Organic Process Research & Development

REGULATORY HIGHLIGHTS

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Regulatory Highlights for September 2010−January 2011

FDA PROCESS VALIDATION GUIDELINE FINALIZED

The US Food and Drug Administration (FDA) has now (January 2011) issued the final version of its Guidance for Industry: "Process Validation, General Principles and Practices", which now officially replaces the 1987 guideline of the same name. The draft revision of this guideline was reviewed in a previous "Regulatory Highlights" (*Org. Process Res. Dev.* **2009**, *13*, 391), and some of the extensive comment on it was summarised in a later article (*ibid.*, p 842). There are no major changes in the final version compared to that draft; the new definition of process validation as "the collection and evaluation of data, from the process design stage through *commercial* production, which establishes scientific evidence that a process is capable of consistently delivering quality product" remains, along with the emphasis on a *lifecycle* approach comprising the three stages of Process Design, Process Qualification, and Continuous Process Verification.

Some aspects which troubled industry commentators have been clarified. In particular, the requirement that CGMP conditions be employed for "viral and impurity clearance studies" has been somewhat softened. The agency believes that "most viral inactivation and impurity clearance studies cannot be considered early process design experiments", even though they are often performed in small-scale laboratories. Thus, "viral and impurity clearance studies intended to evaluate and estimate product quality at commercial scale should have a level of quality unit oversight that will ensure that the studies follow sound scientific methods and principles and the conclusions are supported by the data."

Another subtle difference is that the terms *attribute(s)* (e.g., quality, product, component) and *parameter(s)* (e.g., process, operating, and equipment) are no longer categorized with respect to their *criticality*. With risk-based decision making throughout the process lifecycle, "the perception of criticality as a *continuum* rather than a binary state is more useful". All attributes and parameters should therefore be evaluated in terms of their roles in the process and impact on the product or in-process material, and re-evaluated as new information becomes available. The degree of control over those attributes or parameters should be commensurate with their risk. The agency recognizes that terminology usage can vary and expects each manufacturer to communicate the meaning and intent of its terminology and categorization to the agency.

There is an expanded discussion on the use of Concurrent Validation, which—as in the draft guidance— is expected to be used only rarely. "Conclusions about a commercial manufacturing process can only be made after the PPQ (Process Performance Qualification) protocol is fully executed and the data are fully evaluated." If the PPQ is not successful, then additional design studies and qualification may be necessary. "The new product and process understanding obtained from the unsuccessful qualification study(ies) can have negative implications if any lot was already distributed. Full execution of Stages 1 and 2 of process validation is intended to preclude or minimize that outcome." The guidance insists that the circumstances and rationale for concurrent release be fully described in the PPQ protocol, and emphasises that any lot released concurrently must still comply with all CGMPs, regulatory approval requirements, and PPQ protocol lot release criteria.

A glossary of terminology employed is now included, and the reference list has been expanded to cite a number of ASTM standards and guides. The full document can be downloaded from the FDA Web site: www.fda.gov/drugs. Select "Guidance, Compliance and Regulatory Information", then "Newly Added Guidance Documents".

An example of the application of Continuous Verification (CV) concepts to process validation, as recommended in the new guideline, is provided by Kettlewell et al. from GSK. (*Pharm. Eng.* **2011**, *31*(1), 18−27). This article focuses on the validation of Voltrient tablet manufacturing, and explains how CV facilitated the use of data from development batches as part of the validation, resulting in the requirement to manufacture only one full-scale batch prior to commercialisation. (The validation of the corresponding API, pazopanib, however, was performed using the traditional three-batch approach.)

