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Regulatory Highlights for September 2009 to February 2010

Transatlantic Co-operation

A joint meeting of the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in September 2009 discussed the progress of several ongoing "administrative simplification projects", and a summary of the discussions is now available (http://www.gmp-compliance.org/eca_news_1785_6062,6273,6351,6226, 6210_n.html). One of the most pressing issues for industry is collaboration on inspections between the two authorities. It is reported that two joint inspections of manufacturing sites in the EU were completed successfully in April and July 2009 and that an observed inspection was also carried out in the United States. The experience from these inspections has resulted in some agreed opportunities for improvement which will be developed as part of the ongoing collaborative activities. Greater collaboration is also anticipated in third country inspections of active pharmaceutical ingredients (APIs). To date, 80 sites have been identified for joint collaboration, 4 inspection reports have been exchanged and 1 joint inspection performed, thus facilitating better use of EU/FDA combined inspectional resources. Other topics discussed include

- Dedicated facilities for high risk products
- Critical Path and Innovative Medicines Initiatives
- Combating counterfeit medicines
- Collaboration on product-specific risk management and convergence of risk management formats
- Measures to increase the uptake of parallel transatlantic advice
- Exchange of information on herbal medicines
- Collaboration on biosimilars and follow-on biologicals
- Collaboration on paediatric drugs and advanced therapy products
- Updating/maintenance of the ICH Common Technical Document

CGMP for Dietary Supplements

FDA promulgated new CGMP regulations for dietary supplements in August 2007 (see *Org. Process Res. Dev.* **2007**, *11*, 801). These new rules, published as 21 CFR Part 111, are being enforced incrementally, with full compliance by all manufacturers expected by June 2010. Dietary supplements can comprise substances such as vitamins, minerals or amino acids, many of which are products of the fine chemical industry. Chemists involved with these products may therefore be interested in a recent article which gives a detailed comparison of Part 111 with the equivalent drug product regulations in Part 211 (Angelucci, L. A., III. *J. GXP Compliance* **2009**, *13* (4), 77−85). Unlike drugs, dietary supplements do not require to have their efficacy demonstrated by means of clinical trials, but they do need to be safe and to have appropriate labelling - refraining, for example, from claiming any specific health benefits or physiological responses. In general the structures of the two regulations are similar, with the same set of subparts in each case to deal with Buildings and Facilities, Equipment, Product and Process Controls, Laboratory Controls, etc. However, Part 111 is not written in typical regulatory format but rather as a series of questions and answers. In practical terms, the main difference from Part 211 (GMP for finished pharmaceuticals) would be the lack of any requirement for validation or qualification. Also there are no organizational requirements, such as for a dedicated quality unit, and no mention of a specific audit function in the company.

Warning Letters

Since 1 September 2009, FDA have slightly amended their procedures for issuing Warning Letters to companies in violation of CGMP and other regulations. First, companies must now formally respond to the original inspectional observations (Form 483) within 15 business days; responses arriving after this time will not be considered when deciding if a warning letter is merited (http://edocket.access.gpo.gov/2009/pdf/E9-19107.pdf). Second, the agency will now issue so-called "close-out" letters once the issues identified in the warning letters have been satisfactorily resolved - usually after a reinspection. Close-out letters, like the warning letters, will be published on the agency Web site (http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm).

Some advice for how to draw up an appropriate response to Form 483 observations has also recently appeared (Poska and Graham *J. GXP Compliance* **2010**, *14* (1), 24−33).

New Visual Identity for EMEA (EMA)

In December 2009 the European Medicines Agency unveiled a new official logo to replace the one in familiar use for the past 15 years. The change will be phased in during early 2010. The new Internet address (www.ema.europa.eu) is already functioning. The agency also wishes to discontinue use of the acronym "EMEA", as this has apparently led to confusion in some quarters.

More Changes to the EU GMP Guide

In November 2009 the European Commission published a proposal for the revision of Chapter 1 of the GMP Guide, changing its title from "Quality Management" to "Quality Management Systems". The revisions stem from the requirement to incorporate the Q10 (Quality Management Systems) guideline from the International Conference on Harmonization (ICH) into European law. The chapter is now significantly expanded, for example, with additional sections on the following:

- Quality Management System (QMS)
- Process Performance and Product Quality Monitoring System and Product Quality Review
- Management of Outsourced Activities and Purchased Materials
- Management of Review of the QMS
- Monitoring of Internal and External Factors Impacting the QMS
- Outcomes of Management Review and Monitoring

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There are also more concrete requirements for the documentation of the QMS. For the first time, there is a call for a quality management manual (section 1.5), which details *inter alia* the management's responsibility for the QMS. The requirement to establish a CAPA (Corrective and Preventative Action) procedure is also spelt out in greater detail, with a strong emphasis on quality risk management. For the first time, there is also a statement on design space in the EU GMP Guide. The new draft of Chapter 1 can be found at http://ec.europa.eu/enterprise/newsroom/cf/document.cfm?action=display&doc_id=5587&userservice_id=1&request.id=0.

