

# Guidance for Industry

## Submitting Debarment Certification Statements

### *DRAFT GUIDANCE*

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For questions on the content of the draft document contact Leanne Cusumano at 301-594-2041.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Center for Veterinary Medicine (CVM)

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# Guidance for Industry

## Submitting Debarment Certification Statements

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
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**GUIDANCE FOR INDUSTRY<sup>1</sup>**

**Submitting Debarment Certification Statements**

**I. INTRODUCTION**

Section 306(k) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 335a(k)), as amended by the Generic Drug Enforcement Act of 1992 (GDEA), requires that drug product applicants certify that they did not and will not use in any capacity the services of any debarred persons in connection with a drug product application. If the application is an abbreviated new drug application (ANDA), it must also include a list of all convictions described under section 306(a) and (b) of the Act (21 U.S.C. 335a(a) and (b)) that occurred within the previous 5 years and were committed by the applicant or affiliated persons responsible for the development or submission of the ANDA.

Since the passage of the GDEA, FDA has received requests for clarification of specific aspects of that part of the Act. As a result, the FDA has created this guidance to address the most common questions about the Act's certification and information requirements. The information presented here is drawn from the Act itself and from letters written by the FDA in response to specific questions.

**II. 306(k)(1) CERTIFICATION REQUIREMENTS**

Section 306(k)(1) of the Act states that "any application for approval of a drug product shall include a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [section 306(a) or (b)] in connection with such application."

**A. Applications Subject to the Certification Requirements of Section 306(k)(1)**

The following drug product applications received by the FDA on or after June 1, 1992, should include a certification statement:

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<sup>1</sup> This draft guidance has been prepared by the Debarment Task Force at the Food and Drug Administration (FDA). This guidance document represents the Agency's current thinking on debarment certification statements. 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 approach satisfies the requirements of the applicable statute, regulations, or both.

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- New drug applications (NDAs)
- Abbreviated new drug applications (ANDAs)
- New animal drug applications (NADAs)
- Abbreviated new animal drug applications (ANADAs)
- Export applications for certain unapproved products
- Biological license applications (PLAs and BLAs)
- Supplements to certain drug product applications

### **B. Wording of the Certification Statement**

The FDA regards the following wording, taken from section 306(k)(1) of the Act, as the most acceptable form of certification:

*[Name of the applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.*

Use of conditional or qualifying language, such as *to the best of my knowledge*, is unsatisfactory.

In the case of NADAs and ANADAs, applicants may simply sign the standard certification form 356-V provided by the Agency, which contains the preferred language for certification.

### **C. Domestic Agents**

Domestic agents should countersign the certification for foreign applicants they represent under 21 CFR 314.50(a)(5).

### **D. Persons Covered by the Certification**

Under the Act, the term *person* includes an individual, partnership, corporation, and association. The Agency regards *services* in connection with the application to include any services related to the collection, monitoring, evaluation, analysis, or reporting of data or information that appears or is specifically incorporated by reference in the application. Persons whose services were used in any capacity in connection with the application include, but are not limited to, the following:

- Employees of the applicant
- Certain contractors and their employees (e.g., contract research organizations whose studies were used in the application)

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- Certain subcontractors and their employees (e.g., consultants hired by a contract research organization)
- Clinical investigators
- Persons contributing data and information contained in a drug master file (DMF) or public master file (PMF), incorporated by reference in the application

### **E. Basis of Certification**

To ensure the accuracy of its certification, the applicant should check its list of employees and other persons with whom it does business against the list of debarred persons. This list is available upon written request from the Division of Compliance Policy (HFC-230), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857 and on the Internet at [http://www.fda.gov/ora/compliance\\_ref/debar/debar.txt](http://www.fda.gov/ora/compliance_ref/debar/debar.txt).

The applicant also may request certification statements from employees, contractors, subcontractors, clinical investigators, DMF or PMF holders, and the employees of such persons. The DMF or PMF holder may include a certification in the DMF or PMF, thereby allowing all referencing applicants to rely on that one certification, or the DMF or PMF holder may provide a separate certification to each applicant. The applicant's certification should pertain to all persons who have contributed data or information related to the collection, monitoring, evaluation, analysis, or reporting of data or information that appears or is specifically incorporated by reference in the application, regardless of whether such persons submit certifications directly to the FDA or to the applicant.

