Organic Process Research & Development **2010,** *14,* 1073–1077

Regulatory Highlights

Regulatory Highlights for March−August 2010

New Guidelines from EMA on Real Time Release and Process Validation

In February 2010 the European Medicines Agency (EMA) published the draft of a new guideline on Real Time Release Testing (RTR) of pharmaceutical materials. This provides an opportunity to approve materials on the basis of conformance to in-process acceptance criteria, rather than performing a complete set of tests on the finished product. So far this concept has only been applied to the sterility testing of terminally sterilized products, where it is commonly known as "parametric release", but recent guidelines from the International Conference on Harmonization (ICH Q8, Q9 and Q10) have suggested that a similar release strategy could be appropriate in other areas also. The existing guidelines covering parametric release remain unchanged by the new document, but their scope is now extended to other products, including biological/biotechnological products as well as chemically synthesized drugs. Companies wishing to employ an RTR strategy must obtain regulatory authorization for it, by demonstrating the adequacy and reliability of the approach in determining the relevant quality attribute(s) of the product. The introduction of RTR testing must be based on sufficient experience with the process as well as evaluation of Good Manufacturing Practice (GMP) compliance at the actual site. An application for RTR testing should contain adequate data of a running in period with both end product testing data and RTR testing data. Once approved, the RTR strategy should become the routine method of assessment; it would not be acceptable to substitute it with end-product testing if RTR indicated a batch failure or a trending toward failure. On the other hand, end-product testing may be substituted in the event of a failure of the RTR monitoring equipment; this, however, should be regarded as a process deviation and investigated as such. If the RTR testing is approved at a site outside the European Union (EU), there will be relief from the legislative requirement to fully analyse the material when it is imported into the EU.

Also in February, EMA issued a concept paper signaling their intention to revise the process validation guidelines, which have been in effect since 2001. Again, the aim is to incorporate concepts from more recent ICH guidelines and to utilize up-to-date technology, particularly in the areas of Process Analytical Technology (PAT) and Quality by Design (QbD). The current EU guidance on validation refers only to the traditional approach of manufacturing a number of validation batches to demonstrate that the process is under control. The revised guideline will clarify the extent to which ICH Q8, Q9 and Q10 should be followed when an applicant wishes to use alternative methods. The U.S. Food and Drug Administration (FDA) updated their own validation guideline at the end of 2008 (see *Org. Process Res. Dev.* **2009**, *13*, 391−392 and 842−843); although that draft has still not been finalized, it looks as if the EMA are now following a similar course, thus providing a more harmonized approach across the two regions. It is anticipated that the draft EU guideline could be published for consultation in the autumn of 2010, with final adoption at the end of 2011.

At the end of July 2010 some further revisions to the EU Guide to Good Manufacturing Practices (GMP) came into operation. Annex 13, on Investigational Medicinal Products, has been revised to reinforce the principle of independence between production and quality control functions— even in cases where the number of personnel involved is small. This conflicts with the FDA's latest guidance on phase I manufacturing, which signaled a more relaxed attitude here (see *Org. Process Res. Dev.* **2008**, *12*, 817). Other revisions to this annex are mainly relevant to formulation and final release activities. There is also an amendment to part 2 of the EU Guide, which deals with Active Ingredient manufacturing. A new short section on Quality Risk Management is introduced as section 2.19; the remaining sections of chapter 2 are then renumbered. This means that part 2 is no longer completely identical with ICH Q7, or with the equivalent FDA and Japanese guidelines, but rather introduces some additional requirements.

Copies of these guidelines and concept papers are available from the EMA Web site: www.emea.europa.eu, via the "document library" tab.

