CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-763

PHARMACOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY MEMO TO THE FILE

NDA 21-763.
Submission N-000, stamp-dated 14 April 2004.

Drug: citalopram hydrobromide.
Sponsor: Biovail, Bridgewater, New Jersey, USA; (908) 927-1748.
Indication: Major Depression.

Reviewer: Linda H. Fossom, Ph.D., Pharmacologist
HFD-120

RE: Residual monomers from the excipient Eudragit NE 30 D.

In the Chemistry Review for this NDA (by Dr. Lyudmila Soldatova, finalized 2/7/05), it was noted that the specification for each of the [redacted] used in the production of [redacted] was set at [redacted] which is well below the qualification limit of [redacted]. Neither of the monomers, [redacted] is considered a non-clinical concern for approval of the current NDA. [It should be noted that [redacted] was inaccurately denoted as [redacted] in the Chemistry review for this NDA (personal communication from Dr. Soldatova).]

[redacted] was considered "possibly carcinogenic to humans" by IARC (as of 1999) based largely upon oral gavage studies in rats and mice (reported in 1986, by NTP) that produced tumors only of the forestomach. However, in 2000 (*Report on Carcinogens*, 9th edition), NTP removed [redacted] from its list of carcinogens (where it had been classified as *reasonably anticipated to be a human carcinogen)*, "...based on the fact that the forestomach tumors induced in animal studies were seen only when the chemical was administered by gavage at high concentrations of [redacted] that induced marked local irritation and cellular proliferation, and because exposure to high concentrations of [redacted] is unlikely" (excerpted from NTP's *Report on Carcinogens*, 11th edition, appendix B). [Doses of ethyl acrylate used in the carcinogenicity studies in rats and mice were 100 and 200 mg/kg (presumably 5-10 ml/kg). The maximum human dose of this monomer would be ~3 μg/day, based upon a maximum amount of monomer of [redacted] and a maximum recommended human dose of 60 mg/day.]

The issue of residual [redacted] has been recently considered for another NDA (NDA 21-726) and was been found not to be a safety concern at a higher specification (and higher maximum oral daily dose) than the [redacted] proposed here. [Apparently [redacted] has not been tested for carcinogenicity by oral administration, however, several inhalation studies were performed and failed to demonstrate carcinogenicity in animals.]

Conclusions/recommendations: The [redacted] of [redacted] are not of particular concern for the approval of this NDA from a Pharmacology/Toxicology perspective.

Linda H. Fossom, Ph.D., Pharmacologist *{see appended electronic signature page}*
Lois Freed, Ph.D., Supervisor *{see appended electronic signature page}*

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/s/

Linda Fossom
2/9/05 10:35:45 AM
PHARMACOLOGIST

Lois Freed
2/10/05 07:01:41 AM
PHARMACOLOGIST