Some changes are also proposed to Chapter 2 (Personnel), the purpose again being to align it more closely with the internationally harmonized guidelines (Web reference as above, with id=5588).

Another significant change to the EU Guide, announced in December 2009, is the establishment of a new Part III, to supplement Parts I (on drug products) and II (on drug substances). Part III is not intended to establish any new statutory GMP requirements, but rather to provide explanatory notes to complement certain aspects of the existing guidelines. The first installment deals with the preparation and content of a Site Master File (SMF). The SMF concept was originally developed by the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and has become a standard expectation of EU authorities. It is now being linked more formally into the EU regulatory system. It is expected that in the future, further documents will be added to the new Part III, following normal public consultation procedures (Web reference as above with id=5589).

Public Access to EudraGMP 2.0

Since August 2009, members of the public have been able to access the revised EudraGMP database (http://eudragmp.emea.europa.eu), which provides information about manufacturing, importation authorizations and GMP certificates issued by European regulatory authorities. Version 2.0 of the database also contains Non-Compliance Statements, which are issued in cases where the reporting inspection service feels that regulatory action is required to remove a potential risk to public or animal health. The database can be searched by company name, location, or certificate number and provides details of the types of products or activities conducted and the date of the latest GMP inspection. It is therefore a useful initial reference point for quickly checking the GMP status of potential contract manufacturers. At present only some national authorities have provided data; the deadline for all national authorities to be aboard is January 2011.

Assessment of the EU Clinical Trials Directive

The European Commission is also conducting an assessment of the functioning of their Clinical Trials Directive (CTD) and issued a public consultation paper on the subject in October 2009 (http://ec.europa.eu/enterprise/pharmaceuticals/clinicaltrials/docs/2009_10_09_public-consultation-paper.pdf). The CTD came into force across the EU in 2004, and was supposed to harmonize the differing regulatory approaches to clinical trials in the Member States. The Commission believes that the directive has brought about important improvements in the safety and ethical soundness of clinical trials in the EU, as well as in the reliability of clinical trials data. But there has also been widespread criticism that it has led to a significant decline in the attractiveness of patient-oriented research within the EU and that this has negatively impacted the development of new and innovative treatments and medicines (see, for example, *Org. Process Res. Dev.* **2007**, *11*, 312−313). The public consultation document highlights five key issues which now need to be addressed, including multiple and divergent assessments of clinical trials by different member states, inconsistent implementation of the CTD, difficulties in adapting the regulatory framework to practical requirements and to peculiarities in trial participants and trial design, and ensuring compliance with Good Clinical Practices when trials are conducted outside the EU. Several options for dealing with these issues are suggested.

Quality by Design for Generic Drugs

Much continues to be written on the subject of Quality by Design (QbD), but this is still thought of as largely an issue in the development of new drugs. FDA, though, have recently organised a series of joint workshops with the Generic Pharmaceutical Association (GPhA) to explore how QbD concepts could by applied to generic products. The first workshop was held in June 2009, and a summary of the discussion there has now been published (Yu et al. *Pharm. Technol.* **2009**, *33* (10), 122−127). The objectives were to identify gaps in the understanding of QbD between FDA and industry and to build a common understanding of certain key aspects of QbD, including:

- The quality target product profile (QTPP) and critical quality attributes (CQAs)
- Drug substance and excipient properties
- Formulation design and development
- Manufacturing process design and development
- Identification of critical process parameters (CPPs) and critical material attributes (CMAs)
- Risk assessment and design space
- Scale-up and control strategy.

The discussion of "design space" is particularly interesting. The authors, mainly from FDA's Office of Generic Drugs (OGD), make the point that a design space determined at laboratory scale may not be relevant to the process at the commercial scale, and would therefore attract limited regulatory flexibility unless sponsors can provide additional information that shows the design space is scale-independent, or actual verification data at the commercial scale. This seems a significantly more restrictive interpretation of the concept than has hitherto been assumed, and may reduce manufacturers' motivation to adopt the QbD approach.

