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Regulatory Highlights

Regulatory Highlights for March−August 2009

Feedback on FDA Validation Guideline

The Food and Drug Administration's (FDA's) new draft guideline on Process Validation has understandably given rise to a great deal of comment since its publication last November. The details of this guidance were summarized in the previous "Regulatory Highlights" (*Org. Process Res. Dev.*, **2009**, *13*, 391.).

The May/June 2009 edition of *Pharmaceutical Engineering* (Vol. *29*, No. 3) contains three articles which comment on the draft proposals from a variety of viewpoints. N. Clanan, A. Redmond, and S. O'Neill (pp 8−16) provide a "perspective from industry", in which the main provisions of the guideline are summarised, with commentary at appropriate points. In the opinion of these authors, the guide is to be welcomed for the clarity and simplicity of the integrated three-stage lifecycle process, for its emphasis on the need for effective scientific knowledge-led programs, and the elimination of the "three golden batches" rule. However, they also feel that the guidance needs to be better aligned with current European legislative requirements.

This article is balanced by "A Perspective from the FDA" (pp 18−22), which takes the form of an interview with Grace McNally, one of the principal co-ordinators of the guideline. Among other topics, she answers questions on the extent of consultation with other regulatory agencies, the relationship with ICH guidances, the need for investigator (re)training, the emphasis on statistical criteria, extent of full-scale experimentation expected, formalities required during continuous process verification (Stage 3), number of process qualification batches expected (Stage 2), requirements for revalidation, and responsibilities of contract manufacturers. Interestingly, she feels there is actually little substantial difference from the 1987 guidance; although the three-stage lifecycle approach is now given more prominence, it was also implicit in the previous version.

In the third article (pp 24−30) R. E. Chew focuses on the equipment qualification aspects of the guideline and makes detailed comparisons with the provisions of the European Union (EU) GMPs and with ASTM's E2500 standard (for the Design, Specification, and Verification of Facilities, Equipment and Systems (reviewed previously in "Regulatory Highlights"; *Org. Process Res. Dev.* **2008**, *12*, 132.). In this author's opinion, if the E2500 standard is followed, then the expectations of both U.S. FDA and EU regulators will be met; overall the ASTM standard provides the most robust, science- and risk-based methodology of any of the documents discussed.

Many individual companies and industry organizations have made their own direct responses to FDA, and these can all be viewed at the official website www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=FDA-2008-D-0559. Over 40 submissions had been received by the time the public consultation phase closed in March. Although most of these consist of a few (2−5) pages of comments and recommendations, there are more substantive submissions as well; for example APIC, the Active Pharmaceutical Ingredients Committee, representing mainly European API manufacturers, has submitted 38 pages of comments from its individual member companies. Many proposals are simply for editorial changes, or for extra clarity in defining particular terminology, but it is clear that there is also some unease about many of the basic principles on which the new guideline is founded. Among the most common concerns raised are:

- Lack of harmonization with requirements in other parts of the world. In particular, the new guidance differs significantly from ICH Q7A, the internationally harmonized guide to GMP in API manufacturing.
- The proposed new definition of validation is felt by some to be too comprehensive, covering aspects which are more properly regarded as R&D (Stage 1) or routine GMP monitoring (Stage 3).
- Overemphasis on statistical assessments, particularly the recommendation to involve statisticians in the ongoing evaluation of routine commercial production. Many feel that the amount of sampling required to generate "sufficient statistical confidence" would be disproportionately onerous, and that confidence could be gained equally well using nonstatistical methods.
- The guideline only seems relevant to those projects which have utilised the Quality by Design approach to development (described in ICH Q8 (R1)), but this is not mandatory. It is difficult to adapt it to projects which have been developed using the traditional (and still perfectly valid) "minimalist" approach. By the same token, it is not clear how existing products will be affected when changes require those processes to be revalidated. Some have asked how generic products will be affected.
- The requirement to demonstrate that the process is capable of consistently producing acceptable quality products "within commercial manufacturing conditions, *including those conditions that pose a high risk of process failure*". In practice, processes are designed to avoid any such conditions.
- The suggestion that "viral *and impurity* clearance studies" should be conducted under cGMP conditions. This is felt to be unjustified for "small-molecule" impurities in APIs, which are generally detectable by easily validatable analytical methods.
- Requirement to demonstrate that operating ranges should be shown capable of being held *as long as would be necessary during routine production*. This would be particularly difficult for continuous processes.
- Unclear expectations of which validation stages should be reached at the time of application submissions and of preapproval inspections.