REVISED FDA GUIDANCE ON PRE-APPROVAL INSPECTIONS

The FDA has also revised its Compliance Program Guidance Manual on Pre-Approval Inspections (Program 7346.832). The document has been completely reworked to reflect a more risk-based approach to inspection. While this guidance manual is primarily addressed to FDA staff, it also provides industry with valuable information on the procedures surrounding the pre-approval inspection. As the name indicates, preapproval inspections are conducted as part of the agency's assessment of a New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or Biological Licensing Application (BLA). However, whereas in the past these inspections were mandatory for all such applications, under the new system requests for inspection (originating from the reviewing departments) will be dichotomised by the Department of Manufacturing and Product Quality as either "Priority" or "Discretionary", where the discretionary cases are generally not pursued. However, the final decision on whether to inspect rests with the district office concerned. The guidance details the criteria under which an application would be assigned "priority" status, and these are usefully summarised in a flowchart (Figure 1).

The guidance defines three distinct objectives for the inspection:

(1) Determination of readiness for commercial manufacturing
(2) Determination of conformance to the application
(3) Auditing of data integrity

The first objective is itself broken down into five sub-objectives:

(a) Evaluation of manufacturing changes and deviations
(b) Program for sampling, testing, and evaluation of raw materials

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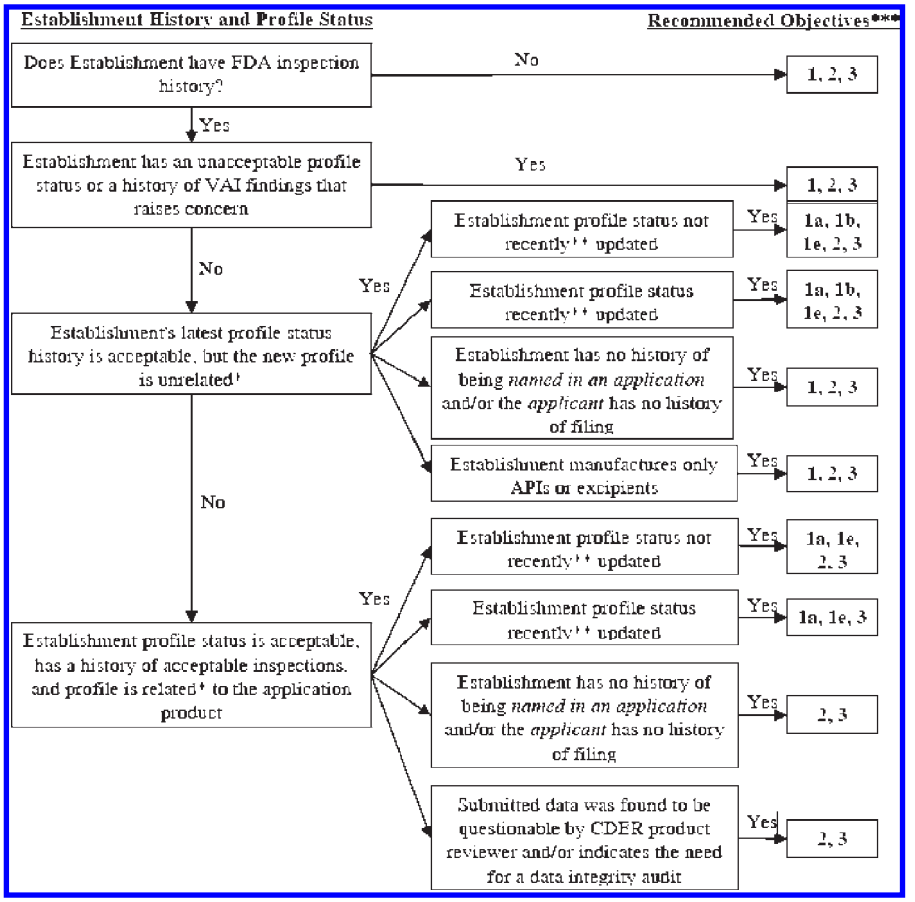

Figure 1. Recommended scope of coverage for a priority pre-approval inspection.

(c) Facility and equipment controls, specifically the prevention of cross-contamination
(d) Procedures for batch release, change control, deviation and failure investigations, complaints handling, and notification of adverse events
(e) The feasibility of the proposed commercial process and the manufacturing batch record. This objective is linked to the firm's process validation program.

