

JOINT PHARMACEUTICAL ANALYSIS GROUP

The challenge of controlling of impurities and degradation products

The increasing need to identify impurities quickly, and to select efficient test procedures, offers continuing challenges for the pharmaceutical analyst, including maintaining awareness of rapidly evolving regulatory requirements. Experts from industry and regulatory agencies reviewed these issues in a symposium organised by the Joint Pharmaceutical Analysis Group at the Royal Pharmaceutical Society London on 8 May. Dr Joseph Chamberlain reports

The regulatory framework for control of impurities in drug substances and drug products is well developed, but guidelines continue to be refined and harmonised. MALCOLM DASH of the Medicines and Healthcare products Regulatory Agency reviewed the most recent developments in the area.

ICH Q3A (impurities in drug substances) became effective in November 1995, but it quickly became evident that the guideline needed revision; clearer guidance was needed, for example, on rounding of percentage impurities, particularly at the pass/fail level of 0.1 per cent, and harmonisation with the corresponding ICH Q3B (drug products) was needed. ICH Q3A(R) became effective in August 2002 and is applicable to impurities in new drug substances arising from chemical synthesis but not applicable during the clinical research stage of development, to extraneous contaminants, polymorphs, enantiomers, biologicals, peptides, fermentation products, semi-synthetics or herbal products. An application should discuss actual and potential impurities, results for all clinical, safety and stability batches, and batches representative of the commercial process.

Any impurity greater than the reporting threshold should be recorded as well as total impurities greater than the threshold. Numerical results should be given rather than a statement of compliance. Values less than 1.0 per cent should be reported to two decimal places; values at or above 1.0 per cent should be reported to one decimal place.

ICH Q3B (impurities in new drug products) is similarly undergoing revision and ICH Q3B(R) will become effective in August 2003.

ICH Q3C (residual solvents) has been effective since March 1998 and most variations are reclassification of solvents according to toxic potential.

The Common Technical document (CTD) is a common format for regulatory submissions in Europe, the United States and Japan. It was adopted by International Committee on Harmonisation in November 2000 and will be mandatory from 1 July 2003 in EU member states. Requirements for impurity testing are to be included in modules 2 (summaries), 3 (quality) and 4 (non-clinical studies) of this document.

The European Pharmacopoeia certification scheme is administered by the European Directorate for Quality of Medicines. A European Pharmacopoeia monograph must be in force before a certificate can be issued, but the certificate is recognised by all EU member states. In fact, a certificate of suitability is the preferred means for receiving details on drug substances and companies who present these are likely to bring joy to the inspector's heart, said Mr Dash.

BIOTECHNOLOGY PRODUCTS

Biotechnology products give rise to many possible variants or degradation entities and a range of purity tests is required to determine the profile effectively. Their manufacture requires complex processes giving a wide variety of impurities and many of these are complex. A previous JPAG meeting (P7, 22 March, p412) provided a good background to the present meeting's topic, said Dr STEVE FLATMAN (Lonza Biologics). It is not considered feasible to standardise analytical methods for biotechnology products as the reagents used in the tests are product-related and production system-related. Hence it is important to define the composition of any impurity. Subsequently the appropriate assay (often a biological assay) can be selected for specific impurities. It is essential to understand the scope and limitations of test methods.

Dr Flatman illustrated the issues involved by reference to assays for host cell proteins. Because host cell-derived proteins are detected by immunochemical methods, antisera must be raised against a preparation of antigens derived from the host organism lacking the specific gene coding for the product. Additional development is required to improve the range and specificity of the antisera. A typical immunoassay such as ELISA (enzyme-linked immunosorbent assay) will have limited use in quantification because of its differing response to different proteins, has no role in identification of impurities and has a typical sensitivity of 1–100ppm. ELISA is suitable for lot-release testing.

GENERIC METHODS

Dr STEPHEN WREN (AstraZeneca) defined a generic method as one with standard and predetermined analytical conditions, rather than a method developed from the properties of a specific analyte. For example an acetonitrile/water/trifluoroacetic acid gradient would be used on a reversed-phase high performance liquid chromatography column. HPLC is almost always the method of choice as there are generally close structural relationships between the active compound and impurities, there are limitations with current spectroscopic techniques, and the typical physicochemical properties of active substances make them suitable for liquid-phase separations.