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- Lack of a glossary with clear definitions of the terminology employed.

Clearly, the radical changes proposed in the new guidance will continue to be a source of controversy. However, the FDA expects to be able to produce a finalized version by the end of 2009.

Combating Counterfeit and Adulterated Drugs

The death of 81 people in the United States last year from adulterated heparin has focussed increased attention on assuring the source of supply of drug product ingredients—both active and inactive—and has encouraged the adoption of increasingly proactive measures to combat counterfeiting. The World Health Organization (WHO) estimates that counterfeits now account for 1% of drugs in developed nations and up to 30% of drugs in developing areas.

An FDA inspection of the Shanghai firm which supplied the contaminated heparin revealed massive attempts at concealment and deception as well as deviations from cGMP. Contrary to this company's initial submission, it turned out that they had never manufactured heparin themselves, but rather repackaged the API supplied by another firm. Subsequent inspection at this subcontractor revealed that they had only been making the product since 2006, prior to which time a third, undisclosed, firm had supplied the heparin. FDA inspectors were unable to investigate the heparin operations there, since they had now ceased entirely. However, at the current manufacturer they discovered several GMP deficiencies, including the failure to conduct a GMP-compliant transfer of the process from the original site. Several lots of heparin delivered to customers were found to be contaminated with a hazardous impurity, oversulfated chondroitin sulfate, yet no investigations into this had been conducted. Warning letters to both companies involved were issued on 14 April 2009, and can be viewed at www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm.

A new industry initiative, RX-360, is now attempting to coordinate efforts of drug companies and their suppliers to avoid such situations in the future, by establishing a framework for shared audits and a clearinghouse for information on drug safety and quality. (*Chem. Eng. News.*, *87* (25, 22 June), **2009**, 24−25) RX-360 is incorporated as a nonprofit consortium and held a launch meeting in early June in Washington, DC. The group is currently studying three types of audit. In one model (sponsored audits) audits are performed by individual member companies, and the results are contributed to a shared database. Alternatively, several members could coordinate a third-party audit that employs the consortium's standards. Third, members could access auditing information in the database and pay a credit to the companies that performed the audit. An audit that would cost a single company between seven and ten thousand dollars could cost between one and two thousand dollars per participant as part of a shared program. The FDA does not formally endorse organizations such as RX-360, but it does encourage collaboration and has long permitted third-party audits.

A number of technological solutions to the problem of supply chain security are discussed in article by A. Pellek (*Pharm. Technol.* **2009**, *33* (6, June), online bonus material). A number of firms now use radio frequency identification (RFID) tags to track their products throughout the supply chain. Another emerging trend is the application of security features to the dosage form itself—an increasingly important technology in a world where everything is repackaged. Companies are also starting to apply a layered approach in which a mixture of overt (e.g., holograms and colour-shifting inks) and covert (e.g., chemical taggants and nanoencryption) features are used together on the packaging and the dosage form. The article spotlights half a dozen companies who develop and supply these security solutions.

FDA are themselves taking an active interest in this technology; this year they have issued two new draft guidelines which touch on it. The first, released in January, is titled "Standards for Securing the Drug Supply Chain - Standardized Numerical Identification for Prescription Drug Packages", and proposes a serialized national drug code (sNDC) made up of the labeller code, product code, package code, and then a unique 8-digit serial number generated by the manufacturer or repackager for each individual package. This code should be applied to the smallest saleable unit of drug product, in both a human-readable and machine-readable format. The second, more substantive, guideline concerns "Incorporation of Physical-Chemical Identifiers (PCIDs) into Solid Oral Dosage Form Drug Products for Anticounterfeiting" (released July 2009). A PCID would be a trace amount of an inactive ingredient(s) added to an existing section of the dosage form. A unique physicochemical characteristic of that ingredient then makes it possible to detect and authenticate legitimate dosage forms and identify counterfeits. Examples of such substances include inks, pigments, flavours, and molecular taggants. Guidance is provided on design considerations, supporting documentation, and the determination of reporting categories for postapproval changes to incorporate PCIDs (annual report, "change being effected" or "prior approval" supplement). Both documents are available from the Web site (www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.)

