



NATIONAL PHARMACEUTICAL ALLIANCE

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

September 22, 1998

Docket # 98D 0514

Gentlemen:

Attached are two copies of the National Pharmaceutical Alliance's Technical Committee's comments on the draft Guidance for Industry, ANDAs: Impurities in Drug Substances. Today is the closing date for comments. We have heard that the deadline may be extended another 60 days but to our knowledge this has not occurred. We appreciate the opportunity to comment but believe that the application of ICH harmonized guidances to generic drugs is unfair since the generic industry did not have the opportunity to participate in the harmonization process.

Very truly yours,

Christina Sizemore
President

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**COMMENTS BY NPA'S TECHNICAL COMMITTEE ON THE DRAFT
"GUIDANCE FOR INDUSTRY ANDAs: Impurities in Drug Substances"**

Docket # 98D 0514
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General Comments:

1. FDA's arbitrary application of the ICH impurity harmonized standards to generic drugs is patently unfair since the generic industry was specifically and repeatedly denied participation in the ICH's discussions on this issue. Moreover, because the U. S. innovator pharmaceutical industry was directly involved in forming the ICH impurity standards, FDA's proposed action would enable the generic industry's direct competitors to dictate requirements for generic drugs.
2. In addition, Attachment I of the Draft Guidance - the Impurities Decision Tree - provides that FDA will refuse to file certain generic drug applications under section 505(j) of the Federal Food, Drug, and Cosmetic Act based on the ICH impurity standards. Instead, FDA will require that these generic drug applications be filed under section 505(b) of the Act, thereby removing them from the abbreviated classification. Through this policy decision, FDA assists the innovator industry in impeding generic competition by implementing specifications that were established by an international body of mostly innovator companies. FDA's complicity in this action directly contravenes the letter and spirit of the Hatch-Waxman Amendments of 1984, which carved out a means to bring affordable pharmaceuticals to American consumers.
3. Lines 38-41 mention the Ad Hoc Advisory Committee recommendation of a 0.1% impurity threshold for drug substances used in generic drug products but fails to mention that the same committee at the same meeting also recommended that the same threshold should apply to drug substances in OTC drug products. If the Agency is going to use recommendations from an advisory committee, why the selective use? If so called unqualified impurities in generic drug substances at $\geq 0.1\%$ are a health risk, why aren't they also in OTC drugs which are taken without medical supervision?
4. Lines 41-47 mention that the USP has adopted the 0.1% threshold for impurity identification in the Sixth Supplement to USP 23 dated November 15, 1996. We opposed that specification in a letter to the USP. In addition, the stated threshold level was not of USP's own making. Rather, the USP was allowed observer status at the ICH negotiations where 0.1% impurity levels were discussed well before November, 1996. The generic industry was denied observer status. Thus the USP preempted FDA's guidance re the threshold level by prematurely including such limits in the Sixth Supplement. Its placement in USP is not support for this guidance but rather a result of the same

negotiations that produced the guidance.

5. What is the rationale for the 0.1% threshold level proposed in the Draft guidance? Although a scientific rationale is necessary for an educated discussion of the issues related to impurity standards, such a rationale has not been provided in the Draft Guidance. Why was 0.1% selected, and not 0.2% or 0.05% or even 0.5%? Currently, it appears that 0.1% is an arbitrary value based neither on good science, nor FDA's experience, nor evidence of untoward effects due to impurity levels at 0.1%. Arbitrarily selecting a limit imposes a standard irrespective of its clinical importance.
6. The 0.1% threshold limit was set for new drug substances that are NMEs. This must have been agreed upon by the participants to the harmonization process because not a lot is known about NMEs and impurities in an NME at that level may be a problem. Whereas there is much known about new drug substances that are not NMEs. The latter have been made via various processes and have been used in large patient populations for many years with little or no risk. Therefore, using the same threshold for new drug substances that are not NMEs just doesn't make scientific sense. Had the ICH negotiations included all drug substances initially, it is quite possible that a higher threshold would have been agreed upon.

Specific Comments:

I. Introduction

Lines 34-35 indicate that generic drugs are not covered by ICH Q3A but that many of the recommendations in ICH Q3A are applicable to drug substances used in generic drugs. There is no rationale given in III. as to why this may be true. Applying the ICH Q3A recommendations for identifying and characterizing impurities in new molecular entities to well defined drug substances in ANDA applications negates the purpose of an ANDA i.e. not to have to repeat the safety and efficacy studies performed by the innovator.

III. Rationale for the Reporting and Control of Impurities

A. Organic Impurities

Lines 80-87, page 4 discuss a DMF manufacturing process as though it is newly developed (such as for a NME). However, many generic drug substances come from firms that have used and marketed specific drug substances for some time. Thus, "test results of materials manufactured during the development process" are irrelevant and "assessment of the proposed commercial process" has already been accomplished well before the ANDA candidate firm bought the NDS.

Lines 102-105 discuss rounding, a common practice, but which should not be done for values below 0.1%. What about values above 0.1% such as 0.11 and 0.14%. May they be rounded to 0.1%?

V. Reporting Impurity Content of Batches

Lines 138-139 state that analytical results should be provided for all batches of the drug substance used for stability testing as well as batches representative of the proposed commercial process. This would fit a NME but doesn't fit a generic drug substance since a generic drug product manufacturer usually buys the drug substance and often gets only one batch. Usually, the drug substance manufacturer has long ago arrived at the commercial process.

