

# GlaxoWellcome

September 21, 1998

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Management Dockets, n/a  
Dockets Management Branch  
Food and Drug Administration  
HFA-305, Room 1-23  
12420 Parklawn Drive  
Rockville, MD 20857

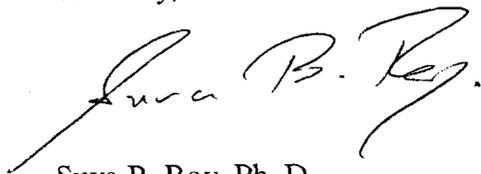
**Re: Docket Number: 98D-0514**  
**General Correspondence: Other**

Dear Sirs:

Please find enclosed GlaxoWellcome's comments on the draft Guidance for Industry – ANDAs: Impurities in Drug Substances.

Please feel free to call me at (919) 483-6408 if you need additional information or clarification regarding the comments.

Sincerely,



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## **Comments from GlaxoWellcome on the Draft Guidance for Industry – ANDAs: Impurities in Drug Substances**

**Lines 84 - 85** - Suggests that the assessment of proposed commercial process may be deferred until the first batch is produced for marketing and the impurity profile of the drug substance intended for marketing should be compared with the development batches. This may be too late. Often bioequivalence studies of new generic products are completed using developmental batches of the drug substance. Changes in properties of the drug substance during scale-up to commercial process can affect the bioequivalence. We suggest that assessment of the commercial process and impurity profile should therefore be completed earlier. We also suggest adding that the drug substance used for bioequivalence studies should be from batches that meaningfully simulate the final manufacturing process of the drug substance.

**Lines 261 - 263** - HPLC or capillary electrophoresis does not have adequate discriminating capability in ensuring exact match in identifying impurities. We recommend that LC-MS and/or LC/NMR should be used for this purpose.

**Lines 263 – 268**- States that an impurity is qualified if it is found at similar levels (no more than two-fold higher for most drug substances). In innovator products the margin for qualified impurity specification are based on process capabilities and often are less than two-fold. We suggest deleting the “no more than two-fold higher for most drug substances”.

**Lines 280 - 285** - While the QSAR database program with its modules can be used to identify the potential toxicity of an impurity, the software has not evolved enough to be used as regulatory tool to establish the safety of a compound. The software is a preliminary prediction tool for research, which requires verification with laboratory data. Applying it as a regulatory tool to justify qualifying an impurity is an immense leap of faith and potentially dangerous. We strongly recommend that scientific literature data or laboratory data as in ICHQ3A supports the QSAR finding. We also recommend CDER's Pharmacology/Toxicology experts are consulted regarding the suitability of the QSAR evaluation alone as a regulatory tool. Generally QSAR alone is not recognized as adequate in the CDER's Pharmacology/Toxicology review practices.

**Line 286 - 291** - The guidance recommends that if no potential concern is indicated by the QSAR evaluation the impurity is considered qualified at a level not to exceed 0.5% or 500 micrograms per day whichever is less without other supporting toxicity data. The 0.5% limit is confusing, it appears as though it is five-fold higher than the ICHQ3A threshold limit of 0.1%. We recommend that like the ICH Q3A the limit be expressed as 0.05% or 500 micrograms/day whichever is lower.

**Lines 298 - 301** - If genotoxicity testing raises a concern additional toxicity testing (ICH Decision Tree for Safety studies regarding general toxicity studies) should be the automatic default requirement not subject to case-by-case evaluation.

**Lines 301 - 306** - Again, the 1% limit is confusing, it appears as though it is ten-fold higher than the ICHQ3A threshold limit of 0.1%. We recommend to assure consistency with the ICHQ3A the limit should be expressed as 0.1% or 1 milligrams/day whichever is lower.

As a general comment, the Hatch-Waxman Act did not require generic equivalents to conduct safety studies because of the assumption that these drugs have been shown to be safe by their innovator during the drug development. However, the safety of these drugs is established using drug substance containing impurities produced by the innovator's synthetic pathways, reagents, solvents and reaction conditions. Generic drug substance manufacturers often use synthetic pathways, reagents, solvents and reaction conditions different from the innovator. This often

produces drug substances with different synthetic impurities and impurity profiles, which can have different toxicity profiles.

In order that generic drug products also have equivalent safety profile as the innovator the generic drug substances should be required to meet the same quality and safety standards. These standards are set out in the ICHQ3A, ICHQ3C guidances. The ICH standards have been adopted by an international body of experts and reflect the state-of-the-art understanding of the issues. The generic drug substances should also comply with all provisions of these standards to assure continued safety. Anything less has the potential of exposing unsuspecting patients to less than optimally tested impurities in these drugs and thus unnecessary risks.