Organic Process Research & Development **2007**, *11*, 311–317

Regulatory Highlights

Regulatory Highlights for 2006 to March 2007

This is the first in a series of reviews which will survey important developments in the area of pharmaceutical regulation, covering new initiatives and guidelines from agencies such as FDA, EMEA, ICH that particularly affect chemists developing or manufacturing active ingredients. It will also draw attention to published research and comment in the general literature which touch on these areas. It is anticipated that this section will appear twice yearly. This first article highlights developments since the beginning of 2006.

Manufacturing for Phase I Clinical Trials

In January 2006, the U.S. Food and Drug Administration (FDA) issued a draft guideline on "INDs − Approaches to Complying with CGMP During Phase 1" (www.fda.gov/cder/guidance/6164dft.pdf). While the Food, Drug and Cosmetic Act specifies that drugs (including clinical drugs) must be manufactured in accordance with Current Good Manufacturing Practice (CGMP) regulations (21 CFR Parts 210 and 211), this guidance acknowledges that not all of those regulations are relevant to the small-scale, one-time production that is typical of Phase I campaigns (for example, regulations that address expiration dating or warehousing). It thus proposes a less strict interpretation of the regulations for Phase I manufacturing, which FDA believes will still ensure the safety of the subjects enrolled in the study.

The draft guideline was officially withdrawn after a short period, so presumably it is no longer under active consideration. Nonetheless, it is still available on the FDA website, and will give some encouragement to chemists who make early clinical supplies that FDA really are now taking a "risk-based" approach to CGMP.

In the guideline, there remains a strong emphasis on sound Quality Control (QC) principles, such as having written procedures that are well-defined, using equipment that is adequately controlled, and accurately and consistently recording data from production and testing. More detailed advice is given on the implementation of these principles in the specific areas of personnel, quality management, facility and equipment, control of components, production and documentation, laboratory controls, container closure and labelling, distribution and record-keeping.

The new approach is signalled as much by the language of the draft guideline as its content. The phrase "We recommend that..." occurs throughout, replacing the verb "should" which normally dominates FDA guidelines, and the "shall" which is typical of their regulations. Even their "recommendations" are softened by the concession that "producers may have acceptable alternative ways of meeting the objectives described in this guidance". It is interesting that even the segregation of QC from production need not be considered absolutely sacrosanct in this context. "...[I]n some small operations, it may be justified to have the same individual perform both production and QC functions, including release or rejection of each batch. Under such circumstances, we recommend that another qualified individual not involved in the production operation carry out an additional, periodic review of production records."

This guideline is mainly addressed to drug product (dosage form) manufacturers; in a sense the manufacture of active ingredients (APIs) for clinical trials has already been dealt with in Section 19 of the now familiar Q7A guidelines, which have been operational since 2001. However, this new guideline is far more detailed than that brief section.

Disputes with FDA

Also in January 2006, FDA finalised their guideline on "Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP" (www.fda.gov/cder/guidance/5880fnl.pdf). Their original draft guideline appeared in August 2003, as part of the "Pharmaceutical CGMPs for the 21st Century" initiative. Little of substance has changed in the finalised version, although its scope has been expanded to now explicitly include disputes relating to API manufacturing. Briefly, the guideline outlines approaches to resolving disagreements on scientific or technical matters that arise during an FDA inspection, *where there is scope for different scientific judgements*. It does not cover disputes over procedural or administrative matters, or situations where there has been a clear failure to observe specific regulations or other requirements.

Wherever possible, manufacturers are encouraged to try to reach agreement informally with the investigator at the time of the inspection. If this is unsuccessful, the manufacturer can initiate the formal dispute resolution process within 30 days of issuance of the appropriate Form FDA 483. (In the draft version, 10 days from the time of inspection was proposed as a time limit.) The formal process comprises two tiers. At Tier-One the matter is considered by the appropriate unit of the Office of Regulatory Affairs (ORA). At Tier-Two, if the manufacturer disagrees with the Tier-One decision, he can request—in writing—that the matter go before a Dispute Resolution (DR) panel, residing at the FDA Commissioner's office. The DR panel will first determine whether or not to consider the appeal, and if they decide it is appropriate for review, they will schedule a meeting to discuss the issue within 90 days. (In the draft guideline, no time limit was proposed for this stage.)

