4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2010-N-0327]

International Conference on Harmonisation; Final Recommendation for the Revision of the Permitted Daily Exposure for the Solvent Cumene According to the Maintenance Procedures for the Guidance Q3C Impurities: Residual Solvents; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a final recommendation for the revision of the permitted daily exposure (PDE) for the solvent cumene according to the maintenance procedures for the guidance for industry entitled "Q3C Impurities: Residual Solvents." The recommendation was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

DATES: Submit either electronic or written comments on Agency guidances at any time.

ADDRESSES: Submit written requests for single copies of the recommendation to the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002, or the Office of Communication, Outreach and Development (HFM-40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. Send one self-addressed adhesive label to assist the office in processing your requests. The draft recommendation may also be obtained by mail by calling

CBER at 1-800-835-4709 or 301-827-1800. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft recommendation.

Submit electronic comments on the recommendation to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Regarding the Q3C guidance:

David Jacobson-Kram,

Center for Drug Evaluation and Research,

Food and Drug Administration,

10903 New Hampshire Ave.,

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Silver Spring, MD 20993,

301-796-0175.

Regarding the ICH:

Michelle Limoli,

Office of International Programs,

Food and Drug Administration,

10903 New Hampshire Ave.,

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Silver Spring, MD 20993-0002,

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SUPPLEMENTARY INFORMATION:

I. Background

In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory Agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission; the European Federation of Pharmaceutical Industries Associations; the Japanese Ministry of Health, Labour, and Welfare; the Japanese Pharmaceutical Manufacturers Association; the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA; and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, Health Canada, and the European Free Trade Area.

In 1999, ICH instituted a Q3C maintenance agreement and formed a maintenance Expert

Working Group (Q3C EWG). The agreement provided for the reconsideration of solvent PDEs and allowed for minor changes to the tables and list that include the existing PDEs. The agreement also provided that new solvents and PDEs could be added to the tables and list based on adequate toxicity data. In the Federal Register of February 12, 2002 (67 FR 6542), FDA briefly described the process for proposing future revisions to the PDEs. In the same notice, the Agency announced its decision to delink the tables and list from the Q3C guidance and create a stand alone document entitled "Q3C--Tables and List" to facilitate making changes recommended by ICH.

II. Revised PDE for Cumene

In the Federal Register of July 20, 2010 (75 FR 42098), FDA published a notice announcing the availability of a draft recommendation for the revision of the PDE for cumene according to the ICH maintenance procedures. The notice gave interested persons an opportunity to submit comments by September 20, 2010.

After consideration of the comments received and revisions to the guidance, a final draft of the recommendation was submitted to the ICH Steering Committee and endorsed by the three participating regulatory Agencies in February 2011.

The final recommendation addresses the safety classification of cumene. When the Q3C guidance was published in 1997 (62 FR 67377, December 24, 1997), cumene was listed as a class 3 solvent (i.e., a solvent with low toxicity). The Q3C EWG reviewed new toxicity data derived from a carcinogenicity study performed by the National Toxicology Program. The new data suggest a positive systemic carcinogenic effect, and this observation raises the toxicity associated with this solvent. The final recommendation is that cumene be placed into class 2. A PDE of 0.7 milligrams per day and a concentration limit of 70 parts per million are being

declared for this solvent. The analysis and recommendation are available for review on the Internet (see section V of this document on electronic access). The final recommendation is also available from the Division of Drug Information (see ADDRESSES). The Agency will revise the tables in the guidance "Q3C--Tables and List" to reflect the ICH final recommendation for cumene.

The final recommendation for the solvent cumene is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The revised PDE for the solvent cumene contained in the revised guidance "Q3C--Tables and List" represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

III. Comments

Interested persons may submit to the Division of Dockets Management (see ADDRESSES) either electronic or written comments regarding this document. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. The recommendation and received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

IV. Electronic Access

Persons with access to the Internet may obtain the Q3C guidance documents at http://www.regulations.gov, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, or

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. Information on the Q3C maintenance process as well as proposals, data analysis, and draft and final recommendations for revisions to the tables and list are available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm125820.htm.

Dated: February 16, 2012.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2012-4164 Filed 02/22/2012 at 8:45 am; Publication Date: 02/23/2012]