Because the statutory language of the certification statement is both retrospective and prospective (i.e., the applicant *did not* and *will not* use in any capacity the services of any person debarred in connection with the application), the applicant need not later obtain updated written statements from employees, contractors, and others, unless there is reason to believe that the original certification statement is incorrect or that the applicant has used, in connection with the application, amendment, or supplement, the services of a person not used in the previous submission. In such instances, the applicant has an ongoing duty to ensure the continued correctness of the certification.

### **F. Supplements**

Supplements to ANDAs that provide for a *different or additional* use of the drug are the only kind of supplement that should contain a certification.

For the purpose of this Guidance, supplements providing for a *different or additional use*

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of the drug are those that provide for a new use (1) not covered by the application approved for the listed drug and (2) supported by clinical data (i.e., a supplement providing for a new indication, dosage form, or strength that requires supporting clinical data). ANDA requests for approval of a new use not approved for the listed drug and supported by clinical data submitted under section 505(b)(2) of the Act (21 U.S.C. 355(b)(2)) are deemed *applications*, rather than *supplements*, and should include a certification.

For example, a supplement to an ANDA that improves the formulation or manufacturing process, changes ingredient suppliers, or proposes other production changes not requiring clinical data, does not require certification. A supplement to an ANDA that adds an indication to the labeling of the generic drug because exclusivity has expired for that indication need not contain a certification.

### **G. Scope of Debarment**

The Act prohibits a debarred individual from providing services in any capacity to a person that has an approved or pending drug product application (section 306(a)(2) and (b)(1) of the Act). The Agency has interpreted "services in any capacity" to mean any service provided to the drug applicant, regardless of whether related to drug regulation. That means a debarred individual may not provide non-drug-related services to a drug product applicant (e.g., as a landscaper, a computer software supplier, an accountant, a telephone repair person, a janitor, an interior decorator, a landlord) without violating debarment. Both the firm and individual are subject to substantial civil penalties for violation of this provision.

### **H. Scope of Certification**

The scope of certification under section 306(k) of the Act is narrower than the scope of debarment under section 306(a)(2) and (b)(1). Section 306(k) of the Act states that an applicant should certify that it did not and will not use in any capacity the services of a debarred person *in connection with such application*. Thus, the applicant should certify only with regard to any services received in connection with the application. FDA considers such services to include but not be limited to services related to the collection, monitoring, evaluation, analysis, or reporting of data or information that appears or is specifically incorporated by reference in the application.

Persons included in the certification include but are not limited to the applicant's own employees, contractors (e.g., a contract research organization used to run a study), subcontractors (e.g., a special consultant hired by a contract research organization), clinical investigators, DMF or PMF holders, and employees of such persons, regardless of whether foreign or domestic.

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An applicant using the services of a debarred person may certify that they have not used the services of a debarred person as long as the services provided by the debarred person were not provided in connection with the application. However, under section 307(a) of the Act (21 U.S.C. 335b(a)), both the applicant using the services of a debarred person in any capacity and the debarred person may be subject to substantial civil money penalties.

### **I. Limitations on Stock Ownership of Debarred Persons**

A debarred person may own stock in a firm that has an approved or pending drug product application, but may not participate in any capacity in business decisions or operations of such a firm (e.g., participating in shareholder voting) without violating debarment.

In addition, if a debarred person exercises any control over business decisions or operations of a firm that has an approved or pending drug product application, for example, via shares owned by someone other than the debarred person (i.e., any member of the debarred person's family, or any other individual, partnership, corporation, or association), the FDA will regard the debarred person as providing services to a drug product applicant in violation of debarment. In such instances, both the firm and the debarred person would be subject to substantial civil money penalties for violation of debarment.

### **J. Investigational Drugs**

Applications for investigational drugs described under 21 CFR 312.40 (INDs), 21 CFR 312.110(a) (import INDs), 21 CFR 312.110(b) (export INDs), or 21 CFR 511.1 (INADs) do not require a certification statement because INDs and INADs are not considered drug product applications under the GDEA. INDs and INADs are submitted for the purpose of clinical research. However, it should be noted that the certification required in a drug application for approval (e.g., an NDA) precludes the use of a debarred person in connection with any IND associated with that application.

