Table 2. Guidance documents adopted by the EC CPMP

Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Cardiac Failure **(CPMP/EWP/235/95, revision 1, draft 9)**

Adopted by the CPMP in November 1999. Effective from June 2000.

This revised *Note for Guidance* supersedes the version of the guideline adopted in November 1995 (*see The Regulatory Affairs Journal*, 1996, **7**(5), 406). The document provides guidance on the clinical investigation of medicinal products for the treatment of cardiac failure and should be read in conjunction with Part 3 of the Annex to Council Directive 75/318/EEC, as amended and any relevant guidelines. Topics covered in the guideline include: efficacy criteria; methods for the assessment of efficacy (e.g. assessment of clinical symptoms, morbidity, survival and the quality of life); selection of patients for inclusion in clinical trials; design of clinical studies (i.e. human pharmacology and exploratory and confirmatory therapeutic studies); *and* safety aspects.

Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances **(CPMP/ICH/367/96) [ICH Topic Q6A]**

Adopted by the CPMP: November 1999. Effective from May 2000.

This *Note for Guidance* concerns the specifications (i.e. test procedures and acceptance criteria) that have a major role in assuring the quality of a new active substance (NAS) or new medicinal product at release and during its shelf-life. Guidance is provided on the establishment and justification of acceptance criteria and selection of test procedures for NASs of synthetic chemical origin and new medicinal products made from them which have not been authorised previously in the EU, Japan or the USA. Active substances or medicinal products in the clinical research stages of drug development are not covered by the guideline. Dosage forms discussed in the document (e.g. solid and liquid oral dosage forms and small and large volume parenterals) are used as models; the guidance provided may apply to other dosage forms (e.g. topical formulations).

General concepts to be taken into consideration and used in developing and setting harmonised specifications (e.g. in-process tests), are discussed. In addition, specific guidance is given on: the definition and justification of specifications; universal tests/criteria; *and* specific tests/criteria.

Concept Paper on the Development of a Committee for Proprietary Medicinal Products (CPMP) Note for Guidance on Requirements for Pharmaceutical Documentation for Metered Dose Inhalers **(CPMP/QWP/2930/99)**

Adopted by the CPMP: November 1999.

The Concept Paper concerns formulation of a guideline by the CPMP Quality Working Party (QWP) on the development and testing of metered dose inhalers that covers issues including:

- details of development and optimisation of the formulation;
- specifications for the active ingredient, excipients, finished product and packaging components;
- method of manufacture and manufacturing controls;
- active ingredient and finished product stability;
- particular aspects of product characterisation that should be addressed; *and*
- the SPC and instructions for use (e.g. product priming).

Availability of a first draft for circulation to the CPMP QWP is expected in June 2000. A finalised QWP version should be available for release for comments in October 2000 and the final document is expected to be submitted to the CPMP in July 2001.

Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Venous Thromboembolic Disease **(CPMP/EWP/563/98, draft 8)**

Adopted by the CPMP: December 1999. Effective from June 2000.

The document provides advice on the type of clinical development programme that will support registration of new medicinal products for the treatment of venous thromboembolism (VTE). The Expert Reports should include an explanation and discussion of any deviations from these guidelines, which should be read in conjunction with Council Directive 75/318/EEC, as amended and relevant guidance provided in current and future EC and ICH guidelines. Topics discussed in the document include:

- patients to be studied in clinical trials;
- diagnosis of VTE;
- efficacy and safety endpoints for exploratory and confirmatory studies; *and*
- design of different types of study.

Recommendations on Electronic Transmission of Individual Case Safety Reports Message Specification **(CPMP/ICH/285/95) (ICH Topic M 2, Step 5, October 1999)**

Adopted by the CPMP: March 2000; effective date: September 2000.

This guideline details the ICH M 2 Document Type Definition of the electronic message for the transmission of Individual Case Safety Reports (ICSR) based on the Step 4 document ICH E2B *Data Elements for Transmission of Individual Case Safety Reports*. Information is provided on:

- essential components;
- the approach to be taken in the preparation of ICSR Standard Generalised Markup Language (SGML) data files; *and*
- feedback on receipt of the ICSR.

Table 3. Documents released for consultation by the EC CPMP

Common Technical Document: Module V: Efficacy; Module III: Quality; Modules: IIA, IIB and IV: Safety **(CPMP/ICH/2887/99) [ICH Topic M4]**

Released for a six-month consultation period in November 1999 (comment deadline was May 2000).

