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September 24, 1998

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry on ANDAs: Impurities in Drug Substances [Docket No.98D-0514]

Dear Sir or Madam:

On behalf of the Science Committee of the Generic Pharmaceutical Industry Association (GPIA), I would like to submit comments to you on "Draft Guidance for Industry on ANDAs: Impurities in Drug Substances", 63 FR 39880. July 24, 1998.

GPIA is comprised of the manufacturers and distributors of generic medicines (as well as the providers of technical services and goods to these firms). Most of our members will be directly impacted by implementation of the draft guidance for ANDAs on impurities in drug substances.

The attached comments were compiled by the GPIA combined Science/Bulk/Topicals Committee.

We are disappointed that we did not receive a response to our request to extend the comment period for this draft guidance and are, therefore, unable to provide a more comprehensive commentary on the guidance. However, we do thank you for your consideration of the comments we are able to submit as you finalize the draft guidance.

Sincerely,

Alice E. Till, Ph.D.
President

Cc S. Hyden, Chair GPIA Science/Bulk Committee
D. Miran, Chair GPIA Topicals Committee
R. Trimmer, FDA

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GPIA comments on draft guidance for ANDAs for impurities in drug substances:

1. The definition of drug substances which are excluded from this guidance - See p. 2, lines 19-21 Semi-synthetic materials such as antibiotics, paclitaxel, conjugated estrogens are example of excluded materials, according to the USP sections dealing with Foreign Substances and Impurities. According to the USP (phone discussions with Dr. Barnstein and Wright), it was reaffirmed that items such as antibiotics are excluded from the USP classification of impurities in drug substances (See General Notices Sections in USP 23, Supplements 6 and 8). However the USP could not vouch for what the FDA would do. Dr. Trimmer (phone discussion) indicated that each FDA Chemistry Reviewer might take a different position depending on the drug substance and history associated with the compound(s).
2. Does the Guidance cover the filing of a "505(b)(2) Paper NDA, using an established drug substance in a manner that cannot be covered by the filing of an ANDA?
3. In a general sense shouldn't a critical factor such as the "Therapeutic Index" of the drug substance be part of the guidance in setting standards for impurities.
4. In the Section on the classification of impurities, under "Residual Solvents", P. 3, line 66, one of the most ubiquitous solvent impurities from virtually every process stream is water. This is not noted, perhaps because it so obvious. On the other hand, testing for water content of drug substances on a more consistent basis may be a good reason to include the name in this section.
5. Excluding "enantiomeric impurities", P. 3, line 70, without clarification is not justified. See for example, thalidomide.
6. As a general statement, we feel that the DMF holder, not the ANDA sponsor should be listed responsible party for summarizing the impurity testing requirements for a drug substance. Since much of the DMF is confidential, there is no way for the ANDA applicant to determine if the studies were performed or that they are adequate. To repeat the studies would often be needless. This lack of information could result in unpleasant surprises during the application review. Therefore, it is recommended that the DMF holder be made solely responsible. See Lines 73, 80, 122, 152, etc.
7. Identifying an impurity, which cannot be fully characterized by a designation such as A, B or X, Y, or Related Substance 1 or 2, and which is a process related impurity should be included in the language of the Guidance. Trimmer basically concurred on the point during my phone discussions with him (September 2 and 4). How to set LOD/LOQ and actual levels being found in the final drug substance is another matter that needs to be addressed.
8. We contacted the USP to see if there is any way of linking the allowed lower purity rubric for a drug substance and the 2% Total of "Impurities", see lines 195-199. For example, a number of USP monographs allow the drug substance purity lower limit to be 97%. Can this be inferred that the USP will allow 3% of total impurities? There was of course no answer back.
9. Page 9 deals with the matter of toxicity studies and other options to qualify impurities present in excess of 0.1% in the drug substance, and which has never "appeared" or been identified as being present in the pioneer drug substance. Tools such as QSAR are surrogates for in-vivo studies. We spoke to Dr. Bob Jerussi on 9/2 and he indicated that if an ANDA filing includes any "in-vivo toxicity studies to qualify impurities, you no longer have an ANDA."