Manufacturers should be aware that "The Agency may not accept a request for dispute resolution concerning a

10.1021/op700057c CCC: $37.00 © 2007 American Chemical Society
Published on Web 03/30/2007

disagreement that was not initially raised by the manufacturer during the inspection...", which may have the unintended consequence of manufacturers objecting to everything an inspector says "on principle", rather than waiting to reflect on the issues at leisure. The draft version had amplified this point as follows: "...the Agency believes that accepting such a request would discourage open discussion of disagreements between investigators and manufacturers and would hinder the agency's ability to quickly and informally resolve disputes in an efficient manner." This sentence, which strikes me as nonsense, has been omitted from the final version, but the practical impact of it still remains. One final point, which was not in the original draft, is that "The Agency may, under appropriate circumstances, take regulatory action while a request for formal dispute resolution is pending." In other words, the procedure is not to be used as a delaying tactic to postpone adverse consequences.

Zero Tolerance

An argument that "Zero-Tolerance Criteria Do Not Ensure Product Quality" is presented by statisticians from Eli Lilly. (Murphy, J. R.; Griffiths, K. L. *Pharm. Technol*. **2006**, January). The particular target of their criticism is recent FDA guidance on the dose uniformity of orally inhaled and nasal spray drug products, but it may have wider relevance. The point at issue is whether the acceptance testing for batches of such products include a criterion that none of the units tested may have a measured amount of active ingredient outside 75−125% of the label claim. The authors argue that the pass-or-fail decisions of such a test are only weakly connected to the actual quality of the batch and are "more of a gambling tool than a quality control test or a stimulant for improvement." It does not encourage manufacturers to do any more than necessary to just meet the standard; in fact it positively discourages the testing of "too many" units, since the more units that are tested, the more likely it is that one will fail. Thus, paradoxically, it would not be possible to thoroughly validate a manufacturing process, if to do so increases the risk of failing the validation. The authors believe that the barriers to eliminating zero tolerance criteria are mainly psychological; there is an erroneous belief that they provide assurance that there are not any nonconforming units within a batch, when in fact nothing short of 100% screening could guarantee this, and even that would still have some percentage error. They propose instead the development of statistically based sampling and acceptance plans, where the risk of accepting a batch with a defined level of defects can actually be quantified.

Laboratory Inspections

An aide-memoire on "Inspection of Pharmaceutical Quality Control Laboratories" was issued by the Geneva-based Pharmaceutical Inspection Co-operation Scheme (PIC/S), for entry into force on January 1, 2006 (www.picscheme.org). This is to provide guidance to GMP inspectors and to assist in training and in the preparation for inspections. It also serves as a useful check-list for the managers of such facilities. PIC/S clearly envisages that such inspections will be very thorough, as evidenced by the 180 or so detailed questions that they suggest: questions such as "Do you assess trends? How and by whom are trends evaluated? SOP exists?" or "What is the sampling plan? (Which norm is used?) How do you ensure the representativity of samples per batch?" The questions are grouped into general areas such as Quality Assurance System, Documentation System, Personnel, Premises and Equipment, Materials and Supplies, Testing, Results and Release of Test Results. There are also specific questions targeted at chemical and physical chemistry laboratories, and at microbiological laboratories.

API Inspections

In February 2006, FDA enacted a revised Compliance Program Guidance Manual (CPGM), giving guidance to their investigators for inspection of API manufacturers (www.fda.gov/cder/dmpq/7356-002f-CDER.pdf). This document reinterprets their Compliance Program Guide of October 2000 in the light of the more specific Q7A guidelines for APIs adopted in 2001. It follows the pattern of the original CPGM in establishing a modular approach, in which six "systems" are defined: Quality System, Facilities and Equipment System, Materials System, Production System, Packaging and Labelling System, and Laboratory Control System. A firm will be judged to be "not in a sufficient state of control" if any one of these systems is found to be noncompliant with CGMPs, and regulatory actions are likely to follow.