### **K. Over-the-Counter (OTC) Monograph Drugs**

The certification requirement applies to any application for approval of a drug product. A monograph is *not* an application; thus, drugs marketed under the conditions of an OTC monograph are not subject to the certification requirement.

### **L. Biologics License Applications**

Upon submission of an application for approval of a biological drug product by the single biologics license application (BLA) (§ 351(a) of the Public Health Service Act), an applicant would be asked to certify that no debarred person was used in connection with the application. This certification, if truthful, would preclude the use of a debarred

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person in connection with both the establishment and the application.

### **M. Debarment Status**

If the services of a debarred person were used in connection with the application prior to that person's debarment or after termination of debarment, a firm could still properly certify because the person was not debarred at the time his or her services were rendered. However, data generated by a person prior to the person's debarment, or data generated after termination by a formerly debarred person, may be subject to closer examination by the Agency. Therefore, the applicant should inspect and ensure the integrity of such data.

### **III. 306(k)(2) CONVICTION INFORMATION REQUIREMENTS**

Section 306(k)(2) of the Act states that “any application for approval of a drug product shall include . . . if such application is an abbreviated drug application, a list of all convictions, described in subsections (a) and (b) [section 306(a) and (b)] which occurred within the previous 5 years, of the applicant and affiliated persons responsible for the development or submission of such application.”

#### **A. Applications Subject to the Conviction Information Requirement**

The Act requires that ANDAs and supplements to ANDAs providing for a *different or additional use* and submitted on or after June 1, 1992, contain a list of all convictions within the previous 5 years<sup>2</sup> committed by the applicant and affiliated persons responsible for the development or submission of such application.

The section 306(k)(2) requirement for conviction information in ANDA supplements for a *different or additional use* is limited to those supplements that provide for a new use (1) not covered by the application approved for the listed drug and (2) supported by clinical data (i.e., supplements providing for a new indication, dosage form, or strength that requires supporting clinical data). ANDA requests for approval of a new use, not approved for the listed drug and not supported by clinical data, submitted under section 505(b)(2) of the Act are deemed *applications*, rather than *supplements*, and should include conviction information.

Note that a supplement to an ANDA that adds an indication to the labeling of the generic

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<sup>2</sup> Section 306(a) and (b) describes *types* of convictions that fall under the scope of the debarment provisions in very broad terms. Therefore, the FDA cannot provide a definitive list of such offenses or a list of all individuals and businesses with convictions for such offenses.

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drug because exclusivity has expired for that indication need not contain conviction information. A supplement to an ANDA that improves the formulation or manufacturing process, changes ingredient suppliers, or proposes other production changes does not require conviction information, unless the supplement contains clinical data.

### **B. Definition of an Affiliated Person**

An *affiliated person* for whom an applicant for approval of an ANDA should provide conviction information includes any individual, partnership, corporation, or association, including employees thereof, involved with development or submission of data that (1) are used to obtain approval of an application and (2) relate to the manufacturing, processing, or testing of the active ingredient(s) or the finished dosage form(s).

The ANDA applicant should provide conviction information for persons falling within the scope of this definition. Generally, the conviction information provided by an applicant for approval of an ANDA pertains to employees of the applicant, contractors, subcontractors, and so on, responsible for the development or submission of the abbreviated application because such persons are within the meaning of *affiliated person*. Some examples follow.

1. Clinical investigators, nurses, technicians, and other parties involved with the development or submission of data related to clinical studies: These are *affiliated persons*.
2. CGMP record keepers: Because the FDA reviews CGMP records when determining whether to grant or continue approval of a drug product, persons who develop and record CGMP data related to the manufacturing, processing, or testing of the active ingredient(s) or the finished dosage form(s) are *affiliated persons*.
3. Commercial manufacturing facility workers: Such persons are *affiliated persons* if they are involved in the development or submission of records or data that are used to obtain and maintain approval of an application or relate to the manufacturing, processing, or testing of the active ingredient(s) or the finished dosage form(s). For example, persons recording and generating data solely for the approved commercial product are *affiliated persons* because FDA reviews such records in determining whether to grant or continue approval of a drug product.
4. Persons working on drug master files (DMFs) or public master files (PMFs): Persons recording and generating data for DMFs or PMFs that are relied on to support approval and that relate to, for example, the manufacturing, processing, or testing of the active ingredient(s) or finished dosage form(s), come within the definition of *affiliated person*.

