a JP monograph exists. Experience has been that excipient monographs from Ph Eur, BP or USP may be acceptable if there is no JP monograph for the material.

Structure "Japanese Pharmacopoeia: structure"

The JP is arranged somewhat differently from the other compendia and comprises five major sections:

- General Rules for Crude Drugs
- General Rules for Preparations,
- General Tests, Processes and Apparatus,
- Monographs,
- General Information

The rules for Crude Drugs are specific to plant and animal materials. There is no general monograph for pharmaceutical substances. In the individual monographs for APIs, there is generally a section entitled 'Purity' that includes tests such as Clarity and Colour of Solution, Heavy Metals, and other inorganic impurities as well as Related Substances.

In general the requirements for types of dosage forms are specified in the test methods rather than in the General Rules. The JP contains monographs for individual medicinal products, but considerably fewer than BP or USP. Similarly to USP, the product monographs follow those of the active pharmaceutical ingredient rather than (as in BP) occupying a separate volume or section. Fewer product monographs than in BP and USP include tests for Related Substances.

The General Rules for Preparations were extended for JP 16 to add a number of new dosage forms. This section provides significant manufacturing directions, for example, how to manufacture tablets, but the only specified requirements are compliance with Dissolution/Disintegration and Uniformity of Dosage Units. There are no "Production" statements. Individual product monographs include Method of Preparation which, for example, states 'Prepare as directed under Injections with Clindamycin Phosphate', but this together with the information under General Rules for Preparations would be insufficient for the user to actually manufacture the product.

The General Tests Processes and Apparatus section includes a test for Acid Neutralizing Capacity of gastrointestinal medicines, which appears to be unique to the JP.

Following the Monographs, there is a General Information section. It is not clearly stated in the General Notices, but this section of the JP is understood to be non-mandatory, similar to the Chapters <1000> and above in USP. The General Information section provides guidance and recommendations on a number of topics such as analytical techniques and the Quality Control of Water for Pharmaceutical Use. The Chapter includes recommendations for:

- Selection of type of water for various purposes, including manufacture of APIs
- Sampling
- Alert and Action Levels
- Microbiological monitoring
- Physicochemical monitoring
- Storage of Water for Injection

In addition, note that the JP has a monograph for Water (feed for other Pharmaceutical Waters and for preparing API intermediates), which currently must meet Japanese drinking water standards. In addition, where well water or industrial water produced on-site is used for feed there is a requirement for not more than 0.05mg/L Ammonium content.

Publication

JP is currently published as a full edition every 5 years with 2 interim Supplements. English versions are published several months after the Japanese publications. In the case of JP16, the Japanese version was published in March 2011, becoming official 1 April 2011, and the English version became available on-line in February 2012. There is a grace period for compliance until 30 September 2012. According to the PMDA website, JP 16 Supplement I is scheduled for publication (in Japanese) in September 2012, and Supplement II in 2014. The English versions will be published within a year of the Japanese versions.

Japanese Pharmacopoeial Forum is published quarterly to provide draft monographs prior to them becoming published officially in JP and thus gives the opportunity for review of developing monographs and policy.

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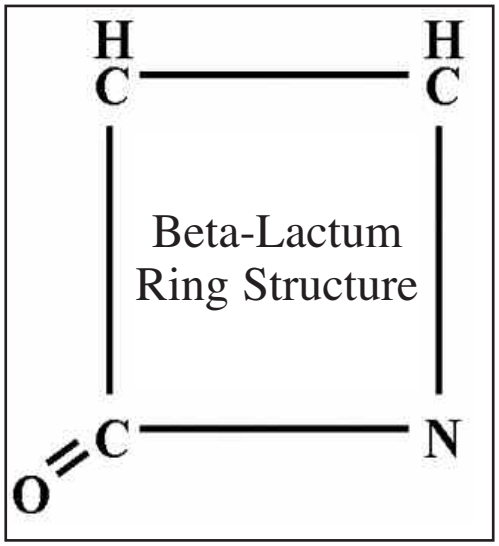
Bye-bye novel beta lactams?

by Patrick Crowley

Beta lactam anti-infectives, whether cephalosporins, penicillins and related analogues like clavams, bactams and penems probably represent the most sustained and successful contributions to combating bacterial infections across at least three generations. They have undoubtedly saved millions of lives, young, old, and "in between".

The story is a familiar one and needs little elaboration. When bacteria evolved a defense mechanism against one or other of these materials, the chemists and biologists came up with a molecular variant or combination of agents to outwit the pathogens and prolong the dominance of man over microbe. The extraordinary safety of these agents, except for their sensitizing capability in a minority of patients made them first choice therapy in many cases.



But bacteria do not stand still. Today's survivor begets tomorrow's resistant strain and, without new antibiotics, infectious diseases will once again become major "killers". Where are the future penicillins and cephalosporins?

Where indeed? To this author's knowledge there are novel cephalosporins around, with promising antibacterial spectra against the most resistant of organisms. Why are they not being evaluated clinically?

The answer is simple. Regulatory requirements are such that beta lactams must be processed in facilities that are separate from "conventional" manufacturing areas. The admittedly laudable thinking at the outset was that cross contamination of conventional medications by beta lactams posed sensitization hazards to patients. As sensitization could be induced by extremely low levels, it was deemed that the only way to ensure patient safety was to keep beta lactams apart. Separate facilities were accordingly stipulated about a quarter of a century ago. As beta lactam patents expired, and as generics companies are not noted for their willingness to manufacture sterile products, because of expense, development facilities were shut down. The upshot is that there are no facilities (to this author's knowledge) where modest quantities of beta lactams, particularly for parenteral administration can be processed in sterile mode to service investigative clinical trials. Small startup organizations (where the creativity resides these days) cannot find facilities to manufacture modest quantities of sterile material for clinical assessment. No facility – no program! CRO's will not touch beta lactams in case involvement puts their other operations at risk.

