

Guidance for FDA Staff

DETENTION WITHOUT PHYSICAL EXAMINATION OF ACTIVE PHARMACEUTICAL INGREDIENTS (API's) THAT APPEAR TO BE MISBRANDED UNDER 502(f)(1) BECAUSE THEY DO NOT MEET THE REQUIREMENTS FOR THE LABELING EXEMPTIONS IN 21 CFR 201.122

Comments and suggestions regarding this document should be submitted by [date] to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 10-61, Rockville, MD 20852.

After [date], submit comments to Thaddeus J. Poplawski, Division of Import Operations and Policy (HFC-170), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Comments should be identified with the docket number 00D-1601.

For questions regarding this document contact Thaddeus J. Poplawski at 301-443-6553.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Regulatory Affairs
October 3, 2000

00D-1601

GDL 1

IA #66-66 - 10/3/00,

IMPORT ALERT #66-66, "DETENTION WITHOUT PHYSICAL EXAMINATION OF APIs THAT APPEAR TO BE MISBRANDED UNDER 502(f)(1) BECAUSE THEY DO NOT MEET THE REQUIREMENTS FOR THE LABELING EXEMPTIONS IN 21 CFR 201.122"

This guidance to FDA field personnel represents FDA's current thinking on the detention without physical examination of bulk chemicals that can be used as active pharmaceutical ingredients. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such an approach satisfies the requirements of the applicable statute, regulations, or both. The guidance is being distributed for comment purposes in accordance with FDA's Good Guidance Practices (65 FR 56468, September 19, 2000)(21 CFR 10.115(g)(2)); the draft guidance has been designated as Level 1 guidance.

ATTACHMENT 11/7/00

TYPE OF ALERT: Detention Without Physical Examination (DWPE)

(Note: This import alert represents the Agency's current guidance to FDA field personnel regarding the manufacturer(s) and/or product(s) at issue. It does not create or confer any rights for or on any person, and does not operate to bind FDA or the public).

PRODUCT: Active Pharmaceutical Ingredients (APIs)

PRODUCT
CODE: GPI = DR (drugs) with PIC = [] [] [] [] S [] []
GPI = AB (antibiotics) with PIC = [] [] [] [] S [] []

PROBLEM: Misbranded drugs

PAF: LBL - Labeling

PAC FOR
COLLECTION: 52002

COUNTRY: See attachment

MANUFACTURER/
SHIPPER FEI#: See attachment

IMPORTER'S
ID#: N/A

OASIS CHARGE

CODE: DIRECTIONS

CHARGE: "The article is subject to refusal of admission pursuant to section 801(a)(3) in that it appears to be misbranded in that it lacks adequate directions for its intended use. [Misbranding, Section 502(f)(1)]."

NOTE: Under 502(f)(1), an API must have labeling that lists adequate directions for its use unless the API is subject to exemptions from labeling found in 201.122.

RECOMMENDING OFFICE:

DIOP (HFC-170)

REASON FOR ALERT:

OASIS records indicate that a large volume of bulk chemicals which can be used as APIs in human medicines that require NDAs, ANDAs, or INDS are being offered for entry into the U.S.

NDA - Imported APIs labeled for further manufacturing and processing or labeled as chemical substances are frequently destined for pharmaceutical processors that formulate finished drug products. These drug substances, consigned to individuals or processors who formulate and distribute human drugs, may be misbranded under Section 502(f)(1).

IND - Sponsors of investigational new drug applications frequently import from foreign countries either the dosage form or the API for use in laboratory research or clinical trials.

Some persons importing APIs have found that they could obtain entry of these articles if they simply supply an NDA or IND number at the point of entry. Districts should be alert to the possibility that: 1) the NDA or IND number provided does not cover the source of the particular API or 2) the persons importing the API have no authorization to refer to the particular NDA or IND number. In the past, the persons importing an API have referred to legitimate numbers to get their APIs released, but the APIs were not destined for use in the application referenced.

