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Regulatory Highlights

Regulatory Highlights for September 2007 to February 2008

In this feature, which appears twice yearly in *Organic Process Research and Development*, we aim to draw attention to recent significant developments in the statutory regulation of drug substances, the evolution of new guidelines, and discuss ongoing controversies of particular interest to process chemists.

Toxicological Concerns: Highly Toxic Impurities

Previous Regulatory Highlights' features (*Org. Process Res. Dev.* **2007**, *11*, pp 311 and 797) have reported the debate regarding limits for highly toxic impurities in drug substances. Now, a further significant contribution has come in an article by BMS chemist E. J. Delaney, "An impact analysis of the application of the threshold of toxicological concern concept to pharmaceuticals" (*Regul. Toxicol. Pharmacol.* **2007**, *49*, 107–124). He calls into question many of the assumptions used by the European Medicines Agency (EMEA) committee which last year recommended a maximum daily intake of 1.5 μg for substances which are "unusually toxic"—widely interpreted as those bearing potential for genotoxicity. He notes that the Pharmaceutical Research and Manufacturers of America (PhRMA) have proposed a less onerous alternative, involving a staged approach based on anticipated duration of medication, and that the FDA appear favorable to accept this proposal; nonetheless, even that explicitly accepts the underlying premise that a 1.5 μg/day limit is a reasonable long-term standard for API impurities that test positive for mutagenicity in Ames tests. The article argues against this premise.

The 1.5 μg limit is based on the Threshold of Toxicological Concern (TTC) concept. This was originally used by the FDA to regulate food contact materials and food additives, and represents a daily exposure level which would reduce the lifetime probability of an individual developing a cancer as a result of the exposure to below 1 in 1,000,000 for a wide range of substances. Delaney traces the history of this TTC concept and argues that it was originally employed to justify FDA's *threshold of regulation*, a mechanism created to uphold a *statutory* requirement that no food additive could be approved if found to cause cancer in man, or experimentally in animals, at any dose level. Since there is no such statutory requirement for pharmaceuticals, he questions whether it is appropriate to apply the TTC concept in this context. He asks whether the issue of genotoxic impurity limits in pharmaceuticals should be resolved from the "perspective of historical precedent" rather than from "a more carefully considered cancer-risk avoidance and risk-management viewpoint that balances the new regulatory burdens created against the benefits conferred by pharmaceutical products to patients".

It should, for example, be recognised that the "chemicals of concern" that a pharmaceutical R&D chemist might commonly employ as intermediates tend to fall at the weaker end of the TTC carcinogenicity potency spectrum. The data on which the 1.5 μg limit was originally based is heavily skewed by extremely toxic compounds (e.g., aflatoxins) which cannot possibly arise in the typical API synthesis. Further, the limit fails to take account of unavoidable cancer-risk factors present in the environment, such as background ionising radiation—estimated to give a lifetime cancer risk of 2.3%! The EMEA provision also ignores the reality that pharmaceutical syntheses frequently *require* the use of intermediates that are mutagenic in order to be practical. Finally, the disparity between a 1.5 μg daily limit and the 1000 μg daily limit recommended by the ICH Q3A(R) guideline as the threshold for identifying "normal" impurities creates a *cliff of regulatory concern* which would render the ICH guideline meaningless and result in the redeployment of pharmaceutical company resources from new product development toward regulatory compliance.

An alternative default limit is suggested which would be 2−3 orders of magnitude higher. The author argues that this would still meet the "1-in-100,000" risk ceiling deemed acceptable by EMEA regulators, because there is a "hidden buffer" of 10^{-2} to 10^{-3} risk mitigation arising from conservative assumptions which were employed in the published derivation of TTC. This higher default limit would still allow more stringent limits to be applied on those rare occasions where the impurity closely resembles a class of compound that has been shown historically to pose higher risk.

New ASTM Standard for Equipment Verification

For most companies, qualifying equipment is a costly and time-consuming process that in some cases can delay the launch of critical medicines to patients. While the basis for qualification activities lies in the GMP regulations, these have no specific requirements relating to how qualification is carried out—a situation which has caused many firms to adopt rigid qualification practices that add little value in a misguided attempt to reduce their regulatory risk.