Updated EU Procedures for Inspections and Follow-Ups

The European Commission (EC) and the EMA have this year issued a number of documents which add to or revise their "Compilation of community procedures in inspections and exchange of information". These procedures become effective immediately. Of most interest to process chemists will be the new procedure on "Conduct of Inspections of Pharmaceutical Manufacturers or Importers", which now replaces the previous version of 2006. This procedure covers general GMP inspections as well as inspections related to a specific product, e.g. as part of the assessment of a application for manufacturing or marketing authorization. It details the planning and preparation required on the inspectors' part, as well as the steps to be taken during the visit, with special emphasis on the final meeting and the issuing of the inspection report. A final section deals with the quality management of the inspectors' activity, with the aim of ensuring a consistent approach across the community. Annex 2 describes the conduct of inspections for investigational medicinal products, while Annex 3 relates to inspecting active substance manufacturers. One point of interest here is a reference to Section 19 of the API manufacturing guideline (ICH Q7A, or Part II of the EU GMP guide). This section covers the manufacture of new active substances used in the production of investigational medicinal products. It is here

10.1021/op1002215
Published on Web 08/20/2010

pointed out that "although recommended its (Section 19's) application in this case is not required by Community legislation".

At the same time, a new "Procedure for dealing with serious GMP non-compliance" has come into force, as has a revision of the 2006 "Procedure for handling rapid alerts arising from quality defects". Again, the procedures are available from the EMA Web site.

Manufacturing Changes Reportable in Annual Reports

In July 2010 the FDA issued a new draft guideline on "CMC Postapproval Changes Reportable in Annual Reports". The appendix lists some 40 categories of change to the Chemistry, Manufacturing and Controls (CMC) section of a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) which will no longer require any advance notification to the agency. It is not clear, however, if this new guideline is intended to apply to active pharmaceutical ingredient (API) CMC changes, or only to changes to finished product CMC. The reporting requirements associated with changes to the manufacturing of API intermediates were comprehensively dealt with in FDA's 2001 "BACPAC 1" guideline (Bulk Actives Postapproval Changes). At that time, the agency indicated that a "BACPAC II" guideline would in due course follow, dealing with changes to a final API, but this guidance has not yet emerged. Instead, BACPAC I was itself officially withdrawn in 2006 and then reissued in a version which applied only to veterinary drugs. The situation regarding API changes is therefore confusing. This new draft guideline considers changes in six categories: Components and Composition, Manufacturing Sites, Manufacturing Process, Specifications, Container/Closure System, and Miscellaneous Changes. Examples of changes subject to the reduced reporting requirements, and which could be relevant to API manufacturing, include:

- (3.3) replacement of equipment with that of the same design and operating principle that does not affect the process methodology or in-process control limits
- (3.4) addition of a duplicate process chain or unit process
- (3.6) reduction of open-handling steps if there is an improvement with no change to the process
- (4.2) change to a specification to comply with official compendia
- (4.3) change in the approved analytical procedure if the revised method maintains basic test methodology and provides equivalent or increased assurance
- (4.4) replacement of a nonspecific identity test with a discriminating identity test
- (4.5) addition of an in-process test
- (4.10) addition of a test for packaging material to provide increased assurance of quality

All current FDA guidelines, both draft and finalised, can be downloaded from the Web site www.fda.gov/cder. Reporting of changes (variations) in the European Union has also been discussed recently (see *Org. Process Res. Dev.* **2009**, *13*, 844).

Handling of Highly Active Substances

In June 2010 the World Health Organization (WHO) published new guidelines on the handling of hazardous or highly active substances. This is contained in Annex 3 of WHO Technical Report No. 957, which comprises the 44th report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. This 300 page document summarises various technical meetings held over the previous 12 months, but the main interest lies in its copious appendices, which occupy about two-thirds of the whole. Annex 3 details the "WHO good manufacturing practices for pharmaceutical products containing hazardous substances" and is intended to complement national legislation for protection of the environment and personnel and other WHO guides to GMP. At 60 pages, it contains more technical detail than commonly encountered in most regulatory guidelines. There is no definition of what is to be regarded as hazardous; individual manufacturers must determine this for themselves on the basis of risk assessments, taking account of the potency of compounds, amounts handled, phases of product production, control and distribution, and the hazards to operators and the environment which could result in each case. Assuming that a potential for risk is identified, the document offers guidelines for the design and operation of the facility, with individual chapters on product protection, personal protection equipment and breathing air systems, environmental protection, facility layout, air-handling systems, air-handling units, safe change filter housings, personnel decontamination systems, effluent treatment, maintenance, qualification and validation. Official guidance on handling of highly potent materials and the extent to which dedicated facilities should be required has been mooted by the EU for some years now (see *Org. Process Res. Dev.*, **2008**, 12, 135−136), but has not so far been finalised.