A small number of such systems can be set up to provide an initial screen for longer-term development of specific methods. A generic method can be highly specific by including a mass spectrometer as the detector. Thus, ideally, the generic method should also have a mobile phase compatible with these devices.

Generic methods are used because of their speed (the equipment is immediately ready for use), they can detect variable impurity and degradation profiles in early development when synthetic routes or process scales are continually changing, and they allow open access for the synthetic or development chemist. For these chemists, generic methods are particularly suitable for route selection monitoring, method screens and batch analyses. A single generic method can sometimes be used to monitor all stages of a synthetic process.

Dr Wren described how generic methods could then be efficiently modified for specific purposes once the optimum routes and scales have been established. The retention in HPLC is related to the hydrophobicity of the analyte, which in turn depends on the pK_a . Manipulation of the pH of the mobile phase provides a way of optimising separation. The selectivity of the mobile phase can be improved by the use of organic modifiers, most commonly acetonitrile, methanol or tetrahydrofuran, each of which can offer a unique selectivity for a particular analyte. Thus relatively little experimental development is needed to convert a generic method to a workable assay for a particular substance.

Dr Chamberlain is a former editor of the Journal of Pharmacy and Pharmacology

STRUCTURE ELUCIDATION

Dr ADRIAN DAVIS (Pfizer Global R&D) described the tools available for the identification of impurities in drug substances and products with particular emphasis on mass spectrometry and nuclear magnetic resonance spectrometry, usually coupled with conventional separation methods.

Generally the spectroscopist is presented with a chromatogram with a request to assign structures to the individual peaks. The usual strategy is therefore to present the chromatographic output to a spectrometer and it helps if the chromatographic system is compatible with the requirements of the spectrometer. Generally, analytical scale HPLC is extremely compatible with modern mass spectrometers; flow rates are usually less than 1ml/min, the water content of the mobile phase is acceptable and the mass spectrometer itself acts as a chromatographic detector. However, involatile buffers are unsuitable in the mobile phase and TFA may give rise to ion suppression in the spectrometer. Sensitivity is not a critical issue for impurities present at greater than 100ppm. Finding an ionisation method that works is important.

NMR is not so accommodating. Typical column loadings do not usually contain enough analyte for NMR and overloading the column will compromise the chromatographic separation. The analyst then must resort to isolation strategies such as preparative chromatography or concentration steps prior to analysis by NMR. Typically, isolation via semi-preparative chromatography will need 100mg of the active substance to yield 100µg of impurity. Nevertheless the convenience of directly interfacing the separation step with NMR may be achieved using large columns and peak-trapping devices.

Dr Davis described a typical elucidation of the structure of an unknown impurity. First, high-resolution mass spectrometry (giving an accurate molecular weight) yielded information on the molecular formula and judicious interpretation reduced the possible formulae from 14 to three; proton NMR, by pinpointing the number of hydrogen atoms, reduced this to a solitary candidate. Further proton and carbon NMR interpretation yielded the final details of structural elements in the unknown.

TOXIC IMPURITIES

Dr DAVID SNODIN (Parexel International) returned to the setting of impurity limits described in ICH Q3A and ICH Q3B. When there is increased concern over the safety of actual or potential impurities, then the limit-setting procedure is normally based (at least in part) on toxicological data. For non-carcinogens, LOAEL (lowest observed adverse effect level) or NOAEL (no observed adverse effect level) is determined in the most relevant animal species by an appropriate route. Safety factors are then applied to arrive at an impurity limit in the dosed levels of the substance. In making a final estimate of the impurity limit, account should also be taken of the pharmaceutical

contribution; although this may not be an issue for new chemical entities, it is important where there may be exposure from an additional source such as might be the case for solvent residues.