The other major contamination issue to surface in the past few years is the adulteration of certain foodstuffs with melamine for the purpose of boosting nitrogen assays. This has caused several human fatalities in China and killed domestic pets in the United States. Although this problem is thus far confined to food products, FDA have now (August 2009) issued a guideline to drug manufacturers on "Pharmaceutical Components At Risk From Melamine Contamination". This identifies some two dozen substances commonly used in formulations, for which the absence of melamine should be specifically assured. Assay methods for measuring melamine contamination in foods using liquid chromatography/triple quadrupole tandem mass spectrometry (LC−MS/MS) and gas chromatography/mass spectrometry (GC−MS) have also been posted on the Web site.

Impurities in Generic Drug Substances

In July 2009 the FDA published a revised guideline "ANDAs: Impurities in Drug Substances", replacing their previous guidance of November 1999. The revisions are in

response to changes in the corresponding ICH harmonized guideline Q3A(R); although the ICH guideline is strictly intended for new drugs, FDA believes that much of its content applies to generic versions as well. ANDAs (abbreviated new drug applications) are expected to provide a list of organic and inorganic impurities, and residual solvents, together with a rationale for the inclusion or exclusion of impurities in the drug substance specification. If there is a USP monograph that includes a limit for a specified impurity, then the acceptance criteria should be set no higher than that. (If the impurity can be qualified at a higher level, then the applicant may petition the USP for a revision.) However, unspecified impurities should not exceed ICH's identification threshold, even when a higher limit is given by USP. Where there are no compendial limits, the recommendation is to qualify the impurity. An impurity is considered qualified if it meets any of the following criteria:

- The limit does not exceed the level observed in the reference listed drug.
- The impurity is a significant metabolite of the drug substance.
- The limit is adequately justified by the scientific literature.
- The limit has been adequately evaluated as safe by means of toxicity studies. (This is the least favored option.)

Interestingly, an impurity occurring below the ICH qualification threshold is not regarded as automatically qualified (as it would be in the case of a new drug). For example, if impurities in certain drug or therapeutic classes have previously been associated with adverse reactions, a lower qualification threshold would be appropriate. Conversely, a higher qualification threshold could be appropriate when the concern for safety is low. Proposals for alternative qualification thresholds will therefore be considered on a case-by-case basis, taking into account patient populations, drug class effects, and historical safety data. In some circumstances, the acceptance criterion may need to be lower than the qualified level to ensure drug substance quality. For example, if the level of a metabolite is too high, it means that the potency of the product would be unreasonably low.

EU Variations Classification and Procedures

In February the European Commission issued a public consultation paper on the implementation of the revised variation regulations (see *Org. Process Res. Dev.* **2008**, *12*, 818.). The most minor type of variation—type 1A—has now been further subdivided into two categories: type $1A_{IN}$ variations are to be notified immediately after the changes have been implemented, whereas other type 1A variations should be notified within 12 months following implementation. Both type 1B and type II variations need to be approved prior to implementation, although the review of type 1B variations will be more rapid. A draft of the detailed classification guideline is provided; 69 categories of changes are delineated, 11 of which refer specifically to changes in the active substance. Each category is given a number, and a recommendation for the appropriate procedure type, together with any conditions to be fulfilled and documentation to be supplied to qualify for any of the reduced (Type 1) reporting procedures.

To give a flavour of the guidance, a specific example concerns changes in the batch size of an active substance or intermediate (No. 11). Up to 10-fold increases compared to the currently approved batch size can be handled as a type 1A variation provided:

- Any changes to manufacturing methods are only those necessitated by the scale change, e.g. use of different-sized equipment.
- Test results of at least two batches at the new scale are available.
- The product concerned is not a biological or immunological drug (in which case the variation is type II).
- The change does not affect the reproducibility of the process.
- The change is not the result of unexpected events arising during manufacture or because of stability concerns.
- The specifications of the active substance/intermediate remain the same.
- The active substance is not sterile.
- The currently approved batch size was not approved via a type 1A variation.

If the proposed scale-up is more than 10-fold, type 1B procedures should apply. As documentation, applicants should submit the amended section of the Common Technical Document, along with the batch numbers of the tested batches having the proposed batch size and—in the case of scale-up in excess of 10-fold—batch analysis data on a minimum of one production batch manufactured at both the currently approved and the proposed scales, together with a copy of the approved specifications.

Simultaneously, the Commission has published a second consultative document containing the associated procedural guidelines. Here, the submission and review procedures are delineated according to the type of variation (1A, 1B, II, or extension) and the status of the current marketing authorization (whether by the mutual recognition or centralised procedures). Time scales are given, including provision for "clock stops". There is guidance on the grouping of several variations into one submission, recommendations for unforeseen variations, special provisions where urgent safety restrictions may be required, and particular provisions for human influenza vaccines. Procedural guidance for the handling of "worksharing"—where the same change needs to be communicated to several different European authorities—is also given.