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5. Secretaries: If the secretary merely transcribes data, the secretary is not regarded as an *affiliated person* within the intended definition of the Act. In the rare instances that the secretary may develop data used to obtain approval, that secretary is an *affiliated person*.

6. Janitors, packers, production crew, and assembly persons: As long as these persons do not develop or submit data, they are not *affiliated persons*.

### **C. Contents of Conviction Information**

The list of convictions should include the following information:

- The name(s) of the convicted persons(s)
- The title and section of the Federal or State statute involved
- The date of the conviction (for which a person can be debarred, as described in section 306(a) and (b), that occurred within 5 years before the date of the application)
- The date of sentencing
- The court entering judgment
- The case number, if known
- A brief description of the offense
- The role of the person in the development or submission of the application
- The time period of the person's involvement in the development of the application

### **D. Basis of Conviction Information**

Background checks are not necessary. The applicant may request conviction information received from the applicant's affiliated persons.

Under the Act (section 306(k)(2)), conviction information is required for persons no longer working for the firm, but who were affiliated persons involved with the development or submission of the application. However, if the applicant cannot ascertain conviction information for all affiliated persons because of unavailability of the person(s), the FDA may accept the names and job titles of such people (including a description of the responsibilities that person had concerning the application) together with an

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explanation of why the person is unavailable (e.g., the person died or the person no longer works for the firm and reasonable efforts to locate the person have proven unsuccessful) and a statement that the applicant has no knowledge that the person has been convicted of any offense(s) for which a person can be debarred.

### **E. Effect on Review Process**

If the conviction information provided raises a question concerning the integrity of the data or information contained in the application for which the certification is submitted, or in any other application, the application(s) may be subject to closer Agency scrutiny.

## **IV. MISCELLANEOUS 306(k) CERTIFICATION AND CONVICTION INFORMATION REQUIREMENTS**

### **A. Amendments to Pending Drug Product Applications**

As long as the original application contains the required statement of certification and/or conviction information, there is no need to resubmit such statements in amendments described under 21 CFR 314.60(a). However, the applicant has an ongoing duty to ensure the continued correctness of the certification and conviction information. Therefore, if the original statement becomes incorrect (i.e., the applicant has used the services of a debarred or convicted person not used in the previous submission), the applicant has a responsibility to correct the certification and/or conviction information in the amendment as soon as possible.

### **B. Effective Date of Certification and Conviction Information Requirements**

Drug product applications, including certain supplements submitted on or after June 1, 1992, are subject to the certification and/or conviction information requirements.

### **C. Placement in the Application**

The certification and/or conviction information should appear at the beginning of the application and be clearly identified. The applicant may indicate the placement of the information in the table of contents. In the case of an NADA or ANADA, a standard certification form 356-V is provided by the Agency; thus the placement of the certification statement in such applications is already established.

### **D. Missing or Incorrect Information**

If a drug product application, amendment, or supplement submitted on or after June 1, 1992, lacks or contains incorrect certification or conviction information, the applicant

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should amend the application, amendment, or supplement to include or correct the certification or conviction information as soon as possible. Since February 25, 1993, the FDA has not accepted for filing ANDAs that do not contain certification and conviction information. The applicant has an ongoing duty to ensure that the certification or conviction information is correct.

**E. Signature**

The certification and/or conviction information should be signed by a responsible officer of the applicant or by the individual responsible for signing the application.

**V. REFERENCES**

The Generic Drug Enforcement Act of 1992, section 306 (21 U.S.C. 335a).

July 27, 1992, guidance letter from FDA's Deputy Commissioner for Operations.

April 8, 1994, letter from FDA's Acting Director for the Office of Generic Drugs, CDER.

January 15, 1993, letter from FDA's Director for the Office of Generic Drugs, CDER.

