



TEVA PHARMACEUTICAL INDUSTRIES Ltd.

NAVA ROTEM - API DIVISION, TEVA GROUP

P. o. Box 3190 PETAH TIQVA 49131 Israel, Tel. +972-3-9267146, Fax. +972-3-9267325

Date: April 7, 2005

To: Division of Dockets Management (HFA-305)
Center for Drug Evaluation and Research
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

From: Nava Rotem Ph. D.
Global QA/RA Knowledge Management Director
Teva API Division
ISRAEL
Tel. 972-3-9267146, Fax 972-3-9267325

Re: Docket No. 1998D-0514

Comments to Guidance for industry ANDAs: Impurities in Drug Substances

Teva API division has reviewed the above draft guidance and our comments are listed below:

1. Line 131: We recommend that USP limits will be in line with ICH guideline limits and FDA requirements.
2. Lines 167, 217: We recommend to give in the guideline a list of 'scientific literature' which is accepted by the FDA. We recommend that official pharmacopeias (such as Ph. Eur.) will be recognized as scientific literature.
3. Line 163: FDA recommendation regarding the level of impurities in specific drug substance should be available to other manufacturers since testing the RLD may not always give a correct indication regarding the active drug substance due to interactions with excipients.
4. Line 214: A more clear definition should be given to the level of impurities which "reflects" the level observed in the approved drug product. A level of twice the actual result seems reasonable as outlined in the draft FDA guidance: " ANDAs: Impurities in Drug Products", Dec. 1998:
"A degradation product present in the generic drug product would be considered qualified if the amount of identified degradation product in the generic drug product is no more than two times the amount of the corresponding degradation product in the RLD. The two-fold amount is justified for two reasons: (1) the RLD acceptance criteria for degradation products generally are set higher than what is observed in the RLD and (2) the safety studies to qualify the RLD generally are carried out at significantly higher levels than the acceptance criteria. "
5. Line 210: "Comparable samples" should be clarified taking into consideration that the manufacturing date and shelf-life of the RLD is not available. We recommend that the manufacturing date should be written on every package of finished product.



TEVA PHARMACEUTICAL INDUSTRIES Ltd.

NAVA ROTEM - API DIVISION, TEVA GROUP

P. o. Box 3190 PETAH TIQVA 49131 Israel, Tel. +972-3-9267146, Fax. +972-3-9267325

6. Line165: A clarification is needed for "significant metabolite": When a metabolite is considered significant? What is then the qualified limit of the impurity?

Regards,

Nava Rotem

Nava Rotem