After three years of consultation over several drafts, the American Society for Testing and Materials (ASTM) has now approved their consensus standard (E 2500-07 "Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment") which should give clearer guidance and so reduce unproductive efforts. The new standard makes only passing mention of the term "qualification" and ignores the traditional distinctions between IQ/OQ/PQ—which are not in fact mandated by the regulations but instead have become established by custom and practice. Rather it defines "verification" as "an umbrella term that encompasses all types of approaches to

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assuring systems are fit for use—such as qualification, commissioning and qualification, verification, system validation, or other."

The standard describes a risk-based and *science-based* approach which seeks to ensure that manufacturing systems are fit for purpose, support continuous process capability improvements, enable innovation, consistently meet defined quality requirements, and are verified by *processes which are efficient and effective*. One significant change from the traditional approach to qualification is the provision that documentation and testing by an equipment vendor may be used as part of the verification documentation–providing the company is satisfied that the vendor has an acceptable quality system, sufficient technical capability and has applied sufficient Good Engineering Practice (GEP) to meet the regulatory requirements for verification.

A discussion on the relationship of this new standard to GMP regulations is given in an article by R. E. Chew and D. Petko in *Pharm. Eng.* **2007**, *27*, 6, 38–50. These authors see greater flexibility arising through reduction of unnecessary involvement of the Quality Unit in the detailed specification, design and verification activities. Here responsibility should lie more with "subject matter experts" such as engineering, product/process development, operations, etc. The role of the Quality Unit should be ensuring that critical aspects and associated acceptance criteria have been identified, approving the overall project verification plan, and approving the final determination that the system is fit for its intended use. On the other hand, the standard imposes additional requirements beyond traditional GMP in requiring a science-based approach informed by risk-management procedures throughout the stages of defining requirements, specification and design, verification, acceptance and release. The authors note that companies choosing to use the standard must implement it in its entirety and not cherry-pick the parts most favourable to them. Copies of the new standard can be obtained from www.astm.org.

Proposed Changes to European Variations Regulations

In October 2007 the European Commission published a consultation paper entitled "Better Regulation of Pharmaceuticals: Towards a Simpler, Clearer and More Flexible Framework on Variations" (http://ec.europa.eu/enterprise/pharmaceuticals/varreg/consultation_paper_20071024.pdf). At present companies are faced with a substantial administrative burden when making any changes to pharmaceutical products or processes, with the requirement to submit "variations" to their European manufacturing authorizations, often to several different agencies, and in many cases to await approval. This also constitutes a significant workload for the authorities themselves, and involves much duplicated effort. The proposed new legislation would simplify matters by directing individual European Union (EU) member states to align their own drug manufacturing change requirements with community-wide rules.

Currently 90% of medicines in the EU are approved on the basis of purely national authorizations; only those which have become available since 1995 benefit from the community-wide approval procedures introduced by the EMEA (Centralised Procedure and Mutual Recognition Procedure). It is now proposed that the central legislative framework for variations be expanded to include these purely national authorizations within its scope. This means all authorized products would be subject to the same rules on changes, regardless of how the medicine was originally authorized.

The current classification of variations into types IA, IB, and II will remain, but whereas at present all these variations require prior notification to all relevant authorities, it is proposed that in the future type IA variations (minor changes) be handled by a "do and tell" procedure. Depending on the nature of the change, companies would communicate it either forthwith or in their next annual report; in neither case would prior approval by the authorities be required. This would bring the European requirements more in line with FDA procedures in the United States (governed by the SUPAC and BACPAC guidelines for drug products and drug substances, respectively). Type IB and type II variations would still require prior notification, with tacit acceptance after 30 days in the case of type IB. Requirements for supporting documentation generally increase from type 1A through to type II changes.

It is also proposed to allow, under certain circumstances, the grouping of several variations within one single submission, which would then be evaluated in accordance with the procedure of the highest risk variation included in the group.