Not all objectives need be covered by the inspection (as was done in the past). This will depend on the reasons why a priority determination was assigned, as detailed in the flowchart.

Part 3 (Inspectional) describes in detail the inspection scheduling and preparation, including which documents need to be reviewed, the composition of the inspection team, and the inspection strategy based on the objectives named above. Interestingly, the document makes clear that establishments which only manufacture intermediates, rather than the final active ingredients, will not normally be inspected. The complete document (53 pages) can be obtained from the FDA Web site (www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm071871.pdf).

The new procedure is further explained by ISPE technical writer Rochelle Runas (The New and Improved Pre-Approval Inspections Program. *Pharm. Eng.* **2011**, *31*(1), online exclusive article.) This article also includes an extensive public Q&A session with FDA officials focussing on this topic.

■ WHO GMP INSPECTION REPORTS

The World Health Organization (WHO) is also increasing its inspectional activities of both finished product and active ingredient manufacturing sites. In October 2010 they started a pilot programme for the prequalification of certain APIs, complementing their existing programme for medicinal products. (European Compliance Academy (ECA), GMP News, 28/10/2010) At present the API programme is limited to APIs for the three most prevalent infectious diseases: HIV/AIDS, malaria, and tuberculosis. WHO public inspection reports for establishments judged to be satisfactory are now also freely available via the Web site http://apps.who.int/prequal/WHOPIR/pq_whopir.htm. At present, 40 finished product manufacturing sites are listed, together with 6 manufacturers of active ingredients and 22 contract research organizations. The vast majority of establishments listed are located in India, with China coming a distant second. Only one US site appears on the list. Warnings of noncompliance (here called "Notices of Concern", NOCs) are published in a related page: http://apps.who.int/prequal/assessment_inspect/info_inspection.htm#6. At present only one NOC is listed on the site.

■ EMA HARMONISED POLICIES FOR IMPURITIES

The European Medicines Agency (EMA) has used its Q&A web page (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000071.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058002c2af#section9) to clarify their expectations for the setting of

specifications for three types of critical impurity in a drug substance: namely, potentially genotoxic impurities, heavy-metal catalyst residues, and class 1 solvent residues. Each type of impurity is to be considered in an analogous manner. Thus, if the impurity under consideration is just a theoretical impurity, but not found in practice as demonstrated by studies during development, then the impurity does not need to be included in the drug substance specification. If the impurity is formed or introduced in a step before the final synthesis step, it may still be excluded from the specification if it is controlled by a suitable limit in a synthesis intermediate and if it is unambiguously demonstrated by analysis results (spiking experiments are encouraged) that the impurity level does not exceed 30% of an acceptable limit (e.g., Threshold of Toxicological Concern (TTC)) in the drug substance. If these conditions are not met, the impurity has to be included in the drug substance specification, and the test has to be routinely performed. If the impurity is formed or introduced in the final synthesis step, it should be included in the specification regardless of the control measures adopted and the actual levels achieved. However, it could be possible to follow a skip-testing regime if the level of the impurity does not exceed 30% of the acceptable limit. In this case, data should be presented for at least six consecutive pilot-scale batches or three consecutive production-scale batches. These principles are also reiterated in EMA's latest update on "Questions and Answers on the 'Guideline on the Limits of Genotoxic Impurities'" (Revision 3), released 23 September 2010.

On the subject of genotoxic impurities, a new book from Wiley: *Genotoxic Impurities: Strategies for Identification and Control*, February 2011, 978-0-470-49919-1, 452 pages, hardcover: $125.00 US/CAN $150.00/£76.95/€99.90, edited by Andrew Teasdale (of AstraZeneca and the Product Quality Research Institute) promises to be a useful source of information on this hot topic.

