

NAPM



NATIONAL ASSOCIATION OF PHARMACEUTICAL MANUFACTURERS

320 OLD COUNTRY ROAD, GARDEN CITY, NY 11530-1752 • (516) 741-3699 FAX: (516) 741-3696

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Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive Rm 1-23
Rockville, MD 20857

RE: Docket No. 98D-0514 - Guidance for Industry: ANDAs: Impurities in Drug Substances

The National Association of Pharmaceutical Manufacturers (NAPM) appreciates the opportunity to comment on the document, "Guidance for Industry: ANDAs: Impurities in Drug Substances" (Docket No. 98D-0514). These comments represents the consensus of leading domestic and international manufacturers of bulk active pharmaceuticals.

We wish to compliment the Agency in producing a document that covers most issues regarding impurities in drug substances. Our recommended changes to this document are intended to clarify the document and not rewrite it.

NAPM is the national trade organization representing manufacturers, distributors and repackagers of generic multisource prescription drugs, OTC drugs, dietary supplements and veterinary drugs. The organization prides itself in serving the needs of its members and has been heavily involved in legislative, legal, regulatory and technical issues.

We thank you for the opportunity to submit our comments. We hope that our comments are clear and welcome any questions that you may have.

Sincerely,

A handwritten signature in cursive script that reads "Leon Shargel".

Leon Shargel, Ph.D.
Vice President and Technical Director

cc: Eric Sheinin, Ph.D.

98D-0514

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**GUIDANCE FOR INDUSTRY:
ANDAs: IMPURITIES IN DRUG SUBSTANCES [Docket No. 98D-0514]**

Comments

General Comments

The Guidance uses the terms "drugs," "drug substances" and "drug products" in a manner that is not always clear to the reader. We would like the Guidance to use the terms "drug substances" and "drug products" to differentiate between the active drug substance and the finished dosage form, respectively, rather than using the term "drug" or "drugs" which tends to be somewhat ambiguous.

I. Introduction

p. 2, Lines 45-47

The USP threshold of 0.1% for identification of impurities is referenced. The USP states that the sum of all other impurities combined with known impurities identified in the monograph does not exceed 2.0% unless otherwise stated in the monograph. If the Agency accepts the USP 0.1% threshold for an unlabeled impurities, does the agency also accept the 2.0% total of all labeled other impurities and monograph impurities?

III. Rational for the Reporting and Control of Impurities

A. Organic Impurities

p.4, Line 91

Remove "at or", (ie, "....all recurring impurities ~~at or~~ above an apparent level of....")

p. 4, Line 102-105

The application of "rounding" needs clarification. From this sentence, do we infer that normal scientific rounding principles are to be applied to values above 0.1%?

IV. Analytical Procedures

p. 5, Line 122

The sentence should be changed to: "The DMF or abbreviated application should include documented evidence that the non-compendial analytical procedures are validated and that all procedures are suitable for the detection and quantitation of impurities."

VI. Acceptance Criteria for Impurities

p. 6, Line 175

Remove "at or", (ie, "...all recurring unidentified impurities ~~at or~~ above 0.1 percent.")

p. 7, Lines 184-192

This section represents a significant regulatory change that is in conflict with the USP. According to this section, a manufacturer of a drug substance whose process produces a drug substance with low impurity levels and another manufacturer of the same drug substance with higher impurity levels will be held to different impurity specifications based on their manufacturing process. For example, a situation could arise where the USP specification for a known impurity is NMT 1.0%, and a drug substance manufacturer is held to a specification of NMT 0.5% based on their process; whereas, a different drug substance manufacturer is held to a specification of NMT 0.1% based on their process. This regulatory change, as written, is unfair and actually favors the manufacturer with the greater impurity level.

NAPM recommends needs that the agency clarifies this section and the relationship of the FDA guidance with respect to the USP specifications for impurities, and the level of impurities that the manufacturer of the APIs routinely achieves.

p. 7, Line 197

Remove "at or", (ie, "...impurity ~~at or~~ above 0.1 percent.")

p. 8, Lines 219-222

The qualification threshold as stated in the Table is effectively 0.05% for a 2 g/day dose, ie, 0.05% of 2 g per day is equal to 1 mg/day. The qualification threshold of 0.1% for a 2 g per day daily dose would be the equivalent of 2 mg per day intake. An alternative interpretation of the Table is that the qualification threshold is meant to be NMT 1 mg per day for a maximum daily dose between 1-2 g per day. regardless of the maximum daily dose.

The Table needs to be stated more clearly, possibly by providing ranges of the maximum daily dose (e.g., up to 1 g/day, 1 to 2 g/day, greater than 2 g/day) with the corresponding qualification threshold.

p. 8, Lines 223-227

The first two sentences should be changed to read:

“Higher or lower threshold levels for qualifications may be appropriate for some individual ~~drugs~~ drug substances based on scientific rationale and level of concern, including therapeutic drug class effects. For example, qualification may be especially important when there is evidence that such impurities in certain ~~drugs~~ drug substances ~~or therapeutic classes~~ have previously been associated with adverse reactions in patients”.

p. 8, Line 231

The first sentence should read, “Impurities Decision Tree for generic “drug substances” rather than for “generic drugs.”

p. 9, Line 260

It should be noted that of *three or more* lots of the innovator’s drug product might contain only *one* lot of the drug substance.

Attachment I Impurities Decision Trees

The subtitle (Generic Drugs) should be (Generic Drug Substances).

The phrase “observed in the innovators’s drug product and at a similar level” is used in several places. This sentence should be changed to, “observed in the innovators’s drug product and at a similar level **or lower level.**”