In a subsequent article, OGD reviewers discuss the main shortcomings that they currently see in Abbreviated New Drug Applications (ANDAs) (Srinivasan and Iser *Pharm. Technol.* **2010**, *34* (1), 50−59). This first in a series of projected papers concentrates on drug substances (APIs), and provides a list of 20 commonly cited deficiencies which cause delay in application review and approval. Many of these seem very elementary, such as failure to include a control for the relevant diastereomer or enantiomer, or even to include a chiral identity test.

Regulatory Submissions of QbD-Derived Information

The FDA launched its Chemistry, Manufacturing, and Controls (CMC) Pilot Program in 2005 as part of its *Pharmaceutical CGMPs for the 21st Century* initiative. (See *Org. Process Res. Dev.* **2007**, *11* (3), 313.) The purpose of the Pilot Program was to provide an opportunity for companies to demonstrate enhanced process and product understanding and to collect feedback that could enable the agency to develop a new quality-assessment system based on Quality-by-Design concepts. No new guidelines from FDA have appeared on this subject so far; however, one of the industry participants, Wyeth, has now provided an account of their experiences and lessons learned (Venkatashwaran; et al. *Pharm. Technol.* **2009**, *33* (10), 96−102). The company had submitted two (unspecified) small-molecule development compounds to the program, involving three separate NDAs. The article summarizes their extensive discussions with FDA during the NDA reviews and associated site inspections, and makes comparison with their applications for the same compounds in other markets outside the U.S.

QbD in Analytical Development

The application of QbD principles to analytical measurements has been considered by the Pharmaceutical Research and Manufacturers of America (PhRMA) Analytical Development Group (ADG) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) Analytical Design Space (ADS) topic team (Schweizer, M.; et al. *Pharm. Technol.* **2010**, *34* (2), online bonus material). Their main proposal is that companies develop and register an Analytical Target Profile (ATP) for each critical quality attribute to be measured. The ATP would define the minimum performance standards for a suitable test, e.g. precision, accuracy, working range, sensitivity. Thereafter, the company would be free to utilise any analytical method which met the approved ATP criteria, provided it was suitably validated and documented. Changes to existing methods or replacement with new methods would not need to be submitted for regulatory approval, provided the ATP remained unchanged. This would facilitate the adoption of optimal procedures to meet the varying requirements of different sites and different groups.

On the subject of analytical methods, the U.S. Pharmacopoeia is proposing to develop a new General Information Chapter on analytical method transfer, offering guidance for the qualification of a receiving laboratory to perform an analytical procedure that was developed in another laboratory. The basis of the new chapter is presented in a Stimuli article (Quattrocchi; et al. *Pharmacopoeia Forum* **2009**, *35* (5), 1380−1382), to which industry feedback is encouraged. The article summarizes the types of transfers that may occur, which include comparative testing (the most common approach), covalidation between laboratories, and complete or partial validation of the analytical procedures by the receiving unit. There is also a possibility for waiver of any verification requirement, under appropriately justified circumstances. The article also outlines suitable components of a transfer protocol.

Human Error and Retraining

It has long been recognised that the steps which require human intervention are often the weakest points of any manufacturing process. It is unsurprising, therefore, that when carrying out statutory investigations into process deviations, out-of-specification results, or other product quality defects, companies often assign "human error" as the cause of the problem and recommend "retraining" as part of their corrective and preventative action plan. In a recent published interview, Kevin O'Donnell, Market Compliance Manager with the Irish Medicines Board, argues that there is often little justification for this practice (*J. GXP Compliance* **2009**, *13* (4), 47−60) While human error may well be involved in these incidents, it is often not the only causative factor, and other issues, e.g. management, social, and psychological factors, ought also to be considered. The article quotes from numerous behavioural studies, and usefully provides a comprehensive checklist of questions that should be asked in situations where human error is suspected. These probe whether the cause of the incident could be related instead to processes, procedures, equipment, environment, training, communication, or insufficient employee empowerment. The article also discusses issues with the assessment of training and retraining exercises.