Annex 2 of the same WHO report comprises the "WHO good manufacturing practices for active pharmaceutical ingredients". Here the text is identical with ICH Q7A, but it has been supplemented with an additional list of explanations and clarifications on various paragraphs of the guideline, specifically: Definition of API starting material; Role of management in the introduction of a quality management system; Delegating responsibilities in the production area; Qualifying suppliers of critical substances; Examination of containers after receipt and before acceptance; Batch identification; Retention samples.

Other annexes deal with "Good practices for pharmaceutical quality control laboratories" (Annex 1), "Good manufacturing practices for sterile pharmaceutical products" (Annex 4), "Good distribution practices for pharmaceutical products" (Annex 5), "Guidelines on the requalification of prequalified dossiers" (Annex 6), and "Guidelines for the preparation of a contract research organization master file" (Annex 7).

WHO guidelines are often overlooked by western manufacturers, whose attention is more focussed on meeting FDA or EMA requirements. However, they are regarded as mandatory by the regulatory authorities in many developing nations, who are becoming increasingly active on the site-inspection front. The complete report can be downloaded from http://whqlibdoc.who.int/trs/WHO_TRS_957_eng.pdf.

Drug Recalls

The last six months have seen a number of high-profile drug recalls and plant shutdowns, resulting from failures of GMP and quality management at several big name pharmaceutical companies. The McNeil Pharma business of Johnson & Johnson

in particular has suffered a number of embarrassing setbacks. Several products in their Tylenol range were withdrawn in late 2009 after consumer complaints of a musty odor (*Chem. Eng. News* **2010**, June 21, 22−23). The company was apparently slow to react to this but eventually identified the culprit as 2,4,6-tribromoanisole (TBA). This is a degradation product of a fungicide used on the wooden pallets on which packaging materials were stored and transported at the manufacturing site in Puerto Rico. Further details of this incident are contained in FDA's warning letter to the company management (ref SJN-2010-01, 15th January 2010). An FDA spokesman opined that—although the risks from TBA exposure include the potential for temporary gastrointestinal problems—the small amounts transferred to the drugs in this case did not pose a serious risk to health. However, elsewhere it is reported (*Chem. World* **2010**, July, 18−19) that some patients did experience nausea, vomiting, stomach pains and diarrhoea. Subsequently, an FDA inspection of a different McNeil site on the U.S. mainland has led to the suspension of manufacturing operations there until numerous quality defects are remedied. The inspectors found thick layers of dirt covering some equipment, and various raw materials were found to have bacterial contamination. Some medicine was found to contain foreign particles, and some batches were found to have too much active ingredient. Over 100 million bottles of products such as paediatric Tylenol, Motrin, Zyrtec, and Benadryl were recalled as a result. Again, FDA officials stress that the recall is on quality grounds only, and there is no evidence of serious adverse health effects related to the use of those products. However, the company has attracted strong criticism from members of Congress as well as from the FDA over these and other incidents; it is even possible that criminal proceedings could result.

Genzyme is also facing serious quality problems; one of their U.S. plants had to be closed for decontamination after viral contamination was found there in 2009. The incident landed the company with a hefty fine on top of the multimillion dollar cleanup costs, and additionally caused dangerous shortages in important treatments for rare diseases (*Pharm. Technol.* **2010**, *34* (8), 26−30). GlaxoSmithKline (GSK)'s Rotarix rotavirus vaccine also came under suspicion after traces of porcine circovirus-1 was found in it.

Problems also continue to surface with generic products. Manufacturing issues compelled Missouri-based KV Pharmaceutical to shut down their operations and recall multiple generic products and vitamin therapies. Swiss company Acino's generic clopidrogel, an antiplatelet heart drug, ran into problems when German regulators found that their API supplier in India did not meet GMP standards.

