

JOINT PHARMACEUTICAL ANALYSIS GROUP

All you wanted to know about the control of active pharmaceutical ingredients — but were afraid to ask!

The publication of Annex 18 of the EU Guide to Good Manufacturing Practice formally brought active pharmaceutical ingredients within the scope of GMP. The regulatory authorities and industry have been engaged in a voluntary inspection programme using the relevant guidelines of the International Conference on Harmonisation on which the annex is based. A meeting organised by the Joint Pharmaceutical Analysis Group at the Royal Pharmaceutical Society, London, on 5 December 2002 discussed experience of the programme and the implications for monograph development for the official pharmacopoeias. Dr Joseph Chamberlain reports

NIGEL CRYER, vice-president, Danza Healthcare Logistics, opened the meeting by reviewing the International Conference on Harmonisation (ICH) guidance on inspection of active pharmaceutical ingredients (APIs). Historically there had been several attempts to establish appropriate international standards for APIs, culminating in ICH Q7a, the first internationally harmonised Good Manufacturing Practice guidance developed jointly by industry and the regulators and published in November 2000. ICH Q7a establishes one global GMP standard for APIs. Annex 18 to the EU Guide to GMP based on this guidance was published in July 2001. The aims of ICH Q7a are to minimise variations in interpretation among industry and regulatory bodies worldwide. A pragmatic, commonsense approach is needed to make this exercise successful, with careful definition of key concepts. The pragmatic approach also is needed when the manufacturer follows the guidelines. If Q7A says you should do something, you probably should do it, Mr Cryer said. He added, if Q7A prohibits something, you probably should not do it. Conversely, if it does not say you have to do something, you probably do not have to do it and if it does not prohibit something, it is probably all right to do it.

There are a number of topics in ICH Q7a that may be considered new. Starting material was formerly defined as the first step in which impurities are formed which are not removed at a later stage; starting material is now a material used in the production of an API which is incorporated as a significant structural fragment into the structure of the API. Starting material may be an article of commerce, a material purchased from contract suppliers, or may be produced in-house. Starting materials are normally of defined chemical properties and structure. The guidance contains definitions of reworking and reprocessing and the role of agents and brokers. Where agents or brokers are used, the origin of the material needs to be established. This leads to the requirement for certificates of analysis, a

consideration that has important implications as discussed later in the meeting.

Mr Cryer outlined the effect of ICH Q7a on key decisions that are made in the manufacturing process relating to active ingredients. These include increasing GMPs directed towards the pure API, the production of a product quality review (a new EC requirement following the example of the United States Food and Drug Administration), disallowance of blending "passed" and "failed" batches to form a larger "acceptable" batch, and specific directions on storage, distribution and any critical time limits on manufacturing processes. All incoming raw materials must be tested, with certificates of cleaning for non-dedicated bulk deliveries. There must be clearly defined responsibilities for the quality assurance/quality control units and for manufacturing. Mr Cryer concluded by commenting that this had been a successful and commonsense exercise by the regulators and industry, and was a credit to all involved.

THE MCA PERSPECTIVE

BRONWYN PHILLIPS, Medicines Control Agency, reviewed and updated the experience of the agency with its programme of voluntary inspections designed to assist manufacturers in adopting the guidelines in Annex 18. The programme has been in place since 1999 and the MCA has now conducted 38 such inspections, some facilities being inspected for the second time. She described full details of the procedures before during and after the inspection were described. Facilities inspected included mainly commercial scale API manufacturers, with smaller numbers of clinical scale API manufacturers and excipient manufacturers. The MCA, as Ms Phillips mentioned, was not a charitable organisation, and a fee was payable by the facility being inspected.

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So far the inspections have uncovered eight critical deficiencies, 51 major deficiencies and over 250 other issues. Ms Phillips had strong views on the often inadequate sourcing of QA units, believing that the separate roles of QA and QC are often misunderstood or unrecognised. It is also common to find that manufacturers do not distinguish between suppliers and manufacturers of starting materials, a situation which highlights the importance of certificates of analysis.

Tanker cleanliness assurance is often poor, with manufacturers not always being aware whether delivery tankers are dedicated or are merely carriers. There are situations where GMP system changes are implemented without QA input and revalidation of the procedures. In a similar vein, changes are made to manufacturing processes without investigation of the root cause necessitating the change. The blending of failed batches within subsequent satisfactory batches, which is not allowed, is also found in some inspections.

Storage areas are often congested and poorly segregated. In one facility there were signs of bird infestation, and the excuse offered was that the nesting birds were a protected species.

AN INDUSTRY PERSPECTIVE

Mr CRYER also spoke about the industry's perspective. He emphasised the importance of preparation. Preparation is a matter of putting into place the correct procedures and systems that will ensure a satisfactory outcome when an inspection takes place. To achieve this aim there are two major influences: the practical, on-the-ground influences pertaining to the site itself, and the key documents available. The former includes regulatory actions that the site and its manufacturing processes are subject to, corporate policies and corporate audits; the latter documents include the Orange Guide, the FDA bulk inspection guideline, and the ICH guidelines of February 1998.

Central to the consideration of site influences is the establishment of the site

monitoring systems, including an annual review, specific investigations, the monitoring of changes, and facility, system and procedure audits, coupled with appropriate actions arising from the monitoring. Thus, adequate establishment of the monitoring systems would lead to new and better standard operating procedures (SOPs), continued validation, appropriate staff training, and clear statements of individual and departmental responsibilities.