Sampling Plans

When sampling deliveries of incoming raw materials, quality control personnel often use the "square root of $N + 1$" (Sqrt(N) + 1) rule to determine the number of containers to investigate. This practice appears to have originated in the 1920s as a sampling scheme for agricultural regulatory inspectors, but many quality personnel have questioned its validity because it cannot be found in statistical texts. In a 2003 article, Sarandasa (*Pharm. Technol.* **2003**, *27* (5), 50−62) concluded that it gives rise to frequent type-I errors (accepting a lot when it has more than the given maximum rate of defectives) and therefore should not be used as a sampling plan to infer a population defect rate. However, no alternative was suggested. Another popular approach is to use the ANSI/ASQ Z1.4 standard (2008), which tabulates recommended sample sizes according to the lot size. The issue has most recently been considered by Torbeck (*Pharm. Technol.* **2009**, *33* (10), 128), who concludes that Sqrt(N) + 1 in fact is a statistically correct and valid sampling plan and can be used with the same care and caution as Z1.4 General Level I would be used. In fact, with small lot sizes it actually gives larger sample sizes than Z1.4 would do. The key to this is, of course, "care and caution"! If a delivery harbours one rogue container, it is clear that nothing short of 100% sampling would be guaranteed to pick it up. Therefore, the Sqrt(N) + 1 rule, or indeed any other plan, should only be used when it is believed that all containers are from the same batch, and when there is a high degree of confidence in the original supplier's quality control and dispatch procedures.

Removing Endotoxins from Biopharmaceutical Solutions

The control of bacterial endotoxins is a problem long familiar to chemists involved in preparing APIs for parenteral administration because they can cause pyrogenic reactions on entering the bloodstream, potentially resulting in death. (The issue is much less urgent for orally administered drugs.) The problem is discussed thoroughly in a recent article contributed by scientists from Millipore (Salema; Saxena and Pattnaik, *Pharm.*

Technol. Eur., **2009**, *21* (10)). Endotoxin is another term used for lipopolysaccharides (LPS), complexes that are located in the outer cell membrane of Gram-negative bacteria and blue-green algae. LPS subunits are complex amphiphilic molecules with a molecular weight (MW) of approximately 10−20 kDa and vary widely in chemical composition both between and among bacterial species. LPS complexes tend to aggregate and form large structures that have an average MW > 10 kDa. A pyrogenic reaction can be caused by only a small amount of endotoxin—approximately 0.1 ng, or 1 endotoxin unit (EU), per kilogram of body weight. A typical Gram-negative bacterium contains 10^{-15} g of LPS, which means that at least 10^5 bacterial cells are required to contribute one endotoxin unit. Endotoxins are notoriously resistant to destruction by heat, desiccation, pH extremes, and various chemical treatments. However, they tend to form micelles or vesicles in aqueous solution, which can be removed by filtration. Also, their hydrophobic nature allows separation by two-phase extraction or by hydrophobic interaction chromatography. Finally, their negative charge can be used for adsorption on anion exchangers. The article discusses the advantages and disadvantages of these various approaches. In normal small-molecule API manufacturing, the only source of endotoxin contamination would be insufficiently purified water. However, complex biopharmaceuticals are frequently obtained using bacterial expression systems, which provide increased opportunity for endotoxin contamination, as well as greater challenges in removing them.

Good Weighing Practices

Accuracy of weighing operations is a critical feature of analytical procedures and, to a lesser extent, of manufacturing operations. A recent article by engineers from Mettler-Toledo (Reichmuth and Fritsch *Pharm. Eng.* **2009**, *29* (6), 46−58) provides a detailed guide to the selection of appropriate weighing instruments, together with recommendations for their qualification and routine calibration. The instrument's technical specification should quantify several properties which might limit its performance, the most important of which are repeatability, eccentricity, nonlinearity, and sensitivity. The article explains these concepts and outlines how they influence the performance of the weighing instrument. The instrument should be tested for all these properties by trained, authorized personnel, when first installed, as part of its qualification. Routine testing should thereafter be performed by the user at defined intervals—depending on the criticality of the application; this, however, need not involve testing for nonlinearity, which makes only a minor contribution to overall uncertainty. Many instruments have the capability to carry out automatic tests and adjustments; this reduces the effort of manual testing but does not remove it completely. The selection of test weights is also discussed. OIML- or ASTM-certified weights are recommended—one with a weight close to the upper end of the instrument's range, and one at around 2−5% of this.