Docket #98 D - 0713

Index to Docket

Draft Guidance for Industry For the Submission of Debarment Certification Statements and other Information Under the Generic Drug Enforcement Act of 1992

*References*

- Exhibit 1. The Generic Drug Enforcement Act of 1992, section 306 (21 U.S.C. 335a).
- Exhibit 2. July 27, 1992, guidance letter from FDA's Deputy Commissioner for Operations.
- Exhibit 3. April 8, 1994, letter from FDA's Acting Director for the Office of Generic Drugs, CDER.
- Exhibit 4. January 15, 1993, letter from FDA's Director for the Office of Generic Drugs, CDER.



in which case he may authorize a detention period of not to exceed thirty days. Regulations of the Secretary prescribed under this paragraph shall require that before a device may be ordered detained under this paragraph the Secretary or an officer or employee designated by the Secretary approve such order. A detention order under this paragraph may require the labeling or marking of a device during the period of its detention for the purpose of identifying the device as detained. Any person who would be entitled to claim a device if it were seized under subsection (a) may appeal to the Secretary a detention of such device under this paragraph. Within five days of the date an appeal of a detention is filed with the Secretary, the Secretary shall after affording opportunity for an informal hearing by order confirm the detention or revoke it.

(2) —

(A) Except as authorized by subparagraph (B), a device subject to a detention order issued under paragraph (1) shall not be moved by any person from the place at which it is ordered detained until—

- (i) released by the Secretary, or
- (ii) the expiration of the detention period applicable to such order, whichever occurs first.

(B) A device subject to a detention order under paragraph (1) may be moved—

- (i) in accordance with regulations prescribed by the Secretary, and
- (ii) if not in final form for shipment, at the discretion of the manufacturer of the device for the purpose of completing the work required to put it in such form.

**SEC. 305. [335]. HEARING BEFORE REPORT OF CRIMINAL VIOLATION.**

Before any violation of this Act is reported by the Secretary to any United States attorney for institution of a criminal proceeding, the person against whom such proceeding is contemplated shall be given appropriate notice and an opportunity to present his views, either orally or in writing, with regard to such contemplated proceeding.

**SEC. 306. [335a]. DEBARMENT, TEMPORARY DENIAL OF APPROVAL, AND SUSPENSION.**

(a) **MANDATORY DEBARMENT.**—

(1) **CORPORATIONS, PARTNERSHIPS, AND ASSOCIATIONS.**—If the Secretary finds that a person other than an individual has been convicted, after the date of the enactment of this section, of a felony under Federal law for conduct relating to the development or approval, including the process for development or approval, of any abbreviated drug application, the Secretary shall debar such person from submitting, or assisting in the submission of, any such application.

(2) **INDIVIDUALS.**—If the Secretary finds that an individual has been convicted of a felony under Federal law for conduct—

- (A) relating to the development or approval, including the process for development or approval, of any drug product, or
  - (B) otherwise relating to the regulation of any drug product under this Act,
- the Secretary shall debar such individual from providing services in any capacity to a person that has an approved or pending drug product application.

(b) **PERMISSIVE DEBARMENT.**—

(1) **IN GENERAL.**—The Secretary, on the Secretary's own initiative or in response to a petition, may, in accordance with paragraph (2), debar—

- (A) a person other than an individual from submitting or assisting in the submission of any abbreviated drug application, or
- (B) an individual from providing services in any capacity to a person that has an approved or pending drug product application.

(2) **PERSONS SUBJECT TO PERMISSIVE DEBARMENT.**—The following persons are subject to debarment under paragraph (1):

(A) **CORPORATIONS, PARTNERSHIPS, AND ASSOCIATIONS.**—Any person other than an individual that the Secretary finds has been convicted—

(i) for conduct that—

- (I) relates to the development or approval, including the process for the development or approval, of any abbreviated drug application; and
- (II) is a felony under Federal law (if the person was convicted before the date of the enactment of this section), a misdemeanor under Federal law, or a felony under State law, or

(ii) of a conspiracy to commit, or aiding or abetting, a criminal offense described in clause (i) or a felony described in subsection (a)(1),

if the Secretary finds that the type of conduct which served as the basis for such conviction undermines the process for the regulation of drugs.

(B) **INDIVIDUALS.**—

(i) Any individual whom the Secretary finds has been convicted of—

- (I) a misdemeanor under Federal law or a felony under State law for conduct relating to the development or approval, including the process for development or approval, of any drug product or otherwise relating to the regulation of drug products under this Act, or
- (II) a conspiracy to commit, or aiding or abetting, such criminal offense or a felony described in subsection (a)(2),

if the Secretary finds that the type of conduct which served as the basis for such conviction undermines the process for the regulation of drugs.