REVISED EU GUIDELINES FOR COMPUTERISED SYSTEMS AND DOCUMENTATION

The almost constant updating of the European Union (EU) Guide to Good Manufacturing Practice (Orange Guide) continues apace. January 2011 saw the publication of new revisions to Annex 11 on Computerised Systems (http://ec.europa.eu/health/files/eudralex/vol-4/annex11_01-2011_en.pdf), and to Chapter 4 on Documentation (http://ec.europa.eu/health/files/eudralex/vol-4/chapter4_01-2011_en.pdf). These revisions come into force on June 30, 2011. They are of significance to API manufacturers since, taken together, the two sections are equivalent to the FDA's Part 11 regulations for electronic records and signatures. The effect is to increase the scope of documentation and data types to which the EU GMP Guide applies, and to make concrete some requirements which had previously been only implicit. Companies which make extensive use of automated procedures need to be aware of the new requirements, although those systems which already conform to US FDA Part 11 standards are unlikely to require changes. Dr. Bob McDowall, of Pharmaceutical Consulting Alliance, has provided a detailed analysis of the revisions, which can be viewed at the ECA Web site. (www.gmp-compliance.com/daten/download/Annex11_Chapter4_Jan2011.pdf)

FDA BECOMES AN OFFICIAL MEMBER OF PIC/S

The US FDA has finally been accepted as a full member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S), 5 years after their initial application to join the organization. (ECA GMP News, October 6, 2010 and November 25, 2011) This brings the membership of PIC/S up to 38 countries, Ukraine having been accepted at the same time. PIC/S provides a forum for joint co-operation and networking among pharmaceutical authorities. It has been active in developing and supporting harmonized GMP standards and guidelines, training of authorities (especially of inspectors), assessment and reassessment of the regulatory authorities. However, it does not provide for mutual recognition of inspections carried out by fellow-members—merely for the exchange of information between health authorities. Thus, FDA are unlikely to immediately desist from performing inspections in other PIC/S member states.

The current state of transatlantic co-operation between FDA and EMA is discussed in a article by Nathan Jessop (Will Transatlantic Regulatory Co-operation Meet Expectations? *Pharm. Technol. Eur.* **2010**, *22*(11)). Cooperative initiatives include a confidentiality information exchange agreement, moves to simplify certain regulations, and the provision of parallel scientific advice during drug development. The author points out that both agencies have recently undergone heavy criticism relating to product approvals. Although greater cooperation will be beneficial to both patients and industry, some critics may feel that joint regulatory measures will be too lenient on pharma companies.

RISK MITIGATION IN HIGH-POTENCY MANUFACTURING

The International Society for Pharmaceutical Engineering (ISPE) has augmented its Baseline Guide series with a new volume (No. 7) on "Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP)". Founded on the principles outlined in the International Conference on Harmonization's (ICH's) Q9 guideline on quality risk management, the new document establishes a blueprint for safe handling of substances based on their acceptable daily exposure (ADE) levels. It considers the balance between GMP and industrial hygiene aspects: protecting the facility workforce and the wider environment from harmful exposure, but also ensuring against unacceptable cross-contamination of other products. Thus, a great deal of attention is given to cleaning-validation issues. In this way, ISPE hopes to persuade regulatory authorities, particularly the EMA, that science can be used to control the risk of contamination, and that the mandating of dedicated facilities for specific classes of compound is unnecessary. The guide (140 pp, $440 (US), €365) can be ordered or downloaded from the Web site www.ispe.org. A short introduction is presented in an article by Patricia Van Arnum (*Pharm. Technol.* **2010**, *34*(10), 52−56), which also discusses the increasing investment by contract manufacturing organizations in potent-compound-handling capabilities.