Containment and Control of β-Lactam Compounds

β-Lactam antibiotics such as penicillins and cephalosporins give rise to some of the most critical challenges in contamination control and consequently attract enhanced attention from the regulatory authorities. Regulatory Highlights has previously discussed the efforts of the Japanese pharmaceutical firm Toyama to remediate an ex-β-lactam facility (*Org.Process Res. Dev.* **2009**, *13* (3), 394). Their engineers have now outlined a risk-based approach to operating a site which manufactures β-lactams as well as non-β-lactam drugs (Takahashi and Nakamura *Pharm. Eng.* **2009**, *29* (6), online exclusive article). Each building on the manufacturing campus is classified on four levels:

- β-lactam handling facility, comprising the most critical areas where open handling can take place
- β-lactam isolation facility, where the compounds are only present in fully contained equipment
- non-β-lactam facility
- common areas, where no β-lactams are present but there is possible cross-contamination between personnel from β-lactam and non-β-lactam areas—for example, cafeterias, administration offices, or streets

Crucially, each class of building is distributed throughout the campus. The β-lactam handling facilities are further subdivided into six Exposure Predictor Solid (EPS) classes according to the amount of β-lactam expected to be handled and the degree of dustiness of the material at that stage. Control of Substances Hazardous to Health (COSHH) and FDA guidelines were consulted to establish acceptable levels of air and surface contamination in each of these subareas and to inform the choice of air-handling equipment for each. Toyama simulated the environmental conditions appropriate for each area inside a test facility by spraying with piperacillin. Subsequently, they evaluated contamination on clothing used in the area (none detected) and the spread of contamination by walking (some detected up to 200 m from the test area). Assurance against cross-contamination was attained through a combination of engineering and procedural controls—for instance, standard operating procedures (SOPs) to govern changes of clothing, washing, and establishment of permissible and forbidden flow patterns for personnel and materials. All documents written within the β-lactam handling area are sealed in plastic bags before removal and can only be read within a special β-lactam document area. A ongoing monitoring program was developed that involved sampling the exhaust air from critical locations at regular time intervals.

Further information on the design of potent substance handling facilities appears in an contribution from Metrics, a contract manufacturer of clinical and commercial drug products (Gascone *Pharm. Technol.* **2009**, *33* (9)).

Probabilistic Risk Assessment

During the past decade, risk assessments have increasingly become an indispensable aspect informing all areas of drug development and manufacturing. A number of tools such Failure Mode and Effects Analysis (FMEA), Fault Tree Analysis (FMA), and Hazard Analysis and Critical Control Points (HACCP) have been described and summarized in ICH's Q9 guideline and are now widely applied in the pharmaceutical industry. Robert Jones (Foster Wheeler UK) now advocates the use of Probabilistic Risk Assessment (PRA)—particularly for complex operations in biopharmaceutical manufacturing (*Pharm. Eng.* **2009**, *29* (6), 24−38). PRA has been widely used

in high-risk industries such as nuclear, aerospace, and petrochemicals. Once deemed too "difficult" for pharmaceutical applications, it has now reached a mature stage in its development and deserves to be taken more seriously. PRA begins with a list of "initiating events" (IE's) which could cause a change to a system's operating state or configuration. For each IE, the analysis proceeds by determining the additional failures that may lead to undesirable consequences. Then the consequences are determined, as well as their frequencies, and finally they are put together to create a risk profile of the system. Traditional approaches such as FMEA are useful as inputs into the PRA process but do not take into account dependencies and multiple failures. They only show worst-case consequences and thus cannot provide total probabilities of end states with uncertainties. While the mathematics of PRA can become complicated, software is now available to facilitate it. The author notes the current trend in pharmaceuticals toward more self-regulation and draws an analogy with similar moves in the financial sector two decades ago; he argues that the most sophisticated risk management tools must be employed if we are to avoid heading in the same disastrous direction.

Another interesting development on the risk management front is an initiative by the PIC/S, who have designed an example of methodology to meet the demands of operators and inspectors and to comply with all regulatory requirements. The methodology relies on a central interactive database which PIC/S are currently developing. An outline of the approach is available from their Web site: http://www.picscheme.org/bo/commun/upload/document/psinf012010exampleofqrm-implementation.pdf.

Hand Washing, Hygiene, CGMP, and Science

Good personal hygiene is a requirement of all pharmaceutical activities, and regular hand-washing is a key element of this. Hand-washing is an activity that is frequently taken for granted but is often not carried out very effectively. A new article (Sutton *J. GXP Compliance* **2010**, *14* (1), 62−69) explores the issue from a microbiological perspective and offers advice to both company managers and employees. The provision by the company of well-designed washing facilities is the most critical aspect. For example, the mechanism to operate the water flow should not encourage the recontamination of the hands immediately after washing. The author strongly recommends the use of sealed liquid soap dispensers but feels there is no proven benefit for the soap to contain antibacterial additives. Thorough drying of hands after washing is particularly important; hot-air blowers (preferably with integral UV light) or disposable paper towels seem equally efficacious for this. A suggested hand-washing protocol is provided, which could form the basis of a company SOP.

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