The case for separate facilities might make sense if beta lactams are likely to persist in the environment, or be difficult to remove. Yet, as every student and dispensing Pharmacist knows, they are intrinsically unstable. They cannot be formulated in aqueous vehicles due to instability and are also readily degraded by temperature and humidity-related stresses. Parenterals are most likely to be sterilized and presented as lyophiles, processed as solutions. Appropriate washing removes residues and, combined with the above-mentioned instability, the availability of ultra-sensitive analytical techniques and the use of appropriate isolation technology make it eminently feasible to process beta lactams such that the likelihood of residues is extremely low to non-existent. Separation in a completely separate facility is no longer warranted.

Its time to re-think and re-define attitudes. Otherwise, its "bye-bye beta lactams: It's been good to know-ya".

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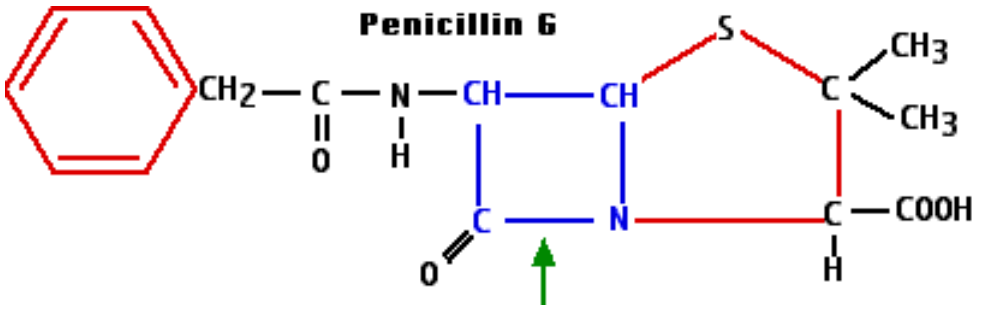
The beta-lactams get their name from the characteristic ring structure – shown here in blue – that they all share. (The green arrow shows the bond that is broken by the betalactamases that are synthesized by many penicillin-resistant bacteria.)



BACK TO BASICS: Contract analysis

by Max Lazar and Frank Böttcher

Introduction

Outsourcing is "in" and for many pharmaceutical companies the use of contract analytical laboratories is normal practice.

Chapter 7 of the EU GMP Guideline defines the requirements for "Contract Manufacture and Analysis", Annex 16 of the EU GMP Guideline, states: "Manufacture, including quality control testing, of a batch of medicinal products takes place in stages which may be conducted at different sites and by different manufacturers."

The regulations in the EU stipulate a clear assignment of the different activities contracted to a test facility. The Qualified Person responsible for batch release of medicinal products has to assure that all necessary information concerning the contracted tests are available or that a Qualified Person at the contract lab certifies that testing is in compliance with the registration.

While contracts and Quality Agreements are common in the United States, there is less specific drug guidance and regulations written about contracts in FDA documents than found in the EU Guideline although both require contractors performing services for a regulatory filing holder to meet GMP. However, 21 CFR 211.22 clearly requires that even under "contract", only the manufacturer's (contract giver's) quality control unit retains responsibility for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company. There is no Qualified Person specified or required in the United States. It is the Quality Control Unit that retains the authority and responsibilities established under US-GMP regulations and guidance. However, all outsourced activities, including analysis, should be included in regulatory filings such as NDA and ANDA and approved by the FDA.

Legal background

In both the EU and USA, all contract analysis is subject to supervision and inspection by the regulatory or competent authorities. But the responsibility of the Qualified Person or the head of quality control of the contract giver for analyses nonetheless remains unaffected.

Therefore a written contract must exist between the contract giver and contract acceptor that clearly defines the tasks of and responsibilities for both parties if a medicinal product is analyzed by one company on behalf of another. Chapter 7.2 EU GMP Guideline states that all arrangements for contract analysis including any proposed changes in technical or other arrangements should be in accordance with the marketing authorization of the medicinal product. The contract giver is in charge of assessing the competence of the contract acceptor and that the contract acceptor follows the GMP rules. The contract giver has to provide any information that is necessary for the contract acceptor to test the medicinal products in compliance with the marketing authorization and has to assess the results of the test, OOS-results or deviations of the provided test instructions. The contract giver must make sure (e.g. by carrying out audits) that the contract acceptor undertakes proper analysis of the medicinal product in accordance with the registered testing procedure.

The contract acceptor has to run an adequate QA-system that is in compliance with the GMP rules and follows the provided test procedures. They must ensure that the contract giver is informed about any critical deviation or occurrence that might influence the quality of the medicinal product.

This paper in the Back-to-Basics series examines contract analysis and answers the following questions:

- Which analyses may be outsourced and to what extent?
- What are the legal requirements?
- Which testing laboratory is suitable?
- What form must a liability limitation contract take?
- What errors frequently occur during collaboration?

Selection of an external testing laboratory

The questions listed in **Figure 1** "Criteria for the selection of an external laboratory" should be addressed when carrying out a suitability test for an external testing laboratory.