The program is intended to provide for a risk-based inspection strategy, the depth of inspection reflecting inter alia the firm's compliance history, the technology employed, and the profile classes of API produced. "Profile class" is determined by whether the API is produced by chemical synthesis, fermentation, or plant/animal extraction and whether or not it purports to be sterile. There are two basic types of inspection: "surveillance", which is routine inspection (biennial), and "compliance", which is inspection "for cause", to investigate specific problems that have come to the agency's attention.

For surveillance inspections, the program provides two options: a full inspection, which examines 4−6 systems, and an abbreviated inspection, which examines only 2−3 of the systems. In all cases the Quality System must be examined, along with at least one other. For a compliance inspection, the full inspection option is strongly recommended.

Across the six systems, approximately 100 issues are specifically highlighted, and 16 types of deficiency are given for which regulatory action would be warranted. Interestingly, although investigators are expected to use the Q7A guidelines, they are instructed not to reference specific Q7A sections in their FDA-483 observations or in the establishment inspection report. Rather, firms should be cited under appropriate federal statutes, which are considerably less specific.

CTD under Fire

The European Clinical Trials Directive (CTD), in force since May 2004, has come in for stinging criticism from the

medical profession (Hemmeniki; A.; Kellokumpu-Lehtinen, P.-L. *Br. Med. J.* **2006**, *353*, 301−302, 2006). Industrial chemists are mainly affected by the CTD because it mandates drug inspectorates to ensure appropriate CGMP compliance in the manufacture of trial materials. Now there are claims that it hinders the process of conducting clinical trials by erecting unreasonable administrative and cost barriers to cash-strapped researchers. Pharmaceutical companies expect to ultimately make substantial profits from a new drug and so may regard these extra costs as tolerable; but as the authors of this editorial article point out, many recent advances in oncology therapy stem from innovative clinical research instigated and conducted by motivated physician-scientists with not much big-pharma backing. It is this valuable research which is threatened by the CTD's catch-all provisions. The European Organization for Research and Treatment of Cancer (EORTC) is quoted as claiming a drop of 63% in new trials between 2003 and 2005, with trial costs increasing by 83% and associated insurance costs by 100%. They find it ironic that a directive aimed at protecting patients and improving research standards should have the effect of delaying patients' access to new, possibly life-saving, therapies. One specific complaint concerns the requirement that "...even phase I trials fulfill pharmaceutical industry grade good manufacturing practice standards...". Another complaint, which seems to me to have less merit, concerns the requirement for comprehensive preclinical biodistribution and toxicity experiments before Phase I. Nonetheless, judging from the response in the letters pages of subsequent issues (*Br. Med. J.* **2006**, *353*, 666), the authors' concerns are widely shared in the medical research community.

Quality by Design

In July 2005, FDA signalled a new approach to their assessment of new drug quality by seeking volunteers to take part in a pilot program to help develop guidance for a new quality assessment system (*Fed. Reg.* **2005**, *70*(134), 40719−40720). Eleven applications were accepted for the expedited review, with Pfizer's Chantix (varenicline tartrate—a smoking cessation drug in tablet form) being the first to obtain FDA approval under this new system in May 2006.

As part of the program, participants were requested to provide two pieces of information in the Chemistry, Manufacturing and Control (CMC) section of the application that would not normally have been submitted: an expanded Pharmaceutical Development section, incorporating elements of the ICH Q8 guideline (www.fda.gov/cder/guidance/6746fnl.pdf) and a comprehensive Quality Overall Summary (QOS) section. For the latter, firms were not told what information to submit, but rather to submit what they thought was relevant to that particular application, the key being to demonstrate their Quality by Design (QbD), product knowledge and process understanding.

Progress on this QbD pilot program was one of the topics aired at last year's Drug Information Association (DIA) annual meeting in Philadelphia in late June. Representatives from Pfizer, Wyeth, and Merck, as well as from FDA, shared their experiences in working with the new system. A summary of their comments appeared in the August 2006 edition of *The Gold Sheet* (Vol. 40, No. 8).