CDER and ORA are in the process of making the Establishment Evaluation System (EES) available to the field. When available, field offices should utilize EES to search and verify the status of an API, its manufacturer, whether it has been referenced in a valid NDA or whether it is the subject of a valid IND. Districts that do not have access to EES should contact Joseph E. Tracey, DIOP, 301-443-6553 to verify this status.

(OASIS entry records can be compared to CDER records for NDAs, ANDAs, and IND exemptions to verify the source and status of an API.)

EXEMPTION UNDER 21 CFR 201.122

API labeling invariably lacks adequate directions for use as required by Section 502(f)(1) of the Act. However, such drugs may be subject to an exemption under 21 CFR subpart 201.122. This regulation requires specific labeling on the package when adequate directions for use are missing, such as "Caution: For manufacturing, processing, or repacking."

However, the exemption under 21 CFR 201.122 will not apply to a substance intended for a use in the manufacture, processing, or repacking of the API which causes the finished article to be a new drug, unless:

A. an approved NDA covers the production and delivery of the API to the application holder by persons named in the application; or

B. if no application is approved with respect to the API, the label statement "Caution: For manufacturing, processing, or repacking" is immediately supplemented by the words "in the preparation of a new drug or new animal drug limited by Federal law to investigational use," and the delivery is made for use only in the manufacture of such new drug or new animal drug limited to investigational use as provided in 21 CFR part 312 or part 511.1.

The API/manufacture combinations listed in Attachment A appear to represent importations of APIs to be used for the manufacture, processing, or repacking of drugs which the Act and regulations require to be the subject of an approved NDA or a valid IND. However, either the person receiving the API or the person importing the API appears not to meet the statutory and/or regulatory requirements regarding labeling.

Further, it appears that the Agency has never inspected the declared manufacturer's GMPs for that imported API.

GUIDANCE:

Detain without physical examination the APIs from the manufacturers named in the attachment to this Import Alert.

Districts may detain without physical examination APIs from the persons listed in Attachment A because it appears that the API is misbranded based on its lack of adequate directions for use as required by section 502(f)(1) of the Act and its failure to meet the requirements of the exemption found in 201.122. Persons importing these APIs may obtain release of the detained articles if these persons can supply evidence establishing that the article is:

1. intended for pharmacy compounding that meets the requirements of section 503A of the Act, including that the API:
 - a. is accompanied by a valid certificate of analysis,
 - b. is manufactured by an establishment registered under section 510 of the Act, and

c. does not appear on a list of drugs identified in 21 CFR 216.24, that have been withdrawn or removed from the market for reasons of safety or effectiveness.

2. intended for use in the manufacture, processing, or repacking of an over-the-counter product or prescription product that does not require an NDA; or
3. a new animal drug, or intended for use in the manufacture, processing, or repacking of a new animal drug, subject to an NADA;

and, therefore, the API is not subject to this import alert.

OR

Persons importing APIs may obtain release of the detained articles by supplying evidence establishing that the article is:

1. intended for use in the manufacture, processing, or repacking of a human drug that is itself the subject of an approved NDA, and that the API is from the appropriate source; or
2. it is covered by IND requirements at 21 CFR 312.110(a).

For questions or issues concerning science, science policy, sample collection, analysis, preparation, or analytical methodology, contact the Division of Field Science at (301) 827-7605.

This guidance is not intended to address new animal drugs or investigational new animal drugs addressed by Import Alert number 68-09. If the imported APIs are intended for use in an NADA or INAD, refer to Import Alert number 68-09.

If the APIs are intended for the compounding of finished drugs by pharmacies, persons importing the APIs must comply with the requirements in 503A of the FDCA.

This guidance does not apply to excipients or APIs intended for use in OTC drugs or prescription drugs that do not require a new drug application.

PRIORITIZATION
GUIDANCE:

N/A

FOI:

No purging is required.

KEYWORDS:

NDA, IND, New Drugs, Bulk Drugs

PREPARED BY:

Ted Poplawski, DIOP, 301-443-6553

DATE LOADED

INTO FIARS:

OCTOBER 3, 2000

ATTACHMENT A FOR IMPORT ALERT# 66-66

(To see the up-to-date list of firms and products, please go to:
http://www.fda.gov/ora/fiars/ora_import_ia6666.html)