Both consultation papers can be found on the Web site http://ec.europa.eu/enterprise/pharmaceuticals/varreg/pubcons_2009-07.htm, as can the Commission's summaries of the comments received from interested parties.

New Guideline on Near Infrared Spectroscopy

In February 2009 the European Medicines Agency (EMEA) published the draft of a revised guideline on the use of near infrared spectroscopy (NIRS) by the pharmaceutical industry and the data requirements for new submissions and variations involving this technique. NIRS is useful for the identification and assay of pharmaceutical starting materials, intermediates, and finished products, as well as for in-process control and monitoring purposes. It is also one of the major methods in Process Analytical Technology (PAT). Normally, NIRS is used

as an alternative method to validated conventional methods. Although it is a very powerful and informative technique, it is very sensitive and highly specific to the equipment and context in which it has been developed. Thus, it cannot be repeated easily in official control laboratories, so the reference methods need to remain as part of the official specifications. While it is acceptable to approve lots on the basis of a validated NIRS method, those lots must also pass according to the reference method, if so tested. The guideline notes that current software makes it possible to develop NIRS methods with minimal understanding of the relevant chemometrics, and consequently there is a high risk of invalid results arising from the influence of unknown hidden variables. It is therefore emphasised that the training and skills of the NIRS analysts responsible for developing the method are critical, and should be documented as part of the submission. The nature of the method is such that the calibration models are continuously extended as more batches are entered into the database. Such augmentation need not necessarily be the subject of an official variation.

The document describes in detail the regulatory expectations for method development, data collection, calibration, validation, change control, and maintenance, according to whether the method is intended to be qualitative or quantitative. It also clarifies and differentiates the data requirements for the marketing authorization dossier and those for GMP.

ICH Guidelines and the Product Quality Lifecycle

In March 2009 the Steering Committee of the International Conference on Harmonization (ICH) published a 10-page Question and Answer document on the implementation of their guidelines Q8 (Pharmaceutical Development), Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality Systems). (http://www.ich.org/MediaServer.jser?@_ID=5290&@_MODE=GLB) Topics dealt with are Design Space, Real Time Release Testing, Control Strategy, Pharmaceutical Quality Systems, Knowledge Management, and the Impact of the Guidelines on GMP Inspection Practices. Particular points of interest include:

- A design space can be applicable to scale-up and to site changes, and can also be developed for existing products.
- Real time release (RTR) can, if justified, be used in lieu of final release testing, but need not be used as a surrogate for all specification tests. The requirement to establish release specifications still remains, and those specifications must be met if/when the tests are performed.
- If RTR testing fails to provide a satisfactory assurance about a particular product, it is not acceptable to go back to end-product testing in order to release that batch.
- The GMP requirements for batch release under a Quality by Design program are the same as for traditional approaches.
- It is not necessary to describe the Pharmaceutical Quality System (PQS) in any regulatory submissions. However, elements of the PQS may be referenced as Supporting Information.
- There are no plans for a specific ICH Q10 certification scheme.
- Inspection processes will remain similar. However, for product-related (preapproval) inspections there could be a need for greater collaboration between the inspectors and the scientific assessors.
- Although some software vendors are now marketing their products as "ICH compliant solutions", ICH does not intend to endorse any commercial products.

Another ongoing effort to facilitate implementation of the ICH guidelines is the International Society of Pharmaceutical Engineers' (ISPE's) Product Quality Lifecycle Implementation initiative (PQLI) (Berridge, J. C. *Pharm. Eng.* **2009** *29* (3, May/June), 36−39). Launched in June 2007, this initiative has established multidisciplinary, multinational teams to flesh out key strategic themes. Through their deliberations, a set of papers has been published (*J. Pharm. Innov.* **2008**, *3* (3, June)) covering issues such as Quality Target Product Profiles, Critical Quality Attributes, Risk Assessments, Design Space, Control Strategy and Batch Release, and Quality Risk Management. Other issues, such as Change Management Systems and Knowledge Management, are under development. In the future it is also intended to tackle Process Performance and Product Quality Monitoring Systems, Corrective and Preventative Action Systems, and Management Reviews.