FDA view the QbD approach as comprising elements such as critical quality attributes, formulation development, risk assessment, design of experiments, impact of raw material attributes on product manufacturability, process development, impact of process parameters on critical quality attributes, and design space for critical component attributes and critical process parameters. Design space is a particularly important concept, being the range of a parameter which has been proven to yield acceptable-quality product; once defined and justified, operational changes within such ranges can be made at the company's discretion without the need for prior agency review or approval. However, FDA's experience of the pilot program so far is that a lot of the necessary information is missing or is addressed by some applicants but not all. They also emphasise the need for manufacturers to reassess their design space in the light of any changes they do make. They take an interest in the company's regulatory strategy for managing such changes.

From the manufacturer's viewpoint, the QbD approach requires the submission of more detailed information than would otherwise be necessary. On the other hand, they would typically have acquired this information in any case as part of process and product development. The reward for the extra up-front effort should be increased regulatory flexibility in the post-approval phase. For example, the agency envisages concluding a "CMC regulatory agreement" for each application whereby, instead of everything being subject to post-approval scrutiny, a very concise agreement would be crafted which focuses on what the firm's change control strategy will be.

One difficulty for manufacturers embarking on this new approach is that it is—for the moment at least—very FDA specific. The format of a submission is significantly different from the standard Common Technical Document (CTD) and so may not be well received in countries outside the United States. The approach is still in an early evolutionary stage, with both the agency and manufacturers tentatively feeling their way.

Quality Risk Management

One of the most significant developments in pharmaceutical regulation in recent years has been the ICH Q9 guideline on Quality Risk Management. This was formally endorsed by the ICH steering committee in November 2005 and adopted as an official FDA guideline in June 2006 (www.fda.gov/cder/guidance/7153fnl.pdf). In the same month, some members of the ICH Q9 Expert Working Group produced a comprehensive set of PowerPoint slides to serve as training material for this important area, directed both at regulators and the industry. The authors are drawn from the ranks of the FDA as well as from well-known pharmaceutical companies in the U.S.A., Europe, and Japan, generic as well as innovator companies. They stress that the slides are for illustrative purposes—to suggest possible interpretations of the Q9 guideline—but do not represent any official policy or guidance.

The manufacturing and use of a drug product necessarily entail some degree of *risk*, which can be defined as the combination of the *probability* of occurrence of harm and the *severity* of that harm. The purpose of the guideline is to suggest how risks can be identified and managed, using a number of tools which are already widely applied elsewhere in industry, business, and government. Tools specifically mentioned in the guidance, and explained more thoroughly in the slide set, include Failure Mode Effects (and Criticality) Analysis (FMEA & FMECA), Fault Tree Analysis (FTA), Hazard Analysis and Critical Control Points (HACCP), Hazard Operability Analysis (HAZOP), Preliminary Hazard Analysis (PHA), and Risk Ranking and Filtering (RRF).

The slides suggest where each tool might be useful, and provide some practical examples. For instance, the implementation of FMEA is shown within the framework of a drying process, while a packaging problem is examined by means of FTA.

The slides are available to download in both PowerPoint and PDF format from www.ich.org/cache/html/3157-272-1.html.

Design of Pharmaceutical Water Systems

A useful article by Joe Manfredi (GMP systems Inc., Fairfield, NJ, U.S.A.) summarises generally accepted design features for pharmaceutical water systems and discusses whether many of these are hard and fast requirements or simply useful guidelines. (Myths, Fantasies, and Rumours about Water System Design. *Pharm. Technol., CGMP Compliance Technology Primer*, September 2006). Among the issues discussed are the specification of 316L stainless steel contact materials, use of sanitary polishes, sloping of lines to drain, requirements for recirculation loops, specifications for sanitary pumps, tank filters, acceptable valve designs, siphon-proof air breaks, and dead legs.

The author contends that a number of commonly accepted standards, practices, and prohibitions are not, in fact, rooted in any official guidelines, but may have been based on verbal comments by inspectors subsequently taken out of context (sometimes by less-than-scrupulous designers). He concludes that water systems require a commonsense approach and good engineering rather than unquestioned acceptance. For example, "added substances" are not acceptable in pharmaceutical waters, and this has discouraged some designers from using chlorine or ozone for sanitization. In fact, the addition of such substances is permissible, provided they are subsequently removed.