On the subject of cross-contamination, an interesting study is reported by containment consultant Julian Wilkins (A Quantitative Study in Cross-Contamination. *Pharm. Eng.* **2011**, *31*(1), 44−51). A client wished to understand how effective their pilot tableting facility was for both operator protection and cross-contamination. To this end, three batches of surrogate tablets (naproxen) were produced, each followed by a batch of placebo tablets. Each placebo batch was analysed for naproxen contamination, supplementing the monitoring of surface- and air-borne-contamination in all areas of the processing suite. Although all sampled placebo tablets were found to be contaminated to some extent, none exceeded the "threshold of toxicological concern"

limit of 1.5 μg, so would be well below a safety-based limit for naproxen. Interestingly, the degree of contamination of the tablets could not be correlated with the levels determined in the environment. While the environmental monitoring showed decreasing contamination for each iteration, consistent with improved operator familiarity, the greatest tablet contamination was found in the third placebo batch. While the results indicate some room for improvement of the operating procedures within the suite, there is no serious risk to patients from cross-contamination. The author concludes that regulatory concern with cross-contamination is currently based more on perception than reality, and that more data is required for a science-based approach to be developed.

SUPPLY CHAIN SECURITY

The ISPE have also published a new "white paper" titled "Supply Chain Security: A Comprehensive and Practical Approach", with the aim of stemming the flow of counterfeit or adulterated drugs reaching the marketplace. This is a fast-growing problem, as evidenced by the FDA's estimate that 10% of all drugs sold in the United States are counterfeit and WHO's estimate that, globally, counterfeit drug sales in 2010 would amount to $75 billion (US). The problem is most acute in developing countries where regulatory and legal oversight is weakest. Janice Abel, of consultants ARC, points out (*Pharm. Eng.* **2010**, *30*(6), online exclusive article) that counterfeiting drugs is a highly profitable activity, and actually less risky than trafficking in illegal drugs, with less severe penalties if caught. Furthermore, counterfeiters can now access sophisticated technologies to copy labels and packaging, including barcodes. This article summarises recent global anticounterfeiting regulatory initiatives as well as some of the technologies available to combat the threat. The problem is also discussed in a piece by Bea Parks in January 2011's edition of *Chem. World* **2011**, *8*(1) 56−59). Here a number of specific examples are given; for instance, some supplies of the antiobesity drug Xenical (orlistat) in the United States were found to contain no active ingredient whatever—these were sold via Internet sites operated outside the United States.

The ISPE white paper is thus timely. It begins by arguing that pharmaceutical quality systems alone cannot ensure supply-chain security. However, augmenting specific quality systems, being alert to signals in the environment, applying risk management principles, and developing specific programs to deal with counterfeiting and illegal diversion will help strengthen an organization's overall supply-chain security. For instance, manufacturers are encouraged to pay careful attention to the destruction of unused packaging and labelling material, which could be used to illegally package counterfeit or diverted product. Customers should be directed to return all unsold product to its manufacturer, where it can be evaluated for authenticity. Companies are particularly encouraged to watch out for tell-tale "signals" from the environment which could indicate potential problems. Examples might be a sudden increase in price or decrease in availability of a key raw material, which might provide an economic incentive to illegal substitution. An unusual complaint or adverse event, or an unusual increase in these, may also be used as a signal. Monitoring criminal activity levels related to cargo theft or counterfeiting in certain geographical locations is likewise a signal. Any signal detected by an environmental scan should be evaluated using multidisciplinary approaches, and plans developed, consistent with the estimated risk. For example, where there is an identified higher risk for cargo theft, changing routes, adding additional drivers/escorts, and/or adding covert tracking devices should be considered. The white paper provides detailed recommendations in the areas of supplier quality management, logistics, and transportation service providers, and the transport and control of materials. It also discusses some of the steps and processes an organization can use to more effectively deter, detect, and disrupt counterfeit activity. These include physical security features on the products, either overt or covert, maintaining a counterfeiting incident management plan, and interacting with customers and distributors to verify their *bona fide* use of the product. The white paper is available free from the ISPE Web site (www.ispe.org); select "publications", then "other publications".