A recent paper from PQLI (Potter, C. *J. Pharm. Innov.* **2009**, *4* (1, March), 4−23) describes how the science- and risk-based approaches can be applied to existing products—with benefits to product quality, process throughput, and cost reductions. The practical application of QbD concepts to existing products should begin with an evaluation of the business case for making a change, and continue with review of the target product profile, an assessment of current product and process knowledge, leading to a plan to further develop product and process understanding. Such greater understanding may not necessarily result in a regulatory submission, but could still be beneficial in improving manufacturing efficiency. Three detailed case studies are provided, with real (though unidentified) examples from Wyeth, GlaxoSmithKline, and AstraZeneca. In AZ's case, they developed a real-time release strategy for an existing marketed oral dosage form, using at-line NIR-based analytical methods supplemented by conventional data taken during production. Review at the end of the project indicated that cycle times had reduced from 12 to 4 days (from dispensing ingredients to availability of the product to the market), with the QA/QC work reducing from 8 days to 8 hours. Thus, the business case was vindicated. The regulatory submission took about 8 months to construct, review, and gain approval in numerous European states.

New PIC/S Aide-Memoire for API Inspections

The Pharmaceutical Inspection Convention and Co-operation Scheme (PIC/S) has recently developed an Aide-Memoire on the Inspection of Active Pharmaceutical Ingredients, which came into force in March 2009. (www.picscheme.org) The intention is to assist inspectors from the 35 scheme member nations—many of whom are more familiar with the inspection of finished products—in preparing for and conducting inspections of API facilities—specifically in assessing compliance with the ICH Q7A harmonized guideline. It should also contribute to a harmonized approach to API inspections between the

different PIC/S members. The aide-memoire consists of a 20-page checklist of items, divided into 18 sections reflecting the structure of Q7A. Each item corresponds to a specific area of operation and comes with some brief notes, suggested questions to ask, and reference to relevant supporting documents.

Follow-on Biologicals

The very high cost of biological drugs, stretching in some cases to $100,000 or more for a year's treatment, is encouraging governments around the world to seek safe pathways for the approval of generic copies of these complex products, sometimes called "biosimilars" or "follow-on biologicals". The principle of generic substitution, after a reasonable period of patent exclusivity for the innovator company, is well-established for small-molecule drugs; but biologicals present extra challenges to demonstrating true equivalence, and not just because of their structural complexity. In contrast to the homogeneity of small-molecule drugs, heterogeneity is often an inherent part of the biologic package. The European Medicines Agency (EMEA) has already developed an approvals procedure, and to date, 13 follow-on biologics have been approved there. Various bills are currently under consideration in both U.S. Houses of Congress. Not surprisingly, there are sharp differences of opinion between innovator companies and follow-on manufacturers regarding the amount and type of supporting data which should be required and on the appropriate period of market exclusivity. A summary of arguments on both sides, along with details of the legislative proposals is provided in an article by E. Greb (*Pharm. Technol.* **2009**, *33* (6, June), 36−42). There is general agreement that some human clinical testing should be required for the regulatory approval of biosimilars, but the extent of this testing is disputed. The argument for full clinical testing is that subtle changes in the manufacturing process, such as different raw material sources, could give rise to significant changes in the product which may not be detected by even the most rigorous analytical examination, but could nonetheless affect the safety and/or efficacy of the drug. On the other hand, it is argued that products such as influenza vaccine are routinely redeveloped and approved every year without clinical trials, and that innovator companies themselves necessarily make changes to their processes all the time. The European approach is to require makers of follow-on biologics to demonstrate that their products have biophysical and chemical characteristics comparable to those of the reference products by characterizing the product at each stage of production and comparing it with the innovator product. EMEA usually evaluates bioequivalence with a case-by-case approach, rather than according to a standard, to provide a degree of regulatory flexibility. There is also a requirement for postapproval monitoring of follow-on biologicals that are administered for long periods. Overall, European clinical requirements for follow-on biologicals are usually much less onerous than for new biologicals. Currently, there is no U.S. law that explicitly enables the FDA to approve follow-on biopharmaceuticals, but two very similar measures—"Promoting Innovation and Access to Life-Saving Medicine Act" and "Pathway for Biosimilars Act" are under consideration in the House of Representatives. At the same time, a "Biologics Price Competition and Innovation Act" is being discussed in the Senate.