Typical errors

Typical errors that occur when working with a contract laboratory:

By the contract giver

- application file for marketing authorization has not been updated
- contract analysis is not included in the change control procedure
- no validation or transfer of test method has been conducted
- incomplete documentation of development and validation of test procedures
- no clear and precise specifications
- no OOS instructions with the contract laboratory
- no integration in the QA system

By the contract acceptor

- application file for marketing authorization is unknown
- no change control procedure
- missing validation or method transfer
- no assessment of test instructions and specifications
- no OOS SOP, no OOS instructions with contract giver
- no compatible QA system

Liability limitation contract

A written contract between the contract giver and contract acceptor that defines the responsibilities must exist. For the USA, all required GMP responsibilities and responsible parties should be identified in a Quality Agreement signed by both the contract giver and the contract acceptor. General legal liability issues and risks are not specifically discussed within USA GMP rules and regulations – GMP compliance requirements are the only subject of importance to be identified within the Quality Agreement. The EU GMP Guideline defines minimal requirements in chapter 7 and demands in 7.11 that "The contract should specify the way in which the Qualified Person releasing the batch for sale ensures that each batch has been checked for compliance with the requirements of the Marketing Authorization".

The following points relating to the liability limitation contract must be taken into consideration:

1. General duty of disclosure of external laboratory to the relevant authorities
2. Confirmation that suitable rooms and equipment are available to carry out the contract analyses
3. Designation of supervising authorities according to applicable regulations
4. Confirmation that medicinal products are checked for the necessary quality in accordance with recognized pharmaceutical regulations, e.g. by referring to the EU GMP Guideline and/or the USA GMP regulations (21CFR Parts 210 and 211) as the basis for testing and documentation.
5. Confirmation that contract giver will be informed of any change in certification or accreditation by the contract acceptor.
6. The final responsibility rests with the head of quality control (Qualified Person in the EU) of the contract giver and cannot be changed under the terms of the contract under any circumstances.
7. Assurance that work awarded to the contract acceptor will not be subcontracted to third parties without the written consent of the contract giver.
8. Information on documentation of the contract analyses (the analysis of starting materials and each medicinal product batch is to be fully documented). Sample documentation is to be provided in an appendix as required (optional).
9. List of persons responsible for all technical questions (appendix)
10. Information on the storage (periods) of documents, raw data and test samples
11. Audit rights for the contract giver and relevant supervisory authorities (see Chapter 7.14 of EU GMP Guideline). As an option, contract manufacturers acting on behalf of contract givers may also be granted indirect rights to carry out audits for their customers.
12. Additional duties of contract acceptor to provide information, e.g. in the event of deviations from the specifications (OOS procedure) or the provided test instructions (deviation procedure)

Mandatory suitability criteria:

- Is the laboratory notified to the national authorities for testing of medicinal products?
- Is the laboratory inspected regularly by a competent authority and found acceptable e.g. by local authorities or by the FDA?
- Is a manufacturing license or a GMP-certificate issued by a competent authority?
- Has the laboratory been accredited in accordance with ISO/IEC 17025?
- Are suitable rooms and facilities available for contract analysis?
- Are GMP standards observed during work at the laboratory?

Desirable suitability criteria:

- Does the external laboratory have a sufficient number of experienced and qualified academic personnel (e.g. pharmacists, vets, chemists, food chemists, biologists)?
- Do FDA approvals exist or have other positive experiences with the FDA been noted?
- Does the external laboratory regularly and successfully take part in suitable inter-laboratory tests?
- Is there an authorized counter-checking expert?

Figure 1: *Criteria for the selection of an external laboratory*

13. Duty of the contract acceptor to inform the contract giver about any change which might influence the provided test instructions (change management)
14. Duty of contract giver to provide information on approval-compliant data for test implementation purposes as well as special safety instructions for hazardous materials, e.g. zytostatics (safety data sheets, waste disposal information)

Test procedure – who is responsible for what?

In practice, meaningful test procedures are not always available or do not correspond to the pharmacopoeias.

Test procedures must generally be compiled in writing prior to the analysis and must also provide information on sampling. These must correspond with the application or registration documents. The pharmaceutical manufacturer either owns the marketing authorization or is acting as the contract manufacturer on behalf of the owner of a marketing authorization. From a legal point of view therefore, the contract giver clearly has that greater proximity to, and sphere of influence over, approval or registration. During the contract award process, the test procedures that have been coordinated with the application file for marketing authorization must be handed over by the contract giver.

In formal legal terms, reference to a pharmacopoeia regulation can be recognized as an adequate test procedure. This of course does not relieve the contract giver from the obligation of regulatory conformity and (re)validation. Contractually, the problem can be solved by arranging for the tests to be carried out according to the specific requirements of the contract giver. If additional information beyond the pharmacopeia test methods is required, an individual product specific test method has to be used.

Certificate of analysis

Once testing is established at the contract laboratory, the contractor receives a certificate of analysis concerning the performed tests. These should contain the results and the applied methods and permit identification of the samples. The raw data is archived at the contracting laboratory. Since the customer must prove that the tests are carried out at the contract laboratory it is helpful if documentation for at least one complete batch test is available there.

The analysis results can be made available to the customer on paper or electronically. The certificate is to be signed personally or electronically by the person responsible for testing. Personnel authorized to sign at the contracting laboratory should, if required, be listed with signature samples in an enclosure to the contract and be subject to a modification service.

What should the Analysis Certificate contain?