Meanwhile, the most serious public health incident of recent years—that of contaminated heparin which caused the death of 150 patients in the United States—is still not completely resolved. Two years on, the identity of the persons or firms responsible for adulterating the drug supplies with oversulfated chondroitin sulfate, has still to be established. In April, members of the U.S. House of Representatives wrote to the FDA Commissioner bemoaning the lack of progress, and the failure to engage more with the Chinese authorities. Their letter points out numerous occasions where opportunities to investigate further had been missed (http://republicans.energycommerce.house.gov/Media/file/News/043010_Letter_to_FDA_Heparin.pdf).

Visible Residue Limits

Previous *Regulatory Highlights* have reported on the development of Visual Residue Limits (VRLs) as criteria for use in cleaning verifications and validations (*Org. Process Res. Dev.* **2007**, *11*, 315 and **2008**, *12*, 821). Now, an article by M. Ovais (*Pharm. Technol.* **2010**, *34* (3), 58−71) claims that published methods for the quantitation of VRLs lack statistical justification, and proposes a modified method based on logistic regression. The problem is that results obtained from spiking studies are binary rather than continuous: an observer either detects the residue or does not. Under current practice, the VRL is typically defined as the lowest residue level which is detected by all observers participating in the study; however, this does not guarantee that any subsequent observer would also detect that residue. In the logistic regression approach, a mathematical relationship is established between a spiked residue level x (e.g., in $\mu g/cm^2$) and the proportion of observers P detecting that residue. The assumed model is represented by the equation:

$$P = 1/(1 + \exp(\beta_0 + \beta_1 x))$$

where β_0 and β_1 are coefficients determined by the regression. This "logit" function fits the data onto a sigmoid (S-shaped) curve where values of P are constrained to lie between 0 (meaning no possibility of detection) and 1 (meaning complete certainty of detection). A VRL could then be defined as the value of x for which P is predicted by that model to meet a user-defined acceptance criterion. A hypothetical data set is presented where, using a traditional approach, a VRL of 1.8 $\mu g/cm^2$ would be established, being the level of residue which was detected by 5 out of 5 observers. The logistic regression of the data, however, predicts that this residue would only be detected by 19 out of 20 observers ($P = 0.949$); to obtain better certainty ($P = 0.999$) the appropriate residue level is predicted to be 2.921 $\mu g/cm^2$, with a 95% confidence interval of 2.266−4.761 $\mu g/cm^2$. The upper range of this confidence interval would represent the most conservative VRL, which is nearly 3 times as high as that determined traditionally. VRL values could be lowered, however, by choosing less stringent acceptance criteria (e.g., $P = 0.99$ or $P = 0.98$). The author feels that logistic regression is a better approach than the current method for estimating accurate and statistically justifiable VRLs based on discrete responses.

A Risk-Management Approach to Cleaning-Assay Validation

An article by B. W. Pack and J. D. Hofer (Eli Lilly and Company, Indianapolis) addresses the determination of swab recovery from different surfaces as part of cleaning validation studies (*Pharm. Technol.* **2010**, *34* (6), 48−55). They note that 95% of all surfaces typically encountered in a pharmaceutical manufacturing area are constructed of 316 L stainless steel, but the remaining 5% comprise many different materials, each of which must be considered during cleaning validation studies. (In Active Ingredient manufacturing, significantly different