The most difficult aspect of any design is the consistent removal of bacteria, because these are living organisms which are inherently unpredictable. For example, the author believes that some biofilm is probably always present in the equipment—even under constant high-temperature conditions. (This theme is further developed by Riedewald, F.; Sexton, A. *Pharm. Eng.* **2007**, *27*(1).) It is therefore wise to assume this "worst case scenario" when considering the total design to ensure it is absent from the water coming from it.

Reconciling CGMPs with Quality Systems

A new initiative by the FDA could signal the wider application of formal quality systems in pharmaceutical manufacturing. International standards for quality management (e.g., ISO9000) have been around since 1987 and are widely implemented on a voluntary basis across a number of industrial sectors. So far, however, there has been little take-up of this within the pharmaceutical sector—largely because the pharma industry must comply with mandatory standards which are much stricter; therefore, ISO9000 is perceived as bringing little benefit.

However, FDA now see advantages in integrating the quality systems approach into the existing regulatory framework—as part of their "Pharmaceutical CGMPs for the 21st Century" program. In September 2006 they published the final version of their Guidance for Industry "Quality Systems Approach to Pharmaceutical CGMP Regulations", superseding their draft guidance of 2 years earlier. The guideline demonstrates how and where the elements of a comprehensive quality system can fit with the requirements of the CGMP regulations (www.fda.gov/cder/guidance/7260fnl.pdf).

The quality management model described in the guideline follows the pattern established by ISO9001:2000 in having four major factors: Management Responsibilities, Resources, Manufacturing Operations, and Evaluation Activities. The management responsibilities should include provision of leadership, structuring the organization, building the quality system to meet requirements, establishing policies, objectives and plans, and reviewing the system. The term "Resources" is held to include personnel as well as facilities and equipment, and refers also to outsourced operations. Unsurprisingly, the Manufacturing section is the most detailed, the specific elements being to (1) design, develop, and document product and processes, (2) examine inputs such as raw materials, process water, gases, containers, and closures, (3) perform and monitor operations, maintaining appropriate records, (4) address any nonconformities, such as batch failures, by documented investigation, conclusion, and follow-up. Evaluation activities should extend beyond testing individual lots and encompass the analysis of data for trends, internal audits, quality risk management, corrective and preventative actions where necessary, and the promotion of improvement. Usefully, each section concludes with a table where the proposed quality-system elements are cross referenced with relevant paragraphs of the CGMP regulations (CFR parts 210 and 211).

This FDA initiative somewhat pre-empts the internationally harmonized guideline on the same subject, expected shortly from the International Conference on Harmonization (ICH). They formally proposed a new tripartite guideline entitled "Q10: Pharmaceutical Quality Systems" in 2005, with the first draft to be available for public consultation in the spring of 2007.

The FDA guideline makes it clear that the adoption by companies of such a formal quality system will remain entirely voluntary, and that the overriding requirement will still be compliance with federal regulations. It is less clear

to what extent the implementation of a quality system might reduce FDA's own inspectional oversight. Companies with ISO9000 registration are subject to annual inspections by accredited auditors—which they pay for themselves. It may be that in the future—provided a firm's ISO9000 registration conforms to the recommendations of this guideline—the authorities might accept this auditing in lieu of their own inspections. Similarly, customers may increasingly seek to substitute a perusal of a contract manufacturer's quality manual for a lengthy on-site audit. There could be benefits all around in terms of an overall reduction in the inspectional burden.

Some thoughts on how companies might implement this guideline are contained in an article by M. Moltalvo (*J. GXP Comp.* **2006**, *11*(1), 66−77).

Visible Residue Limits

A series of articles by Merck scientists illustrates the advantages of establishing visible residue limits (VRLs) in cleaning validation studies. (Forsyth, R. J.; et al. *Pharm. Technol*. **2006**, *30*, Sept/Nov). Under CGMP, equipment should be visually clean before use, but until now authorities have insisted that swab testing is also used to verify that contamination is below an established acceptable residue limit (ARL). The authors argue that for many drug substances, the VRL lies considerably below the ARL and therefore in itself provides sufficient evidence of equipment cleanliness. Of 39 marketed formulations that they evaluated, the VRLs were $<1\ \mu g/cm^2$ in 27 cases; only in one case did the VRL exceed $3\ \mu g/cm^2$ (e.g. VRLs for simvastatin and rofecoxib were 0.485 and 0.871 $\mu g/cm^2$ respectively). For a comparison, a typical ARL would be in the region of $4\ \mu g/cm^2$.