(ii) Any individual whom the Secretary finds has been convicted of—

- (I) a felony which is not described in subsection (a)(2) or clause (i) of this subparagraph and which involves bribery, payment of illegal gratuities, fraud, perjury, false statement, racketeering, blackmail, extortion, falsification or destruction of records, or interference with, obstruction of an investigation into, or prosecution of, any criminal offense, or
- (II) a conspiracy to commit, or aiding or abetting, such felony,

if the Secretary finds, on the basis of the conviction of such individual and other information, that such individual has demonstrated a pattern of conduct sufficient to find that there is reason to believe that such individual may violate requirements under this Act relating to drug products.

(iii) Any individual whom the Secretary finds materially participated in acts that were the basis for a conviction for an offense described in subsection (a) or in clause (i) or (ii) for which a conviction was obtained, if the Secretary finds, on the basis of such participation and other information, that such individual has demonstrated a pattern of conduct sufficient to find that there is reason to believe that such individual may violate requirements under this Act relating to drug products.

(iv) Any high managerial agent whom the Secretary finds—

- (I) worked for, or worked as a consultant for, the same person as another individual during the period in which such other individual took actions for which a felony

conviction was obtained and which resulted in the debarment under subsection (a)(2), or clause (i), of such other individual,  
 (II) had actual knowledge of the actions described in subclause (I) of such other individual, or took action to avoid such actual knowledge, or failed to take action for the purpose of avoiding such actual knowledge,  
 (III) knew that the actions described in subclause (I) were violative of law, and  
 (IV) did not report such actions, or did not cause such actions to be reported, to an officer, employee, or agent of the Department or to an appropriate law enforcement officer, or failed to take other appropriate action that would have ensured that the process for the regulation of drugs was not undermined, within a reasonable time after such agent first knew of such actions,

if the Secretary finds that the type of conduct which served as the basis for such other individual's conviction undermines the process for the regulation of drugs.

(3) **STAY OF CERTAIN ORDERS.**—An order of the Secretary under clause (iii) or (iv) of paragraph (2)(B) shall not take effect until 30 days after the order has been issued.

(c) **DEBARMENT PERIOD AND CONSIDERATIONS.**—

(1) **EFFECT OF DEBARMENT.**—The Secretary—

(A) shall not accept or review (other than in connection with an audit under this section) any abbreviated drug application submitted by or with the assistance of a person debarred under subsection (a)(1) or (b)(2)(A) during the period such person is debarred,

(B) shall, during the period of a debarment under subsection (a)(2) or (b)(2)(B), debar an individual from providing services in any capacity to a person that has an approved or pending drug product application and shall not accept or review (other than in connection with an audit under this section) an abbreviated drug application from such individual, and

(C) shall, if the Secretary makes the finding described in paragraph (6) or (7) of section 307(a), assess a civil penalty in accordance with section 307.

(2) **DEBARMENT PERIODS.**—

(A) **IN GENERAL.**—The Secretary shall debar a person under subsection (a) or (b) for the following periods:

(i) the period of debarment of a person (other than an individual) under subsection (a)(1) shall not be less than 1 year or more than 10 years, but if an act leading to a subsequent debarment under subsection (a) occurs within 10 years after such person has been debarred under subsection (a)(1), the period of debarment shall be permanent.

(ii) The debarment of an individual under subsection (a)(2) shall be permanent.

(iii) The period of debarment of any person under subsection (b)(2) shall not be more than 5 years.

The Secretary may determine whether debarment periods shall run concurrently or consecutively in the case of a person debarred for multiple offenses.

(B) **NOTIFICATION.**—Upon a conviction for an offense described in subsection (a) or (b) or upon execution of an agreement with the United States to plead guilty to such an offense, the person involved may notify the Secretary that the person acquiesces to debarment and such person's debarment shall commence upon such notification.

(3) **CONSIDERATIONS.**—In determining the appropriateness and the period of a debarment of a person under subsection (b) and any period of debarment beyond the minimum specified in subparagraph (A)(i) of paragraph (2), the Secretary shall consider where applicable—

(A) the nature and seriousness of any offense involved,

(B) the nature and extent of management participation in any offense involved, whether corporate policies and practices encouraged the offense, including whether inadequate institutional controls contributed to the offense,

(C) the nature and extent of voluntary steps to mitigate the impact on the public of any offense involved, including the recall or the discontinuation of the distribution of suspect drugs, full cooperation with any investigations (including the extent of disclosure to appropriate authorities of all wrongdoing), the relinquishing of profits on drug approvals fraudulently obtained, and any other actions taken to substantially limit potential or actual adverse effects on the public health,

(D) whether the extent to which changes in ownership, management, or operations have corrected the causes of any offense involved and provide reasonable assurances that the offense will not occur in the future,

(E) whether the person to be debarred is able to present adequate evidence that current production of drugs subject to abbreviated drug applications and all pending abbreviated drug applications are free of fraud or material false statements, and

(F) prior convictions under this Act or under other Acts involving matters within the jurisdiction of the Food and Drug Administration.