- Identification of sample
- Name of client, if applicable customer number
- Batch identification of the customer
- Identification number of the customer at the contracting laboratory
- Results and specifications
- Agreed and applied methods
- Signature of the person responsible for the testing
- If applicable, indication whether an OOS result has been detected and reference to OOS processing
- If applicable, reference to deviations during testing

Figure 2: *Content of the Analysis Certificate.*

Deviations to the specified test procedure or OOS results are disclosed to the customer along with the certificate of analysis through the QA procedures established at the contracting laboratory. The customer is responsible for entering this information into his system and making it available to the person responsible for the clearance of the batch.

Furthermore the tests carried out by order must be evaluated for the preparation of a Product Quality Review (PQR) by the accreditation carrier and the QP responsible for product clearance. It is in the interest of the contract giver that test data as well as required evaluations are received.

Reportable Values

The reportable value has to be clearly defined in the test instructions. This is necessary because there are unequal approaches in different companies concerning the evaluation of OOS results. Some companies examine each result of single injections e.g. in HPLC or GC analysis as reportable value which has to be proven against the specification. Other companies calculate the mean of a number of injections as reportable value that has to be proven against the specification. The contract laboratory must be aware of this especially in case of OOS investigations. Therefore it must be clarified which result – single or mean – has to be proven against the specification and which result is mentioned on the certificate of analysis. The calculation and a clear description must be included in the test instruction.

Adapted from GMP MANUAL, published by Maas & Peither GMP Publishing, Schopfheim, Germany.
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Regulatory Update

by Malcolm Holmes

Introduction

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

- A Draft guideline on Process Validation
- Guideline on Real Time Release Testing
- Revised guideline on quality of biosimilar medicines
- Guideline on quality of biological active substances produced by transgene expression in animals
- Q&A on post approval change management protocols
- Reflection paper on classification of advanced therapy medicinal products
- Compilation of Community Procedures on Inspections and Exchange of Information – Revision 14 May 2012
- BP inhaled product monographs – changes
- e-TACT Round-table Discussion
- UK response – Delegated act on the detailed rules for a unique identifier for medicinal products, and its verification
- MHRA launches new anti-counterfeiting strategy
- Supply of medicines by pharmacy to healthcare professionals
- GMP deficiency data review
- UK comments on the European Commission's draft template for the written confirmation for active substances imported into the European Union

USA

- Amendments to Sterility Test Requirements for Biological Products
- Medical devices – voluntarily submission of audit reports to FDA
- Thiomersal in vaccines

International

Australia

- TGA medicine labelling and packaging review

Brazil

- Proposal for a normative act that regulates GMP for Pharmaceutical Excipients

China

- Draft excipient guidelines

International Conference on Harmonization (ICH)

- Development and Manufacture of Drug Substances ICH Q11

Pharmaceutical Inspection Cooperation Scheme (PIC/S)

- May 2012 PIC/S meeting
- Aide Memoire Quality Risk Management

Documents

- PDA TR 30 Parametric release of pharmaceutical products and medical devices terminally sterilized by moist heat
- Rx-360 publishes 3 new audit checklists

Europe

Draft guideline on Process Validation

This guideline has been released by CHMP for consultation. It replaces the previous guideline on process validation. The guideline is brought into line with ICH Q8, Q9 and Q10 documents

This guideline does not introduce new requirements on medicinal products already authorised and on the market, but clarifies how companies can take advantage of the new possibilities given when applying enhanced process understanding coupled with risk management tools under an efficient quality system as described by ICH Q8, Q9 and Q10.

Continuous process verification (CPV) has been introduced to cover an alternative approach to process validation based on a continuous monitoring of manufacturing performance. Process validation should not be viewed as a one-off event. The guideline indicates that a lifecycle approach should be applied linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production.

The guideline is intended to apply to data generated to validate the manufacturing process of the intended commercial dosage form only. It is intended to apply to medicinal products for human and veterinary use. It is not directly relevant to the manufacture of the active substance or other starting materials, although it may contain information useful for such activities. Although the fundamental principles are applicable to biological products, these should be considered on a case-by-case basis in view of the complex nature and inherent variability of the biological substance.

The document is open for comment until 31 October 2012.

Guideline on Real Time Release Testing (RTRT)

This guideline, formerly the Guideline on Parametric Release, has now been released in its final form and comes into effect 31 October 2012.

The guideline outlines the requirements for applications that propose RTRT for active substances, intermediates and finished products. It also outlines the different requirements that have to be fulfilled in the application and the need for

interaction between quality assessors and GMP inspectors in the approval process.

The principle of RTRT may be applied during the stages of manufacture of chemical and biological products resulting in the elimination of all, or certain, specific tests in the specifications of the finished active substance or finished medicinal product.

It is not applicable to investigational medicinal products although a company may be at various stages of development aiming at RTRT of the final product.

Revised guideline on quality of biosimilar medicines

The EMA has released a revised guideline for public consultation describing how pharmaceutical companies should address the quality aspects of biosimilar medicines.

The guideline updates the previous guidance from 2006, and explains the requirements for the manufacture and comparability testing for biological medicines claiming to be similar to another medicine already on the market. It addresses the requirements regarding manufacturing processes, the comparability exercise for quality, considering the choice of reference medicinal product, analytical methods, physicochemical characterisation, biological activity, purity and quality attributes for relevant specifications of the similar biological medicinal product.

The revised guideline is open for consultation until the end of November 2012.

Guideline on quality of biological active substances produced by transgene expression in animals

This guideline provides guidance on the approaches that should be employed in order to achieve satisfactory quality for biological drug substances proposed to be produced using transgenic animal technology. Its principal aim is to adapt some specific aspects of the quality guidance already in place for other recombinant production systems to the special case of transgenic animal systems.