10. Dealing with testing the innovator or pioneer product for establishing the presence or absence of certain impurities can become a major problem. Firstly, working with the pioneer firm's drug product, to look for trace process impurities opens up an enormous analytical burden. It is very unlikely that a Multisource ANDA filer is going to contact the pioneer firm and request 3 lots of representative drug substance. It is even less likely that the pioneer firm will provide samples to an ANDA sponsor (third party ??). For drug products which are in the mg potency range, there may not be any way to arrive at answers to establish the absence or presence of "trace" impurities found by the new DMF synthesis, and never publicly disclosed or discussed before. See lines 259-272.
11. What happens, when as a result of improved analytical techniques a "new" previously not found or found at levels below 0.1% now is in the critical assessment range of greater than 0.1% appears in routine lots of the drug substance. Further, you show that "old" lots made by the DMF process always had this high level of impurity. What procedures do you go through to qualify the new level of impurity? This could be a particular issue when discovery occurs during the prosecution of an ANDA.
12. Much more guidance and definition is needed to fully qualify the amounts of impurities found. What will be acceptable when there is no reference standard for an impurity?
13. The application of this guidance to all ANDA supplements places an unnecessary and costly burden on the industry, which is unneeded from a safety point of view. The application of this guidance to old products, which are supplemented for any purpose is clearly not the intent. Therefore, it is recommended that the wording be changed to reflect its application only to supplements which involve the addition of a new API or a significant change in the process of synthesizing the API by the current vendor. See Line 23 - 25.
14. Please confirm whether the criteria of 0.1% is based on area or response factor. (see Line 38 - 41)
15. For analytical method validations forced degradation is carried out to show that the method is stability indicating. Hence, we feel that the impurity peaks appearing during degradation studies need not be considered as degradation products and hence, need to be included as probable impurities in specifications. Line 81-84)
16. Line 85 States: "Assessment of the proposed commercial process may be deferred until the first batch is produced for marketing." Does this statement allow that a comparative study between developmental and commercial batches should be filed to the authority after getting the registration certificate?
17. Taking the case of rounding off of figures, we would like to know how many significant figures should the Response Factor value be reported. Line 102-104
18. Referring to Line 113 to 120: For a manufacturing process consisting of say 7 steps for a drug substance (API) we need certain clarifications: Do we need to estimate quantitatively and give limits for all the solvents used from step 1 to step 7 in the final API, or is it sufficient to consider only the solvents used in the last and penultimate step? If a solvent is of petroleum origin (e.g. Heptane), do we need to identify and quantify all the fractions in the final API? For a limit of 100 µg/g for any solvent, what is the acceptable level of LOQ.

19. Referring to Lines 126 - 136, Quantification of impurity against the principal peak of drug substance is acceptable if there is no significant difference between the response factor of impurity and the drug substance. If there is a significant difference in the response factors of the two, a correction factor is to be applied to determine accurate amount of impurity in the drug substance. What should be the criteria when the difference in responses is considered as significant or what range of values should be considered as close. We recommend to consider a value of correction factor between 0.9 - 1.1 to be close. As impurities are available in small quantities performing all tests like NMR, MS, IR, Assay etc. may not be possible. For such a case can the percent purity data (obtained by chromatographic purity methods) be used to calculate the response factor. Also, what is the minimum purity acceptable for an impurity?
20. Line 144 states: Levels of impurities that are present but are below the validated limit of quantitation need not be reported. Are traces of residual solvents supposed to be treated according to this expectation?
21. Line 153 states: "A tabulation should be provided comparing impurity levels between stability and other batches." What kind of and how many batches have to be compared with stability ones? Is this comparison supposed to be made at zero time of stability study? Does this remark inspire the applicant again to file the comparative study between developmental (stability) and commercial batches to the authority after getting the registration certificate?
22. Will the FDA make a database available defining known metabolites, or does this apply only to those published in the literature. See Line 215.
23. The phrase in Line 268, "...in certain dosage forms..." is vague and uninformative. We request the dosage forms this category be defined.
24. The phrase in Line 269, "...no higher than the innovator's level..." is also vague. We recommend the phrase be changed to "...no higher than the highest level seen in the innovator's product..."
25. Does Line 387 - 389 that in all cases the limit of quantification should be at least 50% of the specifications limit.
26. In case of the pharmacopoeial methods for chromatographic purity by HPLC impurities less than 0.05% are rejected based on area %. Is this acceptable for non-pharmacopoeial methods also.
27. The Guidance says, that it is provided for "qualifying impurities found in the drug substance...via a comparison with impurities found in the related USP monograph". The problem is that the USP monographs usually do not specify the individual impurities. (No chemical names, Rf values, etc.) Consequently people do not know whether impurities found in a drug substance are the same as the ones prescribed in the USP monograph or not.