surface proportions would likely be encountered, but the plethora of different surfaces is expected to be similar.) Attempting to establish a swab recovery value for each product-contact surface for every compound would be an arduous activity from an analytical standpoint; a less onerous, risk-based approach is therefore offered as an alternative. Experiments were conducted to evaluate the influence on swab recovery of several factors: materials of construction (seven alternatives), roughness average (two levels), nature of active ingredient (one soluble and one insoluble) and amount spiked (four levels). Material of construction was found to have the greatest influence on recovery levels. The results allowed for all surface materials to be classed into three groups. Group 1, typified by 316 L stainless steel, showed the highest recovery factors (average 95% at the highest spiking levels), and the majority of synthetic surfaces could be placed into this group. Group 2 showed slightly lower recoveries (average 70%) and comprised metals such as cast iron and bronze. Group 3 showed the lowest recoveries (average 40%), but only type III hard anodized aluminium fell into this category. Thus, to validate the cleaning of a novel API, using a risk-based approach, it is sufficient to determine its recovery from just three surfaces—one representative of each group. The other main influence on the recovery was found to be the spiking level. At 50 μg/swab, 95% recovery was typically obtained from Group 1 materials; however this declined to only 60% when the spiking level was reduced to 0.5 μg/swab, and variability within the group was also much greater. Only at the lower spiking levels did the solubility of the API have any influence. Curiously, the average roughness of the surface had no influence at all under any circumstances.

Surface cleanliness is also the subject of the ISO 14644-9 standard "Cleanrooms and associated controlled environments - Part 9: Classification of surface cleanliness by particle contamination", a draft revision of which was made available in July 2010. This proposes a classification of cleanliness levels based on concentration of particles between 0.05 and 500 μm and lists some methods of testing. The standard applies to all solid surfaces in cleanrooms and associated controlled environments such as walls, ceilings, floors, work surfaces, tools, equipment and products. The new standard can be purchased from the Institute of Environmental Sciences and Technology (www.iest.org).

Design Space Development

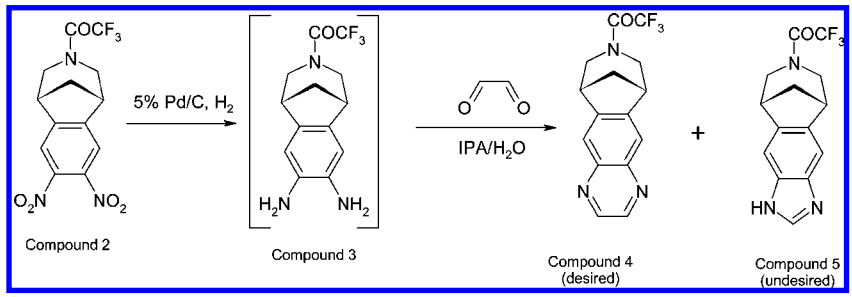
A series of articles has been contributed by statisticians from several major U.S. pharmaceutical companies (J&J, BMS, Merck, Lilly, Pfizer) on the establishment of a design space (Altan, S.; Bergum, L.; Pfahler, L.; Senderak, E.; Sethuraman, S.; Vukovinsky, K. E. Special considerations in design space development. In *Pharm.Technol.* **2010**, *34*). These provide concise answers to frequently asked questions related to the statistical aspects of determining a design space as part of a quality-by-design (QbD) initiative. Part I of the contribution (*Pharm. Technol.* **2010**, *34* (7), 66−70) considers the planning of an experimental design. It answers questions on: the role of prior knowledge such as historical data, including the type of information that can be gleaned and problems that can arise; the role of experimental design and DoE in establishing a design space; choice of responses and factors to include in the study; the appropriate number of factors to study, and selection of ranges for each factor; use of preliminary runs prior to the full DoE study. It also discusses the pros and cons of running one big DoE study encompassing several unit operations, as opposed to several small DoE studies.

Part II (*Pharm. Technol.* **2010**, *34* (8), 52−60) moves on to consider the design of a statistical DoE and subsequent analysis of the data. This explains the differences between screening, interaction, and optimization designs, and circumstances where each could be employed. It also addresses the scaling up of operations, suggesting several strategies to limit the number of experiments required at large scale to confirm the validity of a design space established in the laboratory. For example, one option would be to run just the conditions predicted to give the worst outcome for each critical quality attribute.

Part III is scheduled to appear in the September issue of the journal, and will consider the presentation of the design space and its evaluation.