The guideline addresses the use of transgenic animals as a manufacturing technology for recombinant therapeutic proteins. It concentrates on the quality issues affecting active substances produced by the expression of one or more transgenes stably located in the nuclear genomes of animals, including the selection, generation and control of the production animals and evaluation of freedom from adventitious agents.

Since it is expected that a protein that is produced by a transgenic animal, and its quality attributes, would follow the same standards as a protein produced in mammalian cells in a fermentation system, the general guidance which is already available for downstream processing systems will be applicable. Similarly, the active substances will have to comply with all of the relevant guidance already available for biotherapeutic medicinal products. Many of the principles discussed in the Guideline on Xenogeneic Cell-based Medicinal Products (CHMP/CPWP/83508/09) are also applicable to the generation, testing and maintenance of transgenic animals for the purposes discussed here. In particular, the applicability of the sections on animal husbandry, animal facilities, transportation, testing for infectious agents in source or founder animals and procurement steps should be considered.

Questions and answers on post approval change management protocols

The concept of post approval change management protocols has been introduced in the EU through the Commission's Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products. This Q&A sets some general principles about the content and future use of these protocols and will be updated in the light of more experience, particularly for biological products.

Eight topics are covered in the Q&A:

- What is a Post Approval Change Management Protocol?
- What should be in the content of a post approval change management protocol?
- What is the mechanism for the submission and evaluation of a Post approval Change Management Protocol?
- How will the change be implemented after all the studies described in the approved protocol have been performed?
- Can applicants submit post approval change management protocols for any type of change?
- Can a post approval change management protocol cover multiple changes?
- Where should the requested documents (description of change/change management protocol) be placed in the application?
- Are post approval change management protocols applicable to all types of applications?

Reflection paper on classification of advanced therapy medicinal products

The ATMP classification is a non-mandatory, free of charge, legally non-binding procedure that helps developers to clarify the applicable regulatory framework. It also provides clarity on the development path and scientific-regulatory guidance to be followed. The ATMP classification may sometimes also be a useful tool for applicants to initiate a tailored dialogue on the product development with regulators. Indeed, due to its easy and fast process, the ATMP classification, along with other

tools (e.g. ITF briefing meetings), should be seen as a first opportunity to engage with regulators.

Once the candidate ATMP classification has been clarified and confirmed, the dialogue can continue with the use of other regulatory procedures such as scientific advice and ATMP certification, the latter exclusively set up under the auspices of the dedicated committee (CAT). In addition, and depending on the type of product under development, liaison with other committees such as Committee for Orphan Medicinal Products (COMP) and/or Paediatric Committee (PDCO) may be recommended to the applicant. The ATMP classification may also help developers to gain access to all relevant services and incentives offered by the EMA

e-TACT Round-table

On 21 June 2012 at its Brussels office, the Council of Europe hosted a Round-table Discussion on "Identifying falsified medicines: How best to protect European citizens?" The event was an opportunity to have a high-level discussion on what is at stake in the current discussions at European level on the future architecture of the mass serialisation systems to be used in the legal medicines supply-chain to protect it from counterfeit/falsified medicines.

MHRA

UK response – Delegated act on the detailed rules for a unique identifier for medicinal products, and its verification.

The UK MHRA has provided a comprehensive response to this consultation document. In both the response and the covering letter to DG SANCO it outlines some of MHRA's fundamental concerns about the approach which is implicit in how the concept paper is framed.

MHRA comments are consistent with the positions that the UK adopted during the negotiation of the legislation and were in turn reflected in the final legal texts.

Compilation of Community Procedures on Inspections and Exchange of Information –Revision 14 May 2012

This latest version contains the following new templates under the 'Forms used by regulators' section:

- Union Format for a Wholesale Distribution Authorisation (Medicinal Products for Human Use)
- Union Format for a Good Distribution Practice Certificate (Medicinal Products for Human Use)
- Union Format for a Good Distribution Practice Certificate for Active Substances to be used as Starting Materials in Medicinal Products for Human Use
- Statement of non-compliance with Good Distribution Practice (Medicinal Products for Human use)
- Statement of non-compliance with Good Distribution Practice of a distributor of active substances for use as starting materials in medicinal products for human use
- Union Format for Registration of Manufacturer, Importer or Distributor of Active Substance (used in Medicinal Products for Human Use)
- Co-ordinating GMP Inspections for Centrally Authorised Products

They have been added to facilitate entry into the Union database as required by Directive 2011/62/EU.

In addition a Procedure for Dealing with Serious GMP Non Compliance Information Originating from Third Country Authorities or International Organisations has been added.

Although principally designed for use by regulators the compilation of procedures is also of considerable use to industry.

Changes to inhaled product monographs – BP Draft Policy Document

The British Pharmacopoeia Commission has proposed changes to inhaled product monographs. The changes will be implemented from the BP 2014 onwards. Manufacturers of nebuliser solutions, pressurised inhalers or powder inhalers that are subject to a BP monograph, were invited to send comments, together with any supporting data to the Secretariat via email to by 14 May 2012

The draft policy document contains recommendations on the content of BP monographs for inhalation. The recommendations are supported by rationale. Inhaled products provide a number of peculiar and unique characteristics that make common specifications difficult. This is due to the variety of devices, accessories and formulations that can be used to deliver the active pharmaceutical ingredient (API). The efficient delivery of the API is also dependent on the operator (patient) ability to use the inhaler correctly as well as the inhaler dosage form. Safety and efficacy are critical considerations; the Working Party has taken the view that the inhalation monographs would ensure products that are safe and efficacious by maintaining a standard set of quality tests. These are defined within the Ph. Eur. 'Preparations for Inhalation' general monograph (0671).