In their first article, the authors report a risk-management assessment of using VRLs in place of swab testing. This is in the spirit of the latest ICH Q9 guideline on "Quality Risk Management" going through stages of risk identification, risk analysis, and risk management. They identify three main risks. The most serious is the potential that dirty equipment passes visual inspection and thus compromises the subsequently manufactured formulation. Another risk is regulatory agency challenge to the VRL approach. The third is the subjectivity of visual assessments. Each risk is then analysed to evaluate its possible causes, its seriousness, and its likelihood. For example, the most likely scenario for dirty equipment passing visual inspection is inadequate inspection; the seriousness of this eventuality is high, but its likelihood is judged to be low. Risk management concentrates on reducing the likelihood further—in this case by thorough training of the inspectors, use of multiple inspectors, and ensuring their familiarity with the appearance of each residue. The authors conclude that the associated risks can be successfully mitigated and are outweighed by the many benefits of implementing a VRL approach. These include the ability to assess all visible equipment surfaces, as opposed to the 25 cm^2 samples that are traditionally swabbed, to perform many more cleanliness assessments in a reduced time (with fewer personnel and analytical resources), and with less documentation to collect and archive. There are, however, limitations. One is that so far only stainless steel surfaces have been evaluated, and it is not clear if the same VRLs would also apply to glass. There are also limitations with respect to assessing microbiological contamination—but this is generally less critical in API manufacturing.

In their second article, the authors describe a cleaning validation study in a packaging facility, where they used the VRL approach alongside traditional swab testing. An unspecified "development formulation" and 500-mg metformin tablets served as two representative worst-case products, since both are non-film-coated tablets which produce dust during the packaging process. VRLs were established as 0.51 $\mu g/cm^2$ and 0.97 $\mu g/cm^2$ respectively. The cleaning validation was performed in triplicate on representative pieces of the equipment; it comprised overall visual inspection and swab sampling of 69 selected "hard-to-clean" areas. All results were acceptable; no visible residues were detected, and all swab results were lower than the ARL of 100 μg/swab. Surprisingly, though, a number of swab tests for metformin assayed above the VRL of 24 μg/swab; in one case a result of 88 μg was recorded. A thorough investigation of this discrepancy using diode array HPLC scans suggested that in these cases the metformin had degraded to a compound with a very close retention time but significantly higher absorbance. The degradation product has not been identified; the authors' proposed structure is simply an alternative tautomer of the accepted structure, and thus cannot explain the discrepancy.

Out of Specification Analytical Results

In October 2006 FDA published their finalised Guidance for Industry on the subject of "Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production" (www.fda.gov/cder/guidance/3634fnl.pdf). This has been one of the hottest topics in CGMP compliance since the infamous case of U.S. vs Barr Laboratories in the early 1990s. There has been controversy and misunderstanding regarding the extent of retesting and resampling of products that is acceptable. A draft FDA guideline on the subject has been available since 1998, and this finalised version is not substantially different from that. The recommendations are the same, but they have been expressed rather more clearly, and make more detailed reference to the underlying CGMP regulations.

Formally, the investigation which is required into any OOS result is now conceived in two phases. The first phase is to be conducted immediately by the analyst and the laboratory supervisor—to determine whether an error occurred during the performance of the test. If no such error can be established, the second phase of the investigation should enquire into the circumstances of the batch's production to establish if any mistakes were made at that time, or if there is a more general problem with the manufacturing process. This phase may also involve further laboratory testing of the batch for the purpose of determining whether the original OOS result was unrepresentative.

The finalised guideline lays increased emphasis on evaluating the impact of OOS results on batches already distributed, and on recognising that an OOS result may

indicate a flaw in product or process design. It contains a more detailed discussion on appropriate and inappropriate uses of averaging when reporting test results, with emphasis on ensuring that all results going into the average are compatible with the established variability of the analytical method. In the case where a set of results straddles the acceptance limit, with acceptable variance, companies are urged to err on the safe side and report the average result as OOS.