The precise details of which type of change can be handled by which procedure are currently given in the annexes to the Commission Regulations. It is now proposed that these annexes be replaced by detailed guidelines (yet to be drawn up), which should bring further flexibility. Any changes not foreseen by these guidelines would by default be handled as type IB variations, rather than type II as currently practiced. This provision would be subject to a safeguard clause whereby the competent authority could, within 30 days of submission, "promote" it to type II if it considers the change might have a negative impact on the safety, quality or efficacy of the drug.

The new procedures would formally introduce a number of elements developed at the International Conference on Harmonization (ICH), particularly the notion of a "design space" from their recent Q8 guideline. Henceforth, any changes made within an approved design space would not be considered to require any variation application. Introduction of a new design space or changes to an approved design space would be evaluated as a type II variation.

The short public consultation period on these proposals expired in January. Contributions were sent in by 16 member states, which were generally positive towards the preliminary proposal, although some reservations were expressed regarding the "design space" aspects. Twenty-five pharmaceutical companies and industry representatives/ associations have also sent in comments, and these were more strongly supportive. The full text of all these comments can be seen at: http://ec.europa.eu/enterprise/pharmaceuticals/varreg/cons2008_comitology.htm.

Meanwhile, in the same spirit of increasing regulatory flexibility, U.S. regulators are said to be putting the finishing

touches on a guideline that is expected to downgrade about 50 low-risk changes from their current requirements for a Change Being Effected (CBE) supplement to an annual reporting requirement (*The Gold Sheet* **2007**, *41* (11), 1–5).

ICH Publishes Annex to Q8

In November 2007 the International Conference on Harmonization (ICH) publishedan annex to their *Q8 Guideline on Pharmaceutical Development*, which is intended to provide further clarification of some of the key concepts outlined in the guideline itself (www.ich.org/LOB/media/MEDIA4349.pdf). The annex describes the principles of "Quality by Design" and shows how concepts and tools such as "design space" might be put into practice. It identifies the key elements of pharmaceutical development as Target Product Profile, Critical Quality Attributes (CQAs), Risk Assessment (linking material attributes and process parameters to CQAs), Design Space, Control Strategy, Product Lifecycle Management, and Continuous Improvement. It also offers advice on how to submit pharmaceutical development information in the Common Technical Document format.

Strategies for product development vary from company to company and from product to product, and it remains up to individual companies to decide on their approach to, and extent of, pharmaceutical development—whether to use a purely empirical or a more systematic approach. However, demonstrating greater understanding of the product and its manufacturing process can create a basis for more flexible regulatory approaches—the degree of regulatory flexibility being predicated on the level of relevant scientific knowledge provided in the application. It is the knowledge gained and submitted, rather than volume of data collected, that should form the basis for science- and risk-based submissions and their regulatory evaluations.

The annex provides a table comparing various aspects of a "minimal" approach to those of an enhanced "quality by design" (QbD) approach. Both approaches are acceptable, but only the latter would reap any reciprocal regulatory relief. For example, the minimal approach to developing a manufacturing process would be to fix it rigidly, with validation primarily based on the initial full-scale batches, and a focus on optimisation and reproducibility. In contrast, a QbD process would be adjustable within its design space, and a lifecycle approach would be taken to its validation, ideally with continuous process verification. The focus would be on control strategy and robustness, backed up with statistical process control methods.

The annex contains considerable discussion on the development of design space, usefully illustrated by graphical examples. Design space can be defined in terms of ranges for input variables, or through more complex mathematical relationships, such as time-dependent functions or as a combination of variables, for example as the principle components of a multivariate model. Scaling factors can also be included if the design space is intended to span multiple operational scales. Independent design spaces may be developed for each unit operation, or a single design space may span multiple operations, depending on the degree of operational flexibility the applicant desires. However, design space should not be just a collection of proven acceptable ranges for individual process variables, but must also take account of interactions between the variables. Contour plots are recommended to illustrate the chosen design space. This can take the form of a rectangle (or cuboid) sitting entirely within the acceptable region, or it can encompass the entire acceptable region; the latter gives greater flexibility but is more complex to define, as the acceptable limits for one variable would typically depend on the levels of others, as a result of interaction effects. Design space could also comprise overlap regions of successful operating ranges for multiple CQAs.

This annex has now reached Stage 3 of the ICH process, and is open for public comments until May 2008.