Dr Snodin mentioned that, although impurity science was improved by the ICH guidelines, there were still numerous anomalies, contradictions and illogicalities. Because of the inherent insensitivity of biological testing there will be different outcomes when setting limits based on the toxicity of the whole preparation containing the impurity and that based on the isolated impurity. There is a tendency to focus on obvious cases, such as alkylating agents, rather than a scientific search for unknown toxicities.

There should be a clear distinction between risk assessment and risk management; overzealous limit setting in the absence of appropriate risk assessment will lead to unnecessarily expensive procedures and consequent expensive medicines, Dr Snodin said.

CHEMICAL DEVELOPMENT

Dr STEPHEN ROBINSON (Pfizer Global R&D) discussed impurities likely to be present in a new chemical entity. Although the material is still in chemical development, impurities may arise from reagents or solvents, as by-products, as adducts formed with the counter-ion used, or from impurities in the starting materials. For the chemist, the initial strategy for minimising impurities is to look at the synthetic method. First, the impurities must be identified, and their sources understood. The proposed solutions may involve modification of reagents, solvents or reaction conditions to optimise reactions or may simply need control of the quality of starting materials. In-process control requires an analytical method, which is unequivocal, accurate, reproducible, rapid, simple and cheap. Process development may offer a solution by changing the synthetic route or by combining synthetic steps in a single reaction vessel.

Where an acceptable synthetic solution cannot be found then there is a switch to purification strategies. Recrystallisation is an essential tool as a purification device, although close structural analogues are often difficult to purge. Chromatography is rarely performed except as a continuous process.

Development of a commercial synthetic process requires careful design to ensure consistency of quality, purity and polymorphic form, robustness and scalability, safety, economic viability and freedom to operate, and environmental control. These competing aims must be recognised when developing drug substance impurity specifications during clinical trials.

EU CLINICAL TRIALS DIRECTIVE

Clinical trials in the UK are generally submitted to regulatory authority using the clinical trials exemption (CTX) scheme,

said Dr ELAINE GODFREY rounding up the issues of impurity testing from the perspective of the MHRA. The CTX is based on the provision of summary data about the quality and safety (both pre-clinical and clinical) of the investigational product, any comparator or any placebo being used. The scheme operates on a negative vetting basis — the trial can proceed on the basis that there are no grounds for non-acceptance of the exemption application and the decision on whether or not the application is accepted is taken by the assessors of the clinical trials unit without going to the expert committee and is based on safety considerations. As the regulator is looking for an investigational medicinal product which is safe for use in the proposed clinical trial, ideally the drug substance would have no associated impurities when administered to the trial subject. Since clinical trials are conducted in the real world, steps have to be taken to minimise the potential for harm to the trial subject as a consequence of impurities, from whatever source, that are present in the trial material. Appropriate limits must be set for chemical substances (residual starting materials, intermediates, residual solvents, residual catalysts, by-products, and general impurities), biological or biotechnological substances (adventitious viruses, other microbiological contaminants, residual growth media components, by-products such as truncated species, dimers, aggregates and non-glycosylated variants, and components introduced during the purification process itself) and herbal substances (heavy metals, pesticides, residual solvents, microbiological contaminants and adulterants).

Since industry is also interested in the development of safe products, both industry and the regulator are working to a common goal. Industry should make sure that its clinical trial applications contain sufficient information on the control of impurities and how specifications are set. Specifications should be set on the basis of the data available at that time and not on the basis of wide limits to ensure that all batches of substance or product will comply. It is possible to set relatively wide limits for synthetic impurities provided that there is a commitment to ensure that all batches of material released for use are supported by data from pre-clinical testing.

Dr Godfrey, looking at the situation from a UK perspective, did not expect that much would change in terms of the control of impurities in investigational medicinal products. The commission guideline regarding the submission to the competent authority is not very much different from the current CTX requirements. Impurities are important in terms of the safety of investigational medicinal products and have to be taken into consideration. The approach is, in principle, the same as for products at the time of licensing but there may be more scope in setting limits. The changes to clinical trial submissions as a result of the Clinical Trials Directive will have little effect on the approach to the topic of impurities, Dr Godfrey said.