Some concrete examples of QbD approaches have also been published. GSK scientists have described a novel approach to analytical method validation (Borman, P.; Chatfield, M.; Jackson, P.; Laures, A.; Okafo, G. Reduced method robustness testingof analytical methods driven by a risk-based approach. In *Pharm. Technol.* **2010**, *34* (4), 72−86). Validation of analytical methods has traditionally involved performing robustness and ruggedness testing as one of the last activities after characteristics such as specificity, linearity, range, accuracy, precision, and sensitivity have been studied. However, the effects of method parameters that have not been studied during method development would be unknown until robustness testing is performed, and they could cause failure of the validation, with resulting time delays and extra cost. It is therefore desirable to check robustness in advance of the final method validation; this article suggests a cost-effective approach (called Reduced Method Robustness (RMR) testing) to such prevalidation activity. Risk-based assessment tools are used to identify, score, prioritise, and then group method parameters; these parameters are then studied using reduced fractional factorial designs. The example of a GC-FID-based analytical method for an API starting material (*N*-acetylpiperazine) is provided. Here 19 parameters were initially identified as having potential to influence seven key responses. Fifteen parameters were instrumental settings such as column type, gas flow rate, oven temperature programme, etc.; the remaining four concerned sample preparation. The responses of interest were area % of three impurities, the resolution between two close-running impurities, retention times of a third impurity and of the main substance, and the limit of quantitation. For this exercise, it was decided to concentrate just on the instrumental factors and deal with sample preparation separately. A risk evaluation identified two factors as having negligible risk, and these were excluded from further study. The novel idea was to combine the remaining 13 factors into 7 sets, and to study these sets in an 8-run fractional factorial design. Two factors flagged as having highest risk (type of liner and temperature programme) were assigned as the only members of their sets; the remaining 11 medium-risk factors were then grouped into five sets. It is

Scheme 1



emphasised that considerable prior knowledge and experience are required to successfully group factors in this way, as their influences are completely confounded by the reduced design. For example, column flow and column loading were thought to both affect signal-to-noise ratio, but the direction of their effects was thought to be the same, so it was deemed acceptable to group them together—the results would show whether their joint influence had a significant effect on the results. A traditional fractional factorial design for robustness testing of 13 factors would require 16 runs (excluding centre points and replicates); this RMR approach reduced the requirement to 8 runs. The results of the study indicated that the method was robust for most of the responses; however, significant variability of one response (area % of impurity B) was associated with one group of two factors. It was felt that the most likely cause was the variation in injector temperature rather than its alias (length of time the oven was kept at its minimum temperature) because that impurity was known to be thermally labile. Therefore, a tighter control was placed around the injector temperature prior to proceeding to full method validation.

Another article in a similar vein has been contributed by Pfizer scientists (Quality by Design using an Integrated Active Pharmaceutical Ingredient:Drug Product Approach to Development; McCurdy, V.; am Ende, M. T.; Busch, F. R.; Mustakis, J.; Rose, P.; Berry, M. R. *Pharm. Eng.* **2010**, *30* (4), 12−31). This describes some aspects of the development of varenicline tartrate (Chantix/Champix), a smoking cessation drug which was one of the initial filings that the FDA accepted into their QbD pilot program back in 2005 and was one of the first regulatory filings that utilized a QbD approach for both API and drug product. The entire manufacturing process of varenicline tablets was broken down into smaller "focus areas", each comprising one to three sequential unit operations. An initial risk assessment evaluated 18 focus areas associated with the API manufacturing and a further 7 associated with the formulation activities. This article concentrates on just three focus areas, of which one concerns a chemical step with potential to generate a process-related impurity (compound **5**, Scheme 1).

A combination of one-factor-at-a time experimentation and DoE indicated that this impurity would be minimized by maintaining a slightly alkaline pH throughout the glyoxal addition, which was ensured by the addition of a small quantity of sodium bicarbonate. The model emerging from the DoE analysis predicted that, while the actual level of the impurity was somewhat sensitive to the amount of bicarbonate used together with the amount of glyoxal added, under all conditions investigated the level was below 0.05%, against a specification level of NMT 0.2%. The article also details DoE studies of the crystallization of the final API (where a small particle size was desirable for successful tabletting) and the roller compaction and milling stages of tabletting (where the issue was to ensure tablet potency and content uniformity).

Derek Robinson

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

OP1002215