The main point is that an OOS result should only be invalidated if clear evidence of a laboratory error is obtained during the first phase of the investigation. Under all other circumstances, the OOS result should be retained and considered along with other evidence—including that of passing retest results—in the subsequent assessment of batch quality. Even if the decision is taken to release the batch, the OOS result should still be recorded on the certificate of analysis. An example is given where such a decision would be justified. (An initial OOS assay result of 89.0% is obtained, with no assignable cause determined. Subsequently, seven retest results were found acceptable—around 99.0%. In these circumstances the company could reasonably conclude that the original result "did not reflect the true quality of the batch". However, under this guideline it would remain a valid result.)

Moves to Tighten Regulatory Oversight of API Plants

Recently there has been much discussion regarding uneven enforcement of CGMP regulations and guidelines in different parts of the world. U.S.- and EU-based API manufacturers have a perception that their facilities are more tightly regulated than those in India and China—simply because they are more easily accessed by the responsible inspectorates. The Synthetic Organic Chemical Manufacturers Association (SOCMA) in the United States and the European Fine Chemicals Group (EFCG) have teamed up to urge their respective regulatory authorities to increase inspections of foreign API manufacturers. (EFGC and SOCMA Urge More Inspections of Foreign API Makers. Van Arnum, P. *Pharm. Technol*. **2006**, November.) FDA have traditionally pursued a vigorous foreign inspection program, but SOCMA and EFGC argue that this has not kept pace with changing supply patterns. According to official figures for 2005, 9% of FDA foreign inspections were in China, and 14% in India, whereas these countries are estimated to account for about half of all drug imports to the U.S. and as much as 80% of the total volume of APIs imported to the EU. SOCMA has expressed concern that lack of inspection could mean a large number of unsafe medicines and could also provide foreign firms with a competitive advantage over U.S. and EU firms that do follow the rules.

European Inspectorates have generally been less active in the inspection of API facilities. New EU directives, theoretically enforced since October 2005, insist that drug product manufacturers only use active ingredients that comply with Part II of the EU Compliance Guide (ICH/Q7A). However, the onus is on the drug manufacturers themselves (and their Qualified Persons) to audit their API's sources. Third-party audits are an acceptable alternative, provided due diligence is exercised. (For a discussion on this, albeit in the context of excipients, see *The Gold Sheet* **2006**, *40*(12), 6−7.) European regulators do not see it as their obligation to verify by inspection that all sources of API filed in a marketing application in fact comply with CGMP. (Global API Sourcing: What is Next for Suppliers to the European Union? Villax, G.; Oldenhof, C. *Pharm. Technol. Sour. Manage.* **2006**, July, 10−19.)

Some evidence that foreign-supplied API may not always meet quality standards comes from the European Directorate for the Quality of Medicines (EDQM), which does have a foreign API inspection program and has carried out about 40 inspections in India and China since 1999. EDQM issues certificates of suitability (CEPs) to API sources, mainly based on a review of submitted documentation. As a result of "suspicion-based" inspections, CEPs from five different Chinese and Indian API manufacturers had to be revoked. However, such revocation does not automatically trigger any systematic action by the competent authorities in Europe.

FDA has signalled its intention to tighten up the registration of drug manufacturers, which is mandatory (but patchy in practice). A recent estimate by Office of the Inspector General (OIG) in the U.S. found that some 9000 marketed drugs are not listed in FDA's National Drug Code Directory. They now propose a new system for the electronic registration of all drug manufacturers—both domestic and foreign (www.fda.gov/OHRMS/DOCKETS/98fr/oc94634.pdf). It is not clear, however, whether this will extend to API manufacturers.

On the European front, the European Medicines Evaluation Agency (EMEA) is currently developing an electronic CGMP database, which will provide the public with information of manufacturing and import authorisations, GMP certificates, and non-GMP compliance information (www.emea.eu.int/Inspections/EudraGMP.html).

Best Practices for Qualification Success

A. Aschmann and G. Lawrence (Independent Project Analysis, Virginia, U.S.A.) have published a statistical analysis of characteristics and practices that influence the cost and time requirements for qualification studies (*Pharm. Eng*. **2007**, *27*(1)). Data on 50 qualification projects were collected from nine major pharmaceutical companies—of which 21% concerned API facilities. The study used a standard multilinear regression approach to identify the most significant factors.