Industrial Experience of Quality by Design and Risk Management

A number of recently published articles illustrate the real-life application of some concepts from the Q8 guideline, and the related Q9 guideline on Quality Risk Management.

A group of scientists from major pharmaceutical companies such as Eli Lilly, AstraZeneca, Pfizer, Abbott, Wyeth Biotech, Merck, Schering Plough have discussed the problems faced in "Overcoming Disincentives to Process Understanding in the Pharmaceutical CMC Environment" (L. Foust; et al. *Pharm. Technol.* **2007**, *Sept*). Their view is that larger and strategic sampling and testing plans can improve process understanding and characterization; however, currently applied quality control systems often discourage the gathering of greater amounts of data because, for statistical reasons, this increases the risk of rejecting a perfectly good batch. One example given is in the area of release testing, where there may be 10–20 different properties to test, some associated with multiple acceptance criteria. If a failure of any one of 30 criteria results in batch rejection, and if each test has a 1% chance of falsely exceeding its acceptance criteria, then there would be a 26% risk of falsely rejecting that batch. As a result, manufacturers are motivated to reduce the number of release tests applied, which is strongly at odds with the recent ICH and FDA initiatives. Other examples of such *multiplicity* issues occur with stability testing, shelf life estimation, PAT implementation, validation, and OOS investigations. The problem is that there is no established procedure to modify release standards to account for increased sample sizes or extra testing. The authors propose eight fundamental principles which should lead to improved decision-making processes:

- Recognise that any observed result is only an estimate of the true value.
- Focus on the reliable estimation of the true batch parameters (average values and standard deviations).
- Understand the role and function of different types of limits, distinguishing especially between 3σ control limits and acceptance criteria.
- Recognise that development and end-product testing have a common goal in ensuring satisfactory products.
- Link sample size and acceptance criteria to manage risk.
- Recognise the value of additional testing.
- Use averages where appropriate.
- Make effective use of data through proper statistical analysis.

An article by scientists from GlaxoSmithKline in the United Kingdom focuses on "The Application of Quality by Design to Analytical Methods" (Borman P.; et al. *Pharm. Technol*. **2007**, Oct). These authors believe that current approaches to analytical method validation and transfer, rooted in ICH's Q2(R1) guideline, do not provide a high level of assurance of method reliability, as they typically represent only a one-off evaluation of the method. These approaches really only confirm that the analyst, equipment, and other components can operate the method at the time of the transfer exercise. The desired state is proving that the method will be reliable throughout the lifecycle of its use. They also note that historically, methods transferred into QC laboratories often take into account potential impurities which were detected in earlier synthetic routes but which cannot be formed in the commercial route. Their proposed "Quality by Design" approach to analytical methods parallels that recommended for processes. To begin with, method performance criteria (e.g., precision, selectivity, sensitivity) should be established and used to inform method development. Once developed, the method should be subjected to thorough risk assessment, which leads to the establishment of a design space and an associated control strategy. They recommend Failure Mode and Effects Analysis (FMEA) as a risk-assessment tool, and provide an example of its use in evaluating an NIR method used for in-line monitoring of a drying process. (The on-line article also features a downloadable Excel template for conducting such an analysis.) This exercise identifies all factors which might influence method performance and rates the severity, likelihood, and detectability of each adverse event to arrive at a risk priority number (RPN) for each eventuality. The team then decides which factors should be controlled, which are potential noise factors, and which should be experimented on to determine acceptable ranges. Design of Experiments (DoE) is used to assess the multidimensional combination of the highest-risk factors. For the highest-risk noise factors a ruggedness study is performed using a measurement systems analysis (MSA) design. This study aims to challenge the method, giving maximum opportunity for any problems to surface. The exercise should result in improvements to the method, after which FMEA is again applied to assess the risk in operating the method and to establish proven acceptable ranges. Subsequently, throughout a method's life cycle, there will inevitably be changes in the method environment that can affect its operation. Such changes can be assessed with reference to the information gained from the above exercises and any change that takes the method outside its proven design space subjected to further risk assessment. The authors believe this QbD process offers the opportunity for much greater regulatory flexibility in the future. For example, it would potentially allow the method performance criteria to be registered, rather than the method itself. The method actually used could be submitted as an example of how to attain the required performance criteria, but any subsequent changes to that method would be handled by internal change control procedures only.