Reference-Standard Material Qualification

An article by D. Browne (*Pharm. Technol.* **2009**, *33* (4, April), 66−73,) discusses issues associated with the selection and qualification of reference standards. Scientists performing analytical testing use reference standards to determine both qualitative and quantitative data; the quality and purity of these materials are therefore critical for reaching scientifically valid results. In general, compendial reference standards—obtained from (inter)nationally recognized institutions—are preferred by the authorities. However, in the case of proprietary APIs and their impurities, such sources are unlikely to be available, and companies must usually prepare them for themselves. Chemical suppliers are another potential source of some materials, and these can be acceptable as secondary standards. The primary standard should always be of the "highest purity that can be obtained through reasonable effort" and may therefore need to be subjected to additional purification procedures. The author recommends that the reference standard should be in a salt-free state "to reduce the characterization tests required".

Any noncompendial standards must be actively qualified for use in registration applications, commercial releases, stability studies, or pharmacokinetic studies. Minimal required tests for initial characterization should include HPLC with UV detection for organic impurities, IPC with MS detection for metal contaminants, residue on ignition for noncombustible impurities, GC with flame ionization detection for residual solvents, ^{1}H and ^{13}C NMR, LC−MS, or FTIR for structural confirmation, and elemental (C, H, and N) analysis. Requalification at subsequent points may include a reduced suite of analysis, depending on the initial results. For the initial lot, a suggested requalification period may be 3, 6, and 12 months for the first year and annually thereafter. The reference-standard material qualification program should be started at least one month before the stability or clinical program begins, to help avoid any delays in testing. The material should be stored in a secure environment with controlled access and distribution. The author also recommends storing a back-up sample at a more reduced temperature as a contingency.

Water for Injection

An article by H. Bush and G. Zoccolante (*Pharm. Eng.* **2009**, *29* (4, July/Aug), 20−28) discusses the various methods for producing Water for Injection (WFI), comparing the performance of distillation-based and membrane-based systems in terms of system design, maintenance requirements, reliability, and overall life-cycle cost. Historically, distillation has been the preferred method for producing WFI for the biopharmaceutical industry, but this is almost entirely due to regulatory considerations. The European Pharmacopoeia mandates distillation as the only acceptable WFI production method, although the Japanese Pharmacopoeia permits Reverse Osmosis as well, and the USP allows any method that can be proven to be equal to or superior to distillation. In most other industries which use high-purity water, membrane-based technologies are overwhelmingly preferred, largely because of their significantly

lower operating costs when compared to distillation. They can also routinely meet far higher standards than the WFI requirements in terms of conductivity, total organic carbon, and microbial and endotoxin content. The article includes a case study where a membrane-based WFI system was installed in a U.S. pharmaceutical facility producing pulmonary drug-delivery systems. Dry powder inhalation products are typically not produced under aseptic manufacturing conditions, so WFI was not strictly required in this case. Indeed the initial specification was for the less demanding USP Purified Water; however, a subsequent review identified a potential for tightening microbial specifications in the final drug product. At this point the water system had already been ordered and was in fabrication. The review team decided that the addition of an ultrafiltration step was the best way of meeting the tightened specifications, with minimal impact to cost and scheduling. Monitoring of this augmented system over one year indicated very steady endotoxin levels at 0.05 EU/mL and microbial content at <0.1 CFU per 100 mL respectively 5- and 100-fold less than pharmacopoeial requirements for WFI.

Viracept Incident

One of the most high-profile failures of GMP in recent years was the contamination of Viracept (nelfinavir mesylate) tablets with high levels of a genotoxic impurity ethyl methanesulfonate (EMS). An article by Roche scientists C. Gerber and H. Toelle (*Toxicol. Lett.* **2009**. doi:10.1016/j.toxlet.2009.02.020, published online 9 March) now gives the chemistry side of this story. The problem arose when a hold tank used to store methanesulfonic acid (MSA) was cleaned using ethanol, after some nonroutine maintenance. The standard operating procedure did not require the tank to be dried after cleaning, with the result that the subsequent charge of MSA became contaminated with ethanol. During the prolonged storage period this became converted to increasingly high levels of EMS; these were carried over into the manufactured drug substance, and subsequently to the tablets. At its peak, the API contamination reached 2300 ppm before the problem was detected. However, it was shown that the impurity slowly hydrolyses in the tablet formulation matrix. Considering the decay rate and the time gap between tablet manufacture and earliest possible use of the product by patients, a reasonably cautious assumption for worst case patient exposure would be 920 ppm (±10%) over approximately 90 days.

Recurrence of this problem has now been prevented by discontinuing the use of the hold tank and dispensing the MSA directly from its original containers. The salt-formation process has also been redesigned to decrease the risk of EMS being formed as a side product of that reaction. (Some may consider this an overreaction, since there was never any likelihood of EMS occurring at this stage.)

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