Unsurprisingly, the overall size of the project (measured in dollars) was found to have the greatest influence on both IQ/OQ cost and duration. The type of installation was also found influential. Biological facilities were associated with higher qualification costs (relative to the overall cost), and pilot plants were found to have relatively lower qualification costs than other facilities. Qualification costs were relatively larger for stand-alone projects, as opposed to expansions or revamping of existing ones. While these costs can be seen as inherent in nature of the project (and so beyond the company's control) another major factor was found to be the quality of planning for the qualification phase; projects with good advance planning (e.g., using the Critical Path

Method or milestone schedules) had significantly lower IQ/OQ costs and required significantly less time overall. Similarly, projects which involved "new technology" were found to be more costly in terms of both dollars and time.

One slightly surprising finding was that attempts to overlap the Installation and Operational Qualification (IQ and OQ) phases of a project may be counterproductive, since this practice was found to increase the overall time required. The authors note that in many cases it was difficult to precisely identify all the costs associated with qualification, leading them to conclude that companies do not accurately capture the true costs of these activities.

The recommendations for "best practice" are (1) better definition of project schedules, (2) increased overlap between commissioning and qualification activities (but not between the IQ and OQ phases), (3) creation of a project team with well-defined objectives, documented roles and responsibilities, avoiding multiple or conflicting responsibilities and excessive turnover of key members, (4) improved engineering status and project execution planning, (5) availability of established standard operating procedures (SOPs), so that these do not have to be drafted anew, (6) involvement of equipment vendors in the qualification plan.

Genotoxic Impurities

An article on "The Impact of Impurity Analysis on Future Regulations" (Rios, M. *Pharm. Technol*. **2007**, February) discusses inter alia the issue of setting limits for genotoxic impurities in drug substances and drug products. These are substances which may bind or break DNA molecules even in parts-per-million concentrations; structures as diverse as *N*-hydroxyanilines, carbamates, nitro compounds, and aldehydes may fall into this category and are recognised via the Ames mutagenicity test.

General impurity limits were comprehensively covered by the ICH guidelines Q3A and Q3B, which have been in use for almost a decade now; however, these guidelines only address genotoxic impurities in a brief footnote. For normal process-related impurities, levels below 0.03% need not be reported, but it is recognised that genotoxic, or potentially genotoxic, impurities need to be controlled at significantly lower levels. This may present a substantial analytical challenge to develop quantitative tests below the 50 ppm level. Traditional HPLC may have to be supplemented or replaced with more modern "hyphenated" techniques such as LC−MS−MS. (For a discussion on the implementation of this technique at Pfizer, see Kolodsick, K. J.; Phillips, H.; Feng, J.; Molski, M.; Kingsmill, C. A. *Pharm. Technol*. **2006**, February.)

In January 2007, an EMEA guidance on genotoxic impurities became effective (www.emea.eu.int/pdfs/human/swp/519902en.pdf). This recommends a general limit of 1.5 μg daily exposure for such substances on the basis of on precedent guidelines applied to food additives and food contact materials. (Compare the 0.03% limit that could entail exposure to more than 600 μg daily.) The proposed limit has emerged from a risk assessment using Threshold of Toxicological Concern (TTC) criteria. However, even that low limit is considered unsatisfactory for high potency genotoxic carcinogens such as aflatoxin-like, *N*-nitroso- or azoxy compounds. Members of these groups will require compound-specific toxicity data in order to make a valid risk assessment. The guideline makes no mention of drugs still in clinical development, and it is not clear whether it need strictly be applied there.

The FDA are still developing their guideline on the issue and are expected to release a draft soon. However, the Pharmaceutical Research and Manufacturers of America (PhRMA) has proposed a staged approach that ties permissible impurity levels to the anticipated duration of medication, suggesting that levels of up to 120 μg per day may be acceptable for drugs to be taken for less than 1 month (Müller et al. *Regul. Toxicol. Pharmacol*. **2006**, *44*, 198−211).

Derek Robinson
38 Millbrook Court, Little Mill, Pontypool, Monmouthshire NP4 0HT, United Kingdom

OP700057C