Safety and efficacy are most affected by the delivered dose and fine particle dose. These quality tests are crucial in ensuring that the safety and efficacy of the inhaled product is maintained. Therefore, the quality tests must focus on the current best practices, especially with respect to test methodology. Removal of the opportunity for poor quality inhaled products reaching the British market is also seen as necessary.

In order to ensure quality standards are up to date some older product monographs may need revision of their tests and limits.

MHRA launches new anti-counterfeiting strategy

The new strategy, the Falsified Medical Products Strategy 2012 – 2015, details measures that the MHRA will take to tackle counterfeit medicines and medical devices. It brings together its stakeholders and international partners to combine efforts in raising public awareness and carrying out enforcement policy.

Supply of medicines by pharmacy to healthcare professionals

With effect from July 2012 Section 10(7) of the Medicines Act 1968 will be repealed. Section 10(7) currently provides an exemption in UK law from the requirement for a pharmacist to hold a Wholesale Dealer's Licence if they trade in medicines in certain circumstances. Its repeal is necessary in order to comply with EU legislation, in particular, Articles 77(1) and 77(2) of Directive 2001/83/EC that require anyone undertaking wholesale dealing activities to hold a Wholesale Dealer's Licence.

MHRA has provided guidance for pharmacists working in registered pharmacies and in hospitals on how the MHRA, as the regulator responsible for the enforcement of EU legislation, proposes to address the implications of the necessary repeal of Section 10(7) for the supply of licensed medicines by pharmacy other than direct to the public.

GMP deficiency data review

An annual review of deficiency data trends has been completed by MHRA. The review considered 303 inspections of which there were 26 critical and 644 major deficiencies noted and data have been grouped by licence, product and sector types with examples of actual deficiencies.

UK comments on the European Commission's draft template for the written confirmation for active substances imported into the European Union

MHRA has provided the United Kingdom's response to the consultation on the "draft template for the written confirmation for active substances imported into the European Union for medicinal products for human use. A number of concerns are raised including the ability of 3rd country inspectorates to be able or willing to comply with the expectations placed upon them. MHRA draws particular attention to the situation in India.

USA

The US Food and Drug Administration (USFDA)

Amendments to Sterility Test Requirements for Biological Products

The Food and Drug Administration (FDA) is amending the sterility test requirements for biological products. This rule provides manufacturers of biological products greater flexibility, as appropriate, and encourages use of the most appropriate and state-of-the-art test methods for assuring the safety of biological products. FDA is taking this action as part of its ongoing efforts to comprehensively review and, as necessary, revise its regulations related to biological products.

This rule revises the sterility requirements for most biological products under title 21 of the Code of Federal Regulations (CFR), subchapter F, parts 600 through 680. It is intended to promote improvement and innovation in the development of sterility test methods by allowing manufacturers the flexibility needed for sterility testing of some novel products that may be introduced to the market, enhancing sterility testing of currently approved products, and encouraging manufacturers to utilize scientific and technological advances in sterility test methods as they become available. In the Federal Register of June 21, 2011 (76 FR 36019), FDA published a proposed rule that proposed revisions to update requirements for sterility testing of biological products. Sterility assurance is accomplished primarily by validation of the sterilization process or of aseptic processing under current good manufacturing practice (CGMP), and is supported by sterility testing using validated and verified test.

The final rule came into effect June 4 2012.

Medical devices – voluntarily submission of audit reports to FDA

Under this guidance document, a device manufacturer whose establishment has been audited under one of the regulatory systems implemented by the Global Harmonization Task Force (GHTF) founding members using International Organization for Standardization (ISO) 13485:2003 may voluntarily submit the resulting audit report to FDA. If, based on that report, FDA determines that there is minimal probability that the establishment will produce nonconforming and/or defective finished devices, then FDA intends to use the audit results as part of its risk assessment to determine whether that establishment can be removed from FDA's routine work plan for 1 year.

Thiomersal in vaccines

Thiomersal is a mercury-containing organic compound (an organomercurial). Since the 1930s, it has been widely used as a preservative in a number of biological and drug products, including many vaccines. Over the past several years, because of an increasing awareness of the theoretical potential for neurotoxicity of even low levels of organomercurials and because of the increased number of thiomersal containing vaccines that had been added to the infant immunization schedule, concerns about the use of thiomersal in vaccines and other products have been raised.

Thiomersal has been removed from, or reduced to trace

amounts in all vaccines routinely recommended for children 6 years of age and younger, with the exception of inactivated influenza vaccine. A preservative-free version of the inactivated influenza vaccine (contains trace amounts of thiomersal) is available in limited supply at this time for use in infants, children and pregnant women. Some vaccines such as Td, which is indicated for older children (≥7 years of age) and adults, are also now available in formulations that are free of thiomersal or contain only trace amounts. (1 microgram or less of mercury per dose).

FDA has published a discussion of preservatives, the use of thiomersal as a preservative, guidelines on exposure to organomercurials (primarily methylmercury), thimerosal toxicity, recent and future FDA actions, and the conclusions of the Institute of Medicine's most recent review of thiomersal in vaccines are presented. For quick reference, a number of frequently asked questions (FAQs) and answers are provided

International

Australia

TGA medicine labelling and packaging review

This review is primarily concerned with the presentation of the information on the medicine containers or on the boxes within which they are supplied. Of particular interest are the visual aspects that contribute to the usability of the information provided and facilitate the safe use of the medicine by health care professionals and consumers.

