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December 1, 1998

0633 '98 DEC 10 AIO :35
Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive Room 1-23
Rockville, MD 20857



Docket No. 98D-0514
Draft Guidance for Industry on
ANDA: Impurities in Drug
Substances; Availability

Merck & Co., Inc, is a leading worldwide, human health product company, that invests more than \$1 Billion on Research and Development (R&D), annually.

Merck's global business strategy is to make our products available to patients and other consumers in many countries, at the same time. This strategy relies on our own R&D pipeline to be prolific and efficient. At the same time, we must rely on regulatory authorities who certify the quality, effectiveness and safety of our products, to administer public policies that are scientifically sound and reasonably predictable, as well as economically and socially responsible. We are prepared to live up to the highest of standards and we challenge our research partners and our competition to do the same.

In the course of bringing our research candidates through development testing and clinical trials, our scientists and engineers regularly identify and address issues regarding impurities in drug substances. Indeed, as an innovative company we adhere to the FDA/ICH guidance on Impurities in New Drug Substances. For these reasons, we are very interested in and well qualified to comment on this FDA draft guidance for Industry on ANDA: Impurities in Drug Substances.

GENERAL COMMENTS:

In general we agree with the Agency's intent to consider the issue of impurity levels and their qualification as they apply to ANDAs or ANDA supplements. Toward this end, the use of the ICH Q3A guidance Impurities in New Drug Substances as the basis of the subject guidance is appropriate. However, we are concerned with the latitude afforded to ANDA holders with respect to threshold levels and impurity specifications. As written in the absence of data, the guidance would allow higher levels of impurities than qualified for the innovator's product. We believe, in the absence of additional safety data, a more prudent view is needed. Our specific comments are presented below.

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VII Qualification of Impurities:

Page 8, Line 235: An important sentence from the corresponding ICH guidance appears to have been inadvertently deleted when crafting this guidance. This sentence is needed to give context to the subsequent sentence.

Line 235 should read..."impurity. **If neither is the case, additional safety testing should be considered.** The studies that should be performed to qualify an impurity will depend on a number of..."

Page 9, Third Level (L3b), line 264: "Two-fold higher criteria are justified for several reasons. For example, the innovators' impurity acceptance criteria are set higher than levels observed in drug substances and the safety studies that qualified the innovators' drug substances are carried out at significantly higher levels than". The assumption that impurity acceptance criteria are set 2-fold higher than observed cases is not valid. Use of this assumption could result in impurity levels above those previously qualified. Thus in the absence of additional safety data, qualification of an impurity should be limited to the amount measured in the innovator product.

Page 10, Fourth Level (L4) provides greater latitude in setting upper specification limits for impurities than afforded to innovator products. Innovators are held to an upper specification of 0.1%. Given the absence of data to support the upper specification of 0.5%, an upper specification of 0.1% is warranted.

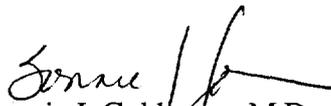
Similarly, Fifth Level (L5) suggest that further toxicity testing, beyond genotoxicity, is not necessary unless the impurity level exceeds 1%. Again, as written, the guidance could allow impurity levels to exceed those allowed for the innovator product or tested in pre-clinical safety assessment studies.

Impurities Decision Tree

Page 12, Decision Tree should include the requirement for performance of safety studies when impurity levels exceed the threshold. FDA should harmonize safety requirements to ensure the same level of safety assessment for innovator and generic products.

We trust that these comments will be considered in further development of the draft guidance.

Sincerely,


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