A concrete example of risk management is given in an article by A. Toledo Rivero et al. from Liorad Laboratories in Cuba, "Improving a Pharmaceutical Water System based on a Risk Analysis Approach" (*Pharm. Technol.* **2007**, *Nov*). They examined their existing water pretreatment and purification (WPP) system using the Fault Tree Analysis (FTA) method as well as FMEA. These are complementary approaches to risk analysis which start from opposite points on the cause-effect spectrum. The model obtained from the FTA method was mainly useful from a qualitative point of view. The model from FMEA was more useful in establishing priorities quantitatively, and informing the corrective actions plan. This re-established cleaning, disinfection, and process control activities in a better documented way through official records managed by QA, and involved the installation and/or replacement of certain units and measuring devices. Performance qualification carried out after the prescribed modifications demonstrated improved functioning from a chemical and microbiological point of view throughout the process stages. However, the authors concluded that with the existing WPP system the risks could not be reduced to a level where it would be suitable to supply water for direct use in parenteral formulations, and recommended its use be limited to washing operations and other technological applications as required.

"Risk Management for Pharmaceutical Change Control" by W. Harclerode and C. Noualhac (*Am. Pharm. Rev.* **2007**, *Sept/Oct*) also focuses on the FMEA approach—this time as a tool for classifying proposed changes as presenting high, medium, or low risk. A number of case studies are presented wherein changes are assessed in terms of severity, likelihood and detectability. A change to replace an item of processing equipment was assessed as high-risk, and thus a development plan followed by full revalidation of the process was recommended. In contrast, a medium-risk change would be sufficiently supported by just one validation run with a limited focus on the conditions actually changed. A low-risk change would require only documented verification that the product remained acceptable.

Dedicated Facilities

GMP regulations and guidelines have always emphasised the need for companies to employ dedicated facilities, rather than multipurpose equipment, when manufacturing drugs which are especially toxic or sensitising. However, up until now there has been little clear guidance as to where and when this is required. "The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities." (EU GMP Guide, Chapter 3.6). (The word *certain* here might equally be rendered as *uncertain*.)

In order to provide some clarification, EMEA produced a concept paper on the use of dedicated facilities in February 2005, (Doc. ref: EMEA/152688/04), which has informed changes to the GMP Guide currently under consideration. Meanwhile, the issue has also been considered at length by the International Society of Pharmaceutical Engineers (ISPE), who published their own white paper on the issue in September 2007. (www.ispe.org/galleries/e-letter-files/EMEA_white_paper.pdf) It is interesting to compare the different approaches these organisations have taken.

The EMEA concept paper proposed two categories of "high-risk" product. Dedicated and self-contained facilities would be mandatory for Category 01 products, comprising cytotoxics/cytostatics, β-lactam antibiotics, radiopharmaceuticals, BCG vaccine, and other highly sensitising, genotoxic, or teratogenic materials. On the other hand, Category 02 materials would be permitted to be made in shared facilities—but only on a campaign basis, provided a risk evaluation had been performed and had had a positive outcome, and subject to the validation of cleaning procedures. Such materials would include non-β-lactam antibiotics, hormones, immunosuppressives, and ecto-parasiticides. Risk assessment should consider the severity of possible harm resulting from cross-contamination and the probability of such harm occurring. The former aspect is related mainly to the pharmacological and toxicological properties of the product, while the latter is related more to physicochemical properties of the API and dosage form, as well as to manufacturing process characteristics.

ISPE, on the other hand, sees little value in pigeonholing product classes in this way, and proposes that risk assessment principles should be used for *all* products in order to make a science-based determination of whether dedicated facilities are required. Their white paper argues that, by requiring segregation or dedication as the default, least risk strategy, the regulator may, unwittingly, have a significant impact on the development, bringing to market and production of novel, life enhancing drugs. It explicitly refers to the ICH Q9 (Quality Risk Management) guideline as a more appropriate decision-making tool. It also stresses that the protection of personnel should be considered alongside the protection of products and that overemphasising the one aspect may lead to difficulties in adequately controlling risks in the other. For example an "over-engineered" solution to reduce operator exposure to a product may make cleaning more difficult, and thus elevate the risk to the patient. An alternative strategy that achieves a better balance, without compromising either quality or safety, may be more appropriate.