GUIDANCE FOR API MANUFACTURING

2010 saw the publication of the latest version (v 6) of APIC/CEFIC's "How-to-do" document on "GMPs for APIs" − an interpretation of the ICH Q7A guide. (http://apic.cefic.org/publications/publications.html) APIC is the Active Pharmaceutical Ingredients Committee of the European Chemical Industry Council. While the Q7A guide contains information on what manufacturers should do to be GMP-compliant, this document fleshes it out with commonly applied solutions and practical advice on how the requirements can be fulfilled while avoiding needless paperwork and administrative burden. It is based on the committee members' considerable experience in dealing with regulatory authorities in Europe. Although there is no guarantee that adhering to the principles laid down in the "how-to-do" document will always result in trouble-free inspections, it should provide both industry and regulators with greater confidence in global API quality.

Particularly interesting is the section on the selection of API starting materials. Q7A is notoriously vague on this subject, and attempts by the USFDA to define starting materials more closely have met with little success so far. For example, FDA have expressed a preference that the starting materials should be separated from the final API molecule by several synthetic steps. In APIC's view, however, the only relevant question is "is there sufficient evidence that the intermediate is analytically fully controlled in terms of identity, assay, and impurities?" If so, that intermediate might be legitimately defined as the starting material—even where it is the final intermediate. The source of the starting material (whether commercial or in-house) should not be a major factor. Where a starting material is close to the final API, it is recommended to ensure that details on the synthetic process and analytical controls used in its manufacture are available in case they are requested by regulators. While starting materials do not need to be manufactured to the GMP requirements defined in Q7A, their manufacturers should be appropriately qualified.

The "how-to-do" document offers an interpretation of the Q7A guideline on a paragraph-by-paragraph basis and is of a similar length overall. Thus, it follows the same 19 chapters as the guideline itself, making clarifications where appropriate. A typical example occurs in regard to paragraph 8.12 in the section on "Production and In-Process Controls". The official guideline states: "Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate

or API." The "how-to-do" document makes two useful points about this. First, that not everything is critical, and the choice should be made on the basis of the known critical parameters which could impact the quality of the API or intermediate. Noncritical weighing or measuring should NOT require witnessing. Second, the word "witnessed" is not intended to mean that the second person must be physically present throughout the operation; a subsequent check would fulfill the requirement of this paragraph.

One irritating feature of the how-to-do document is the poor quality of editing, which goes beyond the usual grammatical errors which are common when documents are translated to English from other languages. At many points, reviewer and editorial comments mysteriously appear as if they were part of the finalised text—sometimes actually contradicting the "official" advice. Nonetheless, when considered alongside the official Q7A guideline, this is an excellent source of practical advice.

VISUAL INSPECTIONS

Previous "Regulatory Highlights" have featured research demonstrating the utility of visual inspection in equipment cleanliness assessments. Care must be taken, though, as evidenced by a recent article from statistician Lynn D. Torbeck (Visual Inspection Goes Viral. *Pharm. Technol.* **2010**, *34*(9), 34−35). The focus is on inspection of incoming materials such as rubber stoppers, glass vials, and ampules for particulate contamination. A situation is described where three consecutive 100% inspections of units continued to reveal defects which were missed by the previous inspection. In another situation, a company found its normal rejection rate of 2−5% suddenly increased to around 20% for no apparent reason. The author points out that 100% visual inspection, even by well-trained and experienced inspectors, has been shown to be only about 80−85% effective. Also, it is essential to define a reference standard size for spots or specks below which they will not be counted as defects. TAPPT dirt estimation charts (http://www.tappi.org/Standards--TIPs/Dirt--Size-Charts.aspx) were recommended for this.

