CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021936Orig1s000

ENVIRONMENTAL ASSESSMENT

B. Environmental Assessment or Claim of Categorical Exclusion

The Applicant applied for categorical exclusion under 21 CFR 25.31(b), which was evaluated and considered adequate during the first review cycle. Refer to CMC review by Dr. Alan Schroeder dated April 18, 2008.

Please refer to the document dated 7.25.14 in the 021936Orig1s000ChemR Review for pages numbered 1-42.

11-16-07

1.12.14 ENVIRONMENTAL ANALYSIS

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) is requesting that the Categorical Exclusion from the preparation of an environmental assessment (EA), as provided by 21 CFR 25.31(b), be approved for this NDA. The basis for this exclusion is the fact that the estimated concentration of the active ingredient (tiotropium bromide) at the point of entry into the aquatic environment will be less than 1 ppb. In fact, the Expected Introduction Concentration (EIC) from manufacture, patient use and disposal of all Boehringer Ingelheim drug products containing the drug substance tiotropium bromide is anticipated to be well below 1 ppb using the calculation procedures explained in "Guidance for Industry Environmental Assessment of Human Drugs and Biologics Applications" (FDA, July 1998) where:

EIC-Aquatic (ppb) = A x B x C x D
A = 100 to 150 Kg/year production (as active moiety)
B = 1/liter per day entering the POTWs*
C = year/365 days
D = 10^9 µg/kg (conversion factor)

* 1.214 X 10^{11} liters per day entering publicly owned treatment works (POTWs).
Source: 1996 Needs Survey, Report to Congress

In addition, BIPI is certifying that to our knowledge there are no extraordinary circumstances surrounding the manufacture, use, or distribution of this drug product. Summaries of environmental studies, i.e. biological and physiochemical properties, on the active ingredient can be provided if requested. These studies show that the active ingredient, tiotropium bromide, has the following properties:

- The toxicity to aquatic life was evaluated using Daphnids and this organism showed no observable effects with the active moiety at the 32 mg/l with a 48-hour exposure time. The 48-hour EC-50 was 69 mg/l.
- The material is not classified as readily biodegradable, but the material is also known to hydrolyze at aquatic pH levels.
- The octanol water partition coefficient is low, log P o/w = -2.28. This suggests the material will remain in the water column.

The results of these studies are not included with this exclusion request; however, they are available upon request. Note, some of the patients using this medication will have

1.12.14 ENVIRONMENTAL ANALYSIS

historically used metered dose inhalation devices that contain CFC. To the extent that this occurs, Spiriva will have a positive impact by reducing emissions ozone depleting CFCs that are currently acquired under an essential use allocation exemption.

Hence BIPI believes that the submission clearly meets the criteria for an exemption from the preparation of an EA and all the requirements for such an exemption will have been met.

I, Mary McConnell-Meachen, Corporate Director, Environmental Affairs and Safety, Boehringer Ingelheim Pharmaceuticals, Inc. certify that the information provided accurately reflects the information available to Boehringer Ingelheim Pharmaceuticals, Inc.

M McConnell-Meachen

Mary McConnell-Meachen,

Executive Director, Environmental Affairs & Safety