By defining "risk" as the product of "hazard" and "exposure", ISPE propose that risk assessment should be strongly geared to the Acceptable Daily Intake (ADI) value of the relevant substances. This should lead to the definition of criteria to assist in the monitoring and control of risk, such as cleaning or acceptable carry-over levels. In their opinion, dedicated facilities should only be *required* in circumstances where physical and/or procedural controls (such as cleaning) cannot show the ability to control potential cross-contamination to acceptable levels. On the other hand, manufacturers should be able to *choose* to segregate a product for purely operational reasons, without being unduly concerned that this would set a precedent for other products with similar hazard/risk profiles.

FDA Modifies cGMP Regulations

In December 2007 the U.S. Food and Drug Administration (FDA) published a number of proposed changes to the cGMP regulations contained in 21 CFR parts 210 and 211. (www-.fda.gov/cber/rules/amendcgmp.pdf) Simultaneously, an older draft proposal for changes, which has been available since 1996, is now officially withdrawn. The new set of changes is part of an incremental programme to update the regulations so that they conform more with the "GMP for the 21st Century" initiative. This first phase comprises changes that are expected to be noncontroversial. Indeed, in some cases they represent only a change in terminology (e.g., replacing "conformance" with "conformity"). A number of paragraphs have been rewritten to acknowledge that, where operations or calculations are pre-formed using automated systems (provided these are appropriately validated and appropriately used), then only one human operator need be involved in the verification of those operations—rather than the two persons which the regulations have appeared to require up until now. Another significant change is to paragraph 48 on "plumbing"; there is now no reference to potable water having to meet the requirements of 40 CFR part 141, only that it be "safe for human consumption". There is still a requirement that such water be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination. Other changes clarify the agency's requirements for performance and validation of aseptic processes.

If no significant adverse comments are received, the amended regulations will take effect from 17 April 2008. A second phase of changes are currently being drawn up; although there is as yet no indication of when these will be published, they are expected to address the role of QA, validation and training. (Of course, these regulations, whether changed or not, strictly apply only to drug products, and not to the APIs, for which more specific guidance is available in ICH Q7A.)

New Reference Literature

The Royal Society of Chemistry (Cambridge U.K.) have published a useful volume on *Good Clinical, Laboratory and Manufacturing Practices: Techniques for the QA Professional*, edited by P. A. Carson and N. Dent, containing contributions from many experts across its 40 chapters (ISBN 078-0-85404-834-2). The book is intended primarily for Quality Assurance auditors with responsibilities across the entire GxP spectrum, but is also a valuable resource for anyone in the industry who may be involved in inspections or audits – whether by the drug regulatory authorities or by customers. The section on "Good Manufacturing Practice" is the one which will have most relevance to the process and manufacturing chemists; this comprises seven chapters, including one on Standard Operating Procedures (SOPs) and another on GMP for Investigational Medicinal Products. Additionally, there is a fourth section dealing with support services to GxPs, including useful chapters on sampling principles, statistical methods, trend analysis, supplier auditing, document control, computing and training.

Also in 2007 Concept Heidelberg have initiated a series of *GMP Reports*, slim volumes comprising articles on a general theme contributed mainly from the pharmaceutical industry in Germany. *Volume 1* has a theme of "FDA Requirements for cGMP Compliance", and *Volume 2* is concerned with "Qualified Persons". The first volume contains a particularly useful article

on "FDA Compliant Sampling" by M. Scholz (Procter & Gamble), pp 77–95. This summarises all official references to sampling across numerous regulations and guidelines, and discusses detailed requirements for sampling areas and sampling tools, usefully illustrated with diagrams and photographs of compliant equipment and operations. The article also discusses statistical rules of sampling and development of sampling plans. Other issues addressed in this volume (ISBN 978-3-87193-363-9) include conduct of inspections, risk analysis, analytical methods validation and out-of-specification (OOS) results.

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