The *Common Technical Document* (CTD) concerns requirements for the composition and organisation of registration documents included in marketing authorisation applications for human medicinal products in the three ICH regions (i.e. the EU, Japan and the USA), which currently differ significantly. The CTD is the common part of an application and has a modular structure with summaries of information and tables as appropriate; it comprises:

- Module II:
  - IIA Executive summaries (i.e. quality (pending), non-clinical (provided in the draft document) and clinical (pending));
  - IIB Non-clinical summaries (i.e. IIB1 Written summary and IIB2 Tabulated summary (both provided in the draft document));
  - IIC Clinical summaries (i.e. written and tabulated summaries (pending));
- Module III: Quality (provided in the draft document; nine attachments pending);
- Module IV: Non-clinical data study reports (provided in the draft document); *and*
- Module V: Clinical study data reports (provided in the draft document).

An application that complies with the format and content of the CTD should be acceptable by the regulatory authorities of the ICH regions provided it is supplemented with regional administration details included in another, separate module (i.e. Module I: Regional administrative information).

Note for Guidance on Stability Testing: Stability Testing of New Drug Substances and Products **(CPMP/ICH/2736/99, draft) [ICH Topic Q1A]**

Released for a six-month consultation period in November 1999 (comment deadline was May 2000).

This document is a revision of stability guidelines prepared under the ICH process, which were adopted as final by the CPMP in December 1993 and issued [originally as III/3335/92 and subsequently] as CPMP/ICH/380/95. Advice is provided on the stability data for new active substances and associated medicinal products that should be included in marketing authorisation applications. Changes to the final version adopted in 1993 concern:

- transfer of the section on stress testing of the active substance from the glossary to the main text;
- amendment of the text (e.g. on test procedures) in line with the CPMP *Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (CPMP/ICH/367/96) [ICH Topic Q6A];
- revision of the text concerning testing frequency under accelerated testing conditions;
- inclusion of a more detailed description of storage conditions which specifically addresses testing at low temperatures (e.g. in a freezer) and of aqueous liquids in semi-permeable containers; *and*
- inclusion of an unambiguous description of the post-approval commitment concerning long-term stability data.

Note for Guidance on Impurities Testing: Impurities in New Drug Substances **(CPMP/ICH/2737/99, draft) [ICH Topic Q3A]**

Released for a six-month consultation period in November 1999 (comment deadline was May 2000).

This document is a revision of a *Note for Guidance* prepared under the ICH process, which was adopted as final by the CPMP [in May 1995] and released as CPMP/ICH/380/95 (*see The Regulatory Affairs Journal*, 1995, **6**(8), 670). The document provides advice on impurities (content and qualification) for new active substances (NASs) produced by chemical syntheses not registered previously in a Member State of the EU, Japan or the USA that should be included in a marketing authorisation application. The following issues are discussed:

- classification of impurities (i.e. organic impurities, inorganic impurities and residual solvents);
- the rationale for the reporting and control of impurities;
- analytical procedures;
- reporting impurity content of batches of the NAS;
- specifications for impurities;
- qualification of impurities; *and*
- new impurities.

The document originally adopted has been revised to:

- clarify the reporting threshold for impurities to be in line with *Note for Guidance on Impurities in New Drug Products* (CPMP/ICH/2738/99, draft) [ICH Topic Q3B];
- introduce a clear interpretation of the 0.1% impurity threshold;
- indicate that rounding is applied when evaluating pass/fail in relation to impurity thresholds and specification; *and*
- include definitions of thresholds and rounding in the glossary.

Note for Guidance on Repeated Dose Toxicity **(CPMP/SWP/1042/99)**

Released for a three-month consultation period in December 1999 (comment deadline was March 2000).

This document is a revision of a *Note for Guidance* (3BS2a) which was adopted in October 1983. The old version has been amended (e.g. guidance on immunotoxicity has been updated) and will be superseded by the revised guidance once it has been adopted. Advice is provided concerning the conduct of repeated dose toxicity studies for pharmaceutical products for human use. The following are addressed in the guideline:

- general recommendations regarding active substance quality and excipients;
- general recommendations concerning the experimental animal used;
- general recommendations with regard to dose and administration;
- study observations; *and*
- data analyses and presentation of results and conclusions.