API MANUFACTURING IN CHINA

The constant drive to cut manufacturing costs has led in recent years to more and more pharmaceutical production being outsourced to developing countries, in particular to China. This trend has, perhaps inevitably, been accompanied by a number of well-publicized quality problems. Various approaches have been adopted by western companies for managing their outsourcing activities. As well as the traditional marketplace approach where the outsourcing company is simply a customer, we have seen the establishment of joint ventures with local companies, the establishment of fully owned subsidiaries in the developing country, and the take-over of locally established companies. Matteo Giovinazzi, of Janssen Pharmaceutica, describes a slightly different arrangement, closer to a partnership, in between the acquisition and the marketplace approach. (*Pharm. Eng.* **2010**, *30*(5), 42−51). For a number of reasons, the company wished to outsource some productions of late intermediates and APIs to Asia but were unable to find a company with the required organizational strength and technical capability to satisfy the strict parameters required. The solution was to start a development program with the company that showed the most promise of reaching such a level. This involved an expansion of production capability with the construction of a new plant, the building being specifically designed to minimize cross-contamination, maximize containment, maximize flexibility, and optimise the life span of the investment. Separate agreements were established as formal attachments to the contract to highlight the importance of Quality (GMP) and of Environmental, Health and Safety (EM&S) issues. In particular, child labour policy and business integrity were explicitly referred to. An EH&S "Maturity Ladder" is described, which aims to lift the external supplier from a status of basic awareness and legal compliance to a sustainable condition of best practices. This ladder comprises six steps; the first two steps comprise the minimum requirements before qualification, the external manufacturer must commit to achieving steps 3 and 4 within a 12−24 month period. Steps 5 and 6 are optional, but the pharmaceutical company is willing to support organizations that desire to achieve this level. The article also discusses some of the cultural and local regulatory issues which impinge on the technical decisions taken, and summarises the benefits which accrue to the pharmaceutical company, the local manufacturer, the local environment, and the worldwide pharmaceutical market. In this outsourcing model, the general accountability and leadership is assigned to the Chinese partner, while the knowledge and expertise come from the western partner. This means that the capital investment is made by the Chinese company, which therefore assumes the entrepreneurial risk. However, depreciation of the plant is paid back by the big pharmaceutical company as part of the product cost. Minimum committed volumes (by the pharmaceutical company) and minimum guaranteed production slots (by the local manufacturer) are among the measures put in place for mutual risk minimization.

QUALIFICATION AND VALIDATION

A number of recent articles address issues of equipment and facility qualification and their relationship to process validation.

- Taketmata et al. provide a Japanese perspective on the selection of targets for qualification of an API manufacturing facility. (*Pharm. Eng.* **2010**, *30*(5)). The principles of ICH Q9 are used to identify the critical functions, both static and dynamic, which require detailed qualification studies. Less critical functions are simply commissioned in accordance with Good Engineering Practices.
- James Agalloco (*Pharm. Technol.* **2010**, *34*(12), 43−46) discusses the situation where several identical or closely similar pieces of equipment are available in a plant, and the opportunities this provides for reducing the effort and cost of validation. He cites numerous FDA documents, which support the regulatory acceptance of the principle of equivalence, and gives examples where this has been applied to achieve savings—mainly from his own experience in sterile dosage form manufacturing.
- Young and Rosas (*Pharm. Eng.* **2011**, *31*(1) online exclusive article) present a case study on the application of the ISPE Baseline Guide to Commissioning and Qualification. The project in question was a $45 million plant retrofit for the manufacture of a small-molecule API; it comprised 30 separate systems—half process-related and half utilities. The cost for C&Q activities came in at 5.8% of the total installed cost, which was 93% of the estimate provided initially. The experience was judged to have been a significant improvement on previous projects undertaken at that site.

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- In another online exclusive article published in the same issue, Jahnsson, Al-Saffar, and Kälvemark, from Swedish consultants Pharmadule AB, present a risk-based work-flow for design and validation of facilities, starting from a set of Critical Quality Attributes. The main objectives are to improve quality assurance and traceability while saving costs and time.

Derek Robinson

38 Millbrook Court, Little Mill, Pontypool, Monmouthshire NP4 0HT, U.K.

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AUTHOR INFORMATION

Corresponding Author
derek@kolvox.net