The European Agency for the Evaluation of Medicinal Products
Pre-authorisation Evaluation of Medicines for Human Use

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ICH Topic Q3C (M)
Maintenance of Note for Guidance on Impurities: Residual Solvents (CPMP/ICH/283/95)

ICH Step 5

MAINTENANCE DOCUMENT FOR NOTE FOR GUIDANCE ON IMPURITIES: RESIDUAL SOLVENTS

Type of Maintenance: Updating Based on New Information

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.eu.int http://www.emea.eu.int

Q3C MAINTENANCE DOCUMENT FOR "IMPURITIES: RESIDUAL SOLVENTS"

Type of Maintenance: Updating Based on New Information

1. Proposal of a "permitted daily exposure" (PDE) for a new solvent or a revised PDE for an already classified solvent is submitted directly to the ICH Secretariat with supporting information through an ICH regional coordinator. This information should be based on significant toxicity data from studies such as genotoxicity studies, repeat-dose studies, reproductive toxicity studies, carcinogenicity studies and/or other relevant toxicology studies. Single-dose toxicity data alone are not sufficient. The toxicity data should be of sufficient quality to calculate a PDE.

2. Revision of an established PDE will be considered only on presentation of previously unrecognised toxicity data sufficient to result in a significant change, or because of convincing evidence that the existing data used to calculate a PDE are invalid. Minor changes in a PDE will not be considered. The rapporteur, with the consensus of the EWG members, will assign data reviews and request subsequent recommendations to the EWG.

3. The ICH Secretariat will distribute the proposal to the rapporteur of the ICH Ad Hoc Expert Working Group on Residual Solvents (Q3C EWG). The rapporteur will be one of the regulatory members of the ICH who will be available for two-year terms (e.g., FDA 1999-2000, MHLW 2001-2002, EU 2003-2004). The ICH Secretariat will also notify the ICH Steering Committee, Coordinators, and Observers that the Q3 EWG has been called to consider the proposal. The Q3C EWG will be comprised of two members (one chemist and one toxicologist) nominated by the six sponsors of the ICH and one member nominated by IGPA, WSMI and by each Pharmacopoeia. As appropriate, ICH observers may be invited to join the working group.

4. The regulatory rapporteur will ordinarily rely on correspondence or teleconferencing to avoid unnecessary travel. Based on the discussion, with requests for further information to the proposing group and/or individual as appropriate, the rapporteur will prepare an assessment report based on committee approval with a recommendation to accept, with or without modifications, or reject the proposed PDE. Ideally, this activity would occur at the rate of 2 residual solvents per calendar year. For particular residual solvent, it is anticipated that a period of six months from receipt of the toxicological information by the rapporteur to the recommendation of a *Step 2* guideline to the Steering Committee will be necessary.

5. After endorsement by the ICH Steering Committee, either at the next formal meeting or earlier as feasible, the recommendation of the Q3C EWG will be published in each region for public comment (Step 2 ICH process). In addition, the proposal will be provided to each pharmacopoeia for their publication.

6. After close of the public comment periods, the rapporteur may convene a meeting of the Q3C EWG or will rely on correspondence or teleconferencing to consider the comments and finalize the proposal for the new/revised PDE. The final recommendation for the new/revised PDE and implementation is then forwarded to the ICH Steering Committee for approval. Implementation will follow regional practices. With approval of the ICH Steering Committee, the change will be provided to the Pharmacopoeias of the three regions for publication.

7. When an existing PDE is revised or a PDE for a new residual solvent is recommended by the EWG, approval by the ICH Steering Committee is required. Once approval occurs, the information should be disseminated as quickly as possible to all ICH participants and other members of the chemical and pharmaceutical communities. It is recommended that the following actions should be taken by the ICH Steering Committee to ensure rapid transmission of the new information:

   a) publish relevant information on the ICH web site.
   b) request publication of revisions by the Pharmacopeias of the three regions in their forums or web sites.
   c) request that each member publish the new solvent PDE information on its respective web sites.
   d) request WHO to distribute this information to its non-ICH member states.