The objective of the review of the requirements for medicine labels and packaging is to develop appropriate regulatory solutions that effectively address the consumer safety risks posed by the following issues:

- information about the active ingredient(s) contained in the medicine is not always easy to find
- use of the same brand name for a range of products with different active ingredients resulting in look-alike medicine branding (this is known as brand extension or trade name extension)
- medicine names that look-alike and sound-alike that can lead to use of the incorrect medicine
- medicine containers and packaging that looks like that of another medicine
- lack of a standardised format for information included on medicines labels and packaging
- dispensing stickers that cover up important information
- information provided on blister strips
- information included on small containers
- information provided in pack inserts

Brazil

Proposal for a normative act that regulates GMP for Pharmaceutical Excipients

The establishment of GMPs for manufacturers of excipients is important to minimize the health risk involved in this production, uniform understandings about the rules of good practice applicable to this activity under the National Health Surveillance System (SNVS), qualify suppliers of such substances and to strengthen domestic manufacturing, and promote legal certainty to the sector. To this end ANVISA has published Public Consultation no 31 which is available only in Portuguese.

China

Draft excipient guidelines

China's State Food and Drug Administration (SFDA) have issued for public comment draft provisions to strengthen the supervision and management of pharmaceutical excipients. Unfortunately the comment period was unusually short, only 4 days June 4 – 8.

The Draft requires pharmaceutical manufacturers to establish a system of ensuring the quality of the excipients they use in their drug production.

Under the draft guidelines, drug manufacturers have the primary responsibility to assure the quality of the excipients and additives they obtain from their excipient suppliers.

International Conference on Harmonization (ICH)

Development and Manufacture of Drug Substances Q11

The Guideline reached Step 4 of the ICH process on 1 May 2012.

This new guidance is proposed for Active Pharmaceutical Ingredients (APIs) harmonising the scientific and technical principles relating to the description and justification of the development and manufacturing process of Drug Substances including both chemical entities and biotechnological/ biological entities.

Pharmaceutical Inspection Cooperation Scheme (PIC/S)

PIC/S meeting

At the May meeting of PIC/S new working groups were established to explore extending PIC/S' mandate to new activities such as:

- Good Clinical Practices (GCP)
- Good Pharmacovigilance Practices (GPP);
- creating a PIC/S Inspectorate Academy to provide cost-efficient, primarily web-based, high quality harmonised training for Inspectorates.

It was also noted that Indonesia had joined PIC/S and that Japan & South Korea had applied for membership.

Aide- Memoire Quality Risk Management

The purpose of this document is to assist GMP inspectors in the assessment of QRM implementation in industry during regulatory inspections. Parts may also be useful (with suitable modification) during other GXP inspections where similar principles of QRM also apply. The Aide-Memoire should also contribute to a harmonised approach for inspection of QRM in industry between the different PIC/S members.

QRM aspects should be an integrated part of the planning and content of all GMP inspections. The existence of this separate Aide-Memoire document does not suggest that specific inspections for QRM systems are performed.

As Annex 20 represents a voluntary standard, this Aide-Memoire relies mainly on the corresponding mandatory articles of Chapter 1 and Annex 15 of the PIC/S GMP Guide:

- During an inspection dedicated time is required to be allocated to review the QRM system.
- During a general inspection the inspector should be able to review how the company has integrated QRM without allocating further specific time to the QRM aspects of the inspection.

Documents

PDA TR 30 Parametric release of pharmaceutical products and medical devices terminally sterilized by moist heat

This 2012 report provides current demonstrated best practices of this sterile product release method with an emphasis on use of science-based approaches during the development of a parametric release program for pharmaceutical and medical device products terminally sterilized by moist heat.

Rx-360 publishes 3 new audit checklists

The following guides/checklists have been published:

- Audit Guide For Pharmaceutical Packaging Materials for Medicinal Products, v.1.0
- Audit Guide For Pharmaceutical Excipients, v 2.0
- Audit Guide For Chromatography Resins

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

by Peter Savin

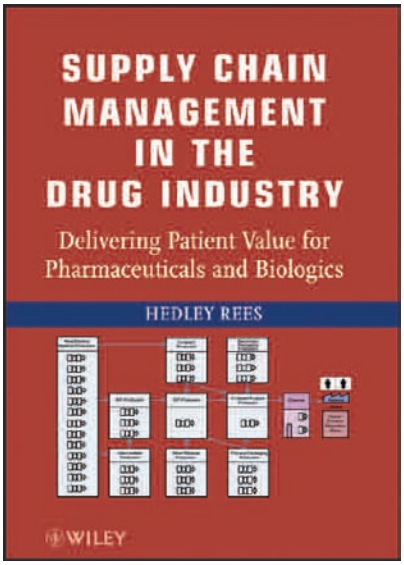
Supply Chain Management in the Drug Industry

Delivering Patient Value for Pharmaceuticals and Biologics.

by Hedley Rees

As the industry faces the challenge of containing costs it is increasingly turning its attention to supply chains across R&D and Manufacturing as it develops supply chain management (SCM) as a competitive strategy.

The stated aims of the book are to produce a practical guide to improving SCM; to engage with SCM professionals outside the industry; to help catalyse change in the industry; to start to realize the importance of, and spark a desire to improve, SCM.



To do this it attempts to bring together the two worlds of SCM and Pharmaceuticals so each can learn from the other. In reality there isn't much of an exchange of lessons (with the possible exception of Part I) as those provided are predominately from SCM to Pharmaceuticals and Biologics.