Turning more specifically to the inspection day itself, vital pieces of preparation include establishment of the subject ownership, a documentation plan, and a presentation to set the scene. Inspections are carried out by two inspectors over two and a half days and consist of a short presentation, a site tour, a document review and a laboratory review, including examination of validation documentation. The audit was detailed and searching. Even with this thorough preparation, Mr Cryer commented that as the review progressed, questions and ideas for improvement would still occur, making the inspection itself a useful learning exercise. The major points coming out of the exercise were that the facility should always keep up to date with draft legislation, institute and act upon annual reviews, and always identify the root cause of any deviation of product from the expected, rather than just change a procedure.

PHARMACOPOEIAL MONOGRAPHS

In theory there is no difference between theory and practice, but in reality there is. Why is this, asked KEN LEIPER, of Benson Associates. It is instructive to consider the changing nature of analytical science over the life-cycle of a medicinal product. Initial synthesis of a new chemical entity to a generic active pharmaceutical ingredient now takes 20 years or more; in a similar period, routine pharmaceutical analysis has progressed from paper chromatography to high performance liquid chromatography-mass spectrometry. Thus, although pharmacopoeial monographs are pivotal in pharmaceutical analysis, the pharmaceutical industry is continually required to respond to rapid change driven by customer need, expectation and available technology. As a highly regulated industry these changes are also driving change in regulatory licensing and inspection requirements.

The role of the pharmacopoeia is to ensure that monographs exist which specify product quality standards and the appropriate application of the technologies necessary to guarantee patient safety. This role has not changed but there is no doubt that the environment in which pharmacopoeias operate has changed markedly.

Although they have developed independently, a strong link exists between pharmacopoeias and GMP and any meaningful review of each must impact on the other. Both are dependent on understanding the underlying science, developing processes on this understanding, and using risk assessment to demonstrate validity.

An area that is increasingly becoming a

source of problems is the specification of one impurity method for materials from different synthetic routes or by using different facilities. For example, the original manufacturer of ranitidine used a single synthetic route. Eighteen possible impurities were available to the analytical laboratory and could be separated. However, only eight impurities were required to be controlled in the manufacturing licence. When a second manufacturer used the originator's synthetic route, two additional impurities were observed, possibly related to different process capabilities. Now 10 related impurities must be declared. For salbutamol, at least four synthetic routes are in common use, all using different process capabilities. Ten impurities are included in the transparency statement. Thus over the life cycle of an active pharmaceutical the methodological drivers for the originating manufacturer relate to the needs of a single synthetic route to cover the API and formulated products, whereas the generic manufacturer needs to control the API, often using multiple synthetic routes.

Several questions now arise from consideration of methodological evolution. How valid is the current pharmacopoeial method? Are the impurities to check method performance available? Where can you find details of the column used in a method? Only the European Pharmacopoeia currently deals with these technical issues.

To manage these methodological issues, Mr Leiper suggested that you should carry out a formal technology transfer of the pharmacopoeial method to the best of your ability with all available information. If there are issues of confidence with its performance and there is an in-house alternative, then equivalence should be demonstrated.

As regards changes in regulatory expectation, it was noted that the expectation is that HPLC will be used for both impurity determination and assay. This inevitably places the methodology in use and its validation under scrutiny.

The standard operating procedure approach to GMP has evolved over 30 years. The science/technology base did not evolve as quickly as in other sectors so that GMP standards are empirical, and not science-based. As a result, ICH standards are largely consensual. The emphasis needs to shift from empirical to science-based standards for manufacturing process quality. We must reassess and re-evaluate our current scientific approach to both the product review process and the GMP programme to achieve a consistent, integrated systems approach to product quality regulation.

STANDARDS — ISSUES AND NEEDS

There is an important distinction to be made between pharmacopoeial reference substances and reference materials, said Dr JOHN MILLER, European Directorate for the Quality of Medicines, Council of Europe, Strasbourg, France. A reference substance is one acknowledged as having appropriate qualities within a specified con-

text, and whose value is accepted without reliance on comparison with another chemical substance. Reference material is a material or substance one or more of whose properties are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement method or for assigning values to materials. A certified reference material (CRM) is reference material for which each certified value is accompanied by an uncertainty at a stated level of confidence. The role of CRMs in chemical analysis is to provide measurement benchmarks that chemists can use to calculate or assess the accuracy of their analyses. When several laboratories can achieve the same analytical results for a given CRM, they demonstrate comparability of their measurements. Thus reference substances are the major constituent of a matrix, are established for a specific method, have negligible uncertainty and do not require a certificate; all information required is in the pharmacopoeial monograph. They constitute an integral part of the monograph and are legally binding standards. Reference materials and certified reference materials are more likely to be minor constituents of a matrix, may be established by a number of different analytical techniques, have larger uncertainty with an expiry date, and will require a certificate.

Chemical reference substances of the European Pharmacopoeia are used in identification tests by infrared spectrophotometry and chromatographic methods, in purity tests (usually chromatographic) for specific impurities, in other assays such as UV and visible spectrophotometry and gas and liquid chromatography, and in microbiological assays.

Standards may also be required to ascertain the suitability of the chromatographic system for separation and quantification of specific impurities, using appropriate criteria such as chromatographic resolution.

The identity of impurities is usually initially by consideration of the synthetic route and from the likely decomposition pathway. Analytical techniques described must control the major impurities for all syntheses and pharmacopoeial limits are set in the knowledge that the levels of impurities in production batches will have been accepted by the licensing authority after a full consideration of the toxicity studies and clinical trials. Manufacturers are requested to inform the European Pharmacopoeia Secretariat of all impurities which have been accepted by the licensing authorities and to identify all recurring impurities present at or above the 0.1 per cent level. It is incumbent upon regulators employed within the European Union to notify the European Pharmacopoeial authority whenever it is believed that the monographs of the European Pharmacopoeia might be in need of amendment.

It is apparent, said Dr Miller, that there will be an increase in the number of reference substances employed as assay standards with an assigned content and an increase in the need for individual impurity reference substances.