Line 143 mentions reporting retention time of an impurity. Relative retention time is a much better indicator since most chromatographic systems can vary from run to run.

Line 144 states that levels of impurities present but below the LOQ need not be reported. Is the assumption being made that the LOQ is at or below 0.1%?

VI. Acceptance Criteria for Impurities

Lines 167-168 state that those impurities selected for inclusion in the specification for the drug substance are referred to as *specified impurities* in this guidance. Lines 378-380 in the Glossary state the same thing. Yet in lines 193-199 it is stated that drug substance acceptance criteria should include "Any *unspecified impurity*, with a limit of not more than 0.1 percent". There seems to be a contradiction here.

Lines 74-75 indicate that a specified identified impurity is one at or above the 0.1% level. With respect to rounding, does this mean at the 0.15% level or higher or anything at 0.1% or higher?

Lines 187-190 seem to be directly contradicted by lines 66-67, 100-111, 116-118, and 144-145. If impurity safety can be demonstrated to be of no concern, the analytical method and safety limits should define product specifications, not the amount seen in various batches, unless those values directly impact on the quality of the drug product. As an example, take the case where a residual solvent specification is 100 ppm and that value falls well below the safety limits, yet the solvent is consistently seen at lower levels or not detected. Redevelopment of methods should not have to take place in order to drop the specification to 25 ppm since at its highest level, 100 ppm, the solvent poses no safety or quality issue.

Lines 190-192 introduces the term "significant variation" in batch to batch impurity levels. This term should be defined. If an impurity varies from 0.01% to 0.09%, would

that be considered significant since the high value is 9 times the lower value?

VII. Qualification of Impurities

Lines 219-222 indicate that the maximum daily dose is either above or below 2 grams/day. The scientific rationale for 2 grams/day should be indicated or the limit changed. A further breakdown of the maximum daily dose would allow higher impurity limits for lower dose drugs such as: 1 gram/day - a threshold of 0.15% and 0.5 gram/day - a threshold of 0.20%

Lines 223-230 indicate that higher or lower threshold levels may be appropriate for some drugs. The only example given is one in which the threshold level would be reduced. However, other examples should be given in this section. For instance, an impurity may be of equal or of less toxicity than the drug substance itself such as certain cancer drugs.

Lines 239-313 discuss the Impurities Decision Tree in Attachment I. L₁ through L₅ indicate that qualification may be obtained by lowering the impurity below the ICH threshold level. The only reasonable way to do this is to purify the drug substance usually by recrystallization one or more times. Thus, each recrystallization will cause a loss of 10-15% of the drug substance, not an inconsequential cost. What is FDA's experience with firms that have recrystallized in an attempt to reduce an impurity below the threshold? Has it worked? What have the losses been?

Lines 289-291 indicate that a determination to accept QSAR data will be made on a case-by-case basis. Unfortunately, a firm that gets QSAR data and then gets rejected by OGD has put itself in a terrible disadvantage and it might have been better to have taken a different route initially to qualify the impurity. Firms need better assurance that QSAR data will be acceptable before they enter into such a qualification route.

Lines 308-313 describe the L6 level in the generic drugs impurities Decision Tree where the drug no longer would be generic but fall under 505(b) of the Act. This is unfair especially since FDA has allowed PhRMA to participate in a harmonization process which, at least in part, arrived at this type of decision tree. The latter results in less competition from generic firms.

The whole decision tree is the type of work that would be required for an NDA and not for an ANDA and ought to be eliminated from this guidance.

VIII. New Impurities

Line 319 contains the phrase "threshold values as noted above". It should provide a reference to the specific section of the guidance that is being referenced.

Attachment III; Glossary of Terms

Impurity: The word "Any" in "Any component" seems misplaced. Since lines 68-70 exclude certain possible impurities from the guidance, "Any" just doesn't seem to fit. A better phrase is "Certain components".

New Drug Substance: There are two items that are wrong with the definition. The first is an inappropriate use of the term "moiety" since the NDS is a whole molecule and not a part of one to which moiety refers ["moiety 1. A half. 2. about a half; a part or portion." Webster's New Collegiate Dictionary]. It is often used in organic chemistry to designate a part of a molecule i.e. the phenyl moiety provides an electron sink, etc. The second is that the NDS is defined as something not previously registered in a region. In the United States that is a NME. All NMEs are NDSs but not all NDSs are NMEs! This definition is not for a NDS but for a NME and should be so titled. Another definition should be given for a NDS such as the active ingredient or principal in a new drug product.

Genotoxicity Tests: The sentence within the parentheses is extraneous and does not belong in the definition. It could be included in the document text.

Specification: *Conformance to specifications* is a unique term that needs to be defined separately. The last sentence under the Specification definition is extraneous descriptive information and could be included elsewhere in the document text.

Starting Material: This definition would be improved if after the phrase "is incorporated as an element" is added "either partially or completely". The second sentence does serve to clarify the definition. However, it is extraneous descriptive information that does not belong in the definition but could be included in the document text.

Validated Limit of Quantitation: This term is not really defined; only a value was assigned to it. Where does the 0.05% come from? What is a firm to do if the validated LOQ is 0.08%? And what's wrong with the latter?