The format of the book works well and breaks up what might otherwise be rather dry and academic. It makes extensive use of "Guest Contributor Slots" with over 40 such contributions. Although the size of contribution varies considerably they are generally very good at explaining the concepts and methods of SCM, which are then supported by the author's own observations, views and experiences. I struggled with some of the author's metaphors but overall they do aid understanding of the concepts.

The book consists of three parts:

- Part I is the current landscape and SCM issues, which "maps the territory" of the industry and will be very familiar to GMP professionals in R&D and manufacturing.
- Part II is referred to as Building a Knowledge foundation into SCM.
- Part III is about planning and executing supply chain change.

The book starts well with the SCM focus on the patient and the servicing of patient needs rather than cost containment. "Supply" is usefully defined as "the transfer of value that has been created within an organization". A concept well worth thinking about and discussing within your company/regulatory body.

On a personal note, I particularly appreciated the "up-front" recognition that the cultural and behavioural aspects are the most important in achieving sustainable change as these are often addressed inadequately in most companies' improvement efforts. Current approaches largely fail to recognize the inherent unpredictability of individuals as they tend to focus the human part of the equation on teams and groups. As such, chapter 16 is particularly recommended as it will challenge many organisations' thinking about the leadership style and approach needed in these changing times. To cut a long story short but not to over-simplify the critical message here, it is about moving from the traditional command and control, egocentric leadership style (that we have all experienced) to one of relational leadership.

This is something that should resonate with any Qualified Person who is effective in filling their responsibilities.

We are all aware of the message from the regulators to become less dependent on them for specific guidance. This book goes a long way to capturing and communicating the best SCM guidance available and everyone in the industry and regulators would gain benefit from it.

I would recommend reading the final chapter first. Chapter 17 is an excellent summary of the 'disease state", the current malaise that affects SCM in Pharma. This chapter also summarises the current barriers to, and agenda for, achieving the necessary improvements. I challenge anybody in industry and regulators to read this and not recognise the problems it outlines and appreciate the advice it offers.

From my own experience of inappropriate metrics one aspect that the book could have usefully advised on is the use of metrics that demonstrate SCM is actually achieving its purpose of "servicing the patient needs" and "transferring the value created in the organization".

In summary, this is quite a book! Hedley Rees and the contributors provide a very timely reference work and resource. It's not the easiest to consume but it is heroic in it's ambition and the variety of format works well. Consequently, it is definitely worthy of investment of GMP professionals' time.

Hedley delivers on his aim to produce a practical guide to improving SCM, only time will tell if the industry and regulators have the sense and testicular fortitude to implement the changes they both need to make to realize the importance and benefits of fundamental changes in their approach to SCM.

Reviewed by Peter Savin

Published by John Wiley & Sons, Chichester, UK. (www.wiley.com).
ISBN: 978-0-470-55517-0. Hardcover. 456 pages.
Price £66.95.

Events

September

3-6 September 2012 – Istanbul, Turkey
Pharmaceutical GMP
www.nsf-dba.com

9-10 September 2012 – Birmingham, UK
RPS Annual Conference 2012
www.jpag.org

10-12 September 2012 – Baltimore, USA
PDA/FDA Joint Regulatory Conference
www.pda.org/pdafda2012

11 September 2012 – York, UK
Computer Validation – Latest Requirements
www.nsf-dba.com

11-12 September 2012 – London, UK
World Biosimilars Congress 2012
www.terrapinn.com

17-21 September 2012 – Bath, UK
GMP – The Fundamentals and Regulation
www.phss.co.uk

20 September 2012 – London, UK
Biosimilars and Biobetters
www.biosimilars-biobetters.co.uk

20 September 2012 – York, UK
"Warning Letters Galore" Causes and Prevention of Severe Regulatory Action
www.nsf-dba.com

21 September 2012 – Frankfurt, Germany
Variations Regulation – Expectations and Reality (In cooperation with APIC)
www.apv-mainz.de

24 September 2012 – Chicago, USA
10th Annual Cold Chain & Temperature Management Annual Forum
www.coldchainpharma.com

October

1-2 October 2012 – Dublin, Ireland
Medical Device Regulation in Europe: Now and the Future
www.topra.org/events

3-8 October 2012 – Amsterdam, The Netherlands
FIP Centennial: Improving Health Through Responsible Medicines Use
www.fip.org/amsterdam2012

7-10 October 2012 – Cortona, Italy
Advances in Pharmaceutical Innovation and Manufacturing Control
www.ifpaccortona.org

23 October 2012 – Manchester, UK
How to Perform Effective Product Quality Reviews
www.nsf-dba.com

23-24 October 2012 – London, UK
Pharmaceutical Labelling
www.informa-IS.com/pharmalabelling

24-25 October 2012 – Berlin, Germany
BioProduction
www.bio-production.com

November

7-9 November 2012 – Manchester, UK
BARQA Annual Conference: Quality Revolution?
www.barqa.com/learning/2012-annual-conference

7-9 November 2012 – Budapest, Hungary
APIC/CEFIC European Conference on Active Pharmaceutical Ingredients
www.api.conference.org

8 November 2012 – Harlow, UK
PQG 35th Anniversary Meeting
www.pqg.org/pharma/events

15-16 November 2012 – Berlin, Germany
Filing Variations
www.pti-global.co.uk/filingVariations

December

12-13 December 2012 – London, UK
Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP) 2012 Symposium
www.mhra.gov.uk/conferences

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