

**PFIZER COMMENTS ON  
FDA DRAFT GUIDANCE ON ANDAs: IMPURITIES IN DRUG PRODUCT**

**August 2005**

Comments Date: Nov. 2005

<u>General Comment</u>
The draft is in need of further editing to be more consistent with other FDA and ICH guidelines. For example, the use of the word 'may' should be replaced by 'can'.

<u>Line #</u>	<u>Item</u>	<u>Key Concerns with Explanation of Position</u>	<u>Proposed change</u>
80	A. Listing of Degradation Products	Firms should be able to prioritize degradants into primary/secondary or major/minor. Otherwise there could be a very long list of degradants without focus on relevant ones.	Modify sentence to read "...specifications for a drug product include a list of <i>major</i> degradation products."
116 - 130	B. Setting Acceptance Criteria for Degradation Products	Pfizer agrees that if the degradation product is specified in the USP, the acceptance criteria should be no higher than the USP level; and if it is not in the USP, the acceptance criteria should be consistent with the FDA-approved human drug product. Pfizer does NOT agree, however, with the ANDA sponsor petitioning the USP to revise the acceptance criteria when the ANDA degradation product level is higher than the USP limit. If the ANDA sponsor qualified the degradation product, an update of the acceptance criteria could be requested from the FDA. If the FDA approves the higher limit, based on safety and scientific data, then the ANDA sponsor could petition the USP for the update.	Remove the sentence (lines 124-125): "Then, if appropriate qualification has been achieved, an applicant may wish to petition the USP for revision of the degradation product's acceptance criterion." Alternatively modify the sentence to indicate that the ANDA sponsor needs to receive approval from the FDA for the new acceptance criteria before petitioning the USP for the revision.
148	IV. Qualification Of Degradation Products	The phrase 'a degradation product is qualified when it is a significant metabolite' contrasts with Q3B(R) which says it can <u>generally</u> be considered qualified. This latter wording is incorporated in line 214 but the guideline lacks self-	Internal consistency between this statement and that in line 214

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		consistency.	
163	A. Qualification Thresholds	The qualification limit of an impurity should have statistical validity. The "qualified limit" should reflect the upper statistical limit determined by analysis of the analytical results for the impurity. Since ICH generally recognizes the upper statistical limit for setting acceptance criteria to be the mean plus three times the standard deviation, this approach should be acceptable to define the qualification limit for an impurity.	Include the ICH approach to define the qualification limit for an impurity.
165	A. Qualification Thresholds	Maximum daily <u>adult</u> dose is implied. There is no mention of adult vs. pediatric dose. A drug product could potentially have more than one threshold depending on pediatric or adult maximum dose. Clarity is suggested.	Modify sentence to read: "...thresholds for degradation products based on the maximum <i>adult</i> daily dose..."
196	B. Qualification Procedures 1. Comparative Analytical Studies	When comparing the stability/degradation profiles, it is important that the different drug products have proposed commercial manufacturing processes (as mentioned in line 84). Two products could have the same route of administration and have different, noncomparable stability profiles. Also, ANDA's products could have different commercial manufacturing processes or formulations that will lead to different, noncomparable stability profiles.	Indicate that the batches used for the studies should be manufactured by the proposed commercial process.  Make statement as to what is meant by comparable (same acceptance levels, equivalent stability profiles).
197 & Note c, Attachment 1	Similar characteristics (e.g., tablet versus capsule)	It is unclear if this wording implies that a tablet is similar to or different from a capsule.	Modify sentence to read: "...similar characteristics (such as, tablets <i>would be considered similar to capsules</i> )..."
201-202	1. Comparative Analytical Studies	"... threshold may not be applicable ... if the maximum daily doses or the routes of administration are different." There are other factors such as basic proposed commercial	Modify sentence to add "for example": "...threshold may not be applicable ... if, <i>for example</i> , the maximum daily doses or the

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		mfg process or formulation that may impact the profile, drug absorption, and possibly the threshold.	routes of administration are different.”
213	2. Scientific Literature...	<p>“ ...if level of ...degradation ...is adequately justified by literature, no further qualification is ... necessary”</p> <p>Sponsor should confirm the degradation product in literature is comparable to proposed commercial process. If drug product used in literature is from another formulation or manufacturing process, then the degradation profile may be different.</p>	Add “Confirm that degradation product in literature is comparable to proposed commercial process.”
225	3. Toxicity Studies	Use of the term ‘toxicity studies’ contrasts with ICH use of ‘safety’. The ICH recommendation to use a drug product (or substance) with the impurity exists because sponsors need to be able to replicate earlier safety studies and provide a comparison to avoid false results. For the ANDA there is no suggestion of a comparison. Instead, this has mutated to be a recommendation to use the drug substance/product itself and is has dropped the part recommending a representative level be present.	Revert to ICH guidance/terminology.