**(d) TERMINATION OF DEBARMENT.—**

(1) **APPLICATION.**—Any person that is debarred under subsection (a) (other than a person permanently debarred) or any person that is debarred under subsection (b) may apply to the Secretary for termination of the debarment under this subsection. Any information submitted to the Secretary under this paragraph does not constitute an amendment or supplement to pending or approved abbreviated drug applications.

(2) **DEADLINE.**—The Secretary shall grant or deny any application respecting a debarment which is submitted under paragraph (1) within 180 days of the date the application is submitted.

**(3) ACTION BY THE SECRETARY.—**

**(A) CORPORATIONS.—**

(i) **CONVICTION REVERSAL.**—If the conviction which served as the basis for the debarment of a person under subsection (a)(1) or (b)(2)(A) is reversed, the Secretary shall withdraw the order of debarment.

(ii) **APPLICATION.**—Upon application submitted under paragraph (1), the Secretary shall terminate the debarment of a person if the Secretary finds that—

(I) changes in ownership, management, or operations have fully corrected the causes of the offense involved and provide reasonable assurances that the offense will not occur in the future, and

(II) sufficient audits, conducted by the Food and Drug Administration or by independent experts acceptable to the Food and Drug Administration, demonstrate that pending applications and the development of drugs being tested before the submission of an application are free of fraud or material false statements.

In the case of persons debarred under subsection (a)(1), such termination shall take effect no earlier than the expiration of one year from the date of the debarment.

**(B) INDIVIDUALS.—**

(i) **CONVICTION REVERSAL.**—If the conviction which served as the basis for the debarment of an individual under subsection (a)(2) or clause (i), (ii), (iii), or (iv) of subsection (b)(2)(B) is reversed, the Secretary shall withdraw the order of debarment.

(ii) **APPLICATION.**—Upon application submitted under paragraph (1), the Secretary shall terminate the debarment of an individual who has been debarred under subsection (b)(2)(B) if such termination serves the interests of justice and adequately protects the integrity of the drug approval process.

(4) **SPECIAL TERMINATION.**—

(A) **APPLICATION.**—Any person that is debarred under subsection (a)(1) (other than a person permanently debarred under subsection (c)(2)(A)(i)) or any individual who is debarred under subsection (a)(2) may apply to the Secretary for special termination of debarment under this subsection. Any information submitted to the Secretary under this subparagraph does not constitute an amendment or supplement to pending or approved abbreviated drug applications.

(B) **CORPORATIONS.**—Upon an application submitted under subparagraph (A), the Secretary may take the action described in subparagraph (D) if the Secretary, after an informal hearing, finds that—

(i) the person making the application under subparagraph (A) has demonstrated that the felony conviction which was the basis for such person's debarment involved the commission of an offense which was not authorized, requested, commanded, performed, or recklessly tolerated by the board of directors or by a high managerial agent acting on behalf of the person within the scope of the board's or agent's office or employment,

(ii) all individuals who were involved in the commission of the offense or who knew or should have known of the offense have been removed from employment involving the development or approval of any drug subject to section 505 or 507,

(iii) the person fully cooperated with all investigations and promptly disclosed all wrongdoing to the appropriate authorities, and

(iv) the person acted to mitigate any impact on the public of any offense involved, including the recall, or the discontinuation of the distribution, of any drug with respect to which the Secretary requested a recall or discontinuation of distribution due to concerns about the safety or efficacy of the drug.

(C) **INDIVIDUALS.**—Upon an application submitted under subparagraph (A), the Secretary may take the action described in subparagraph (D) if the Secretary, after an informal hearing, finds that such individual has provided substantial assistance in the investigations or prosecutions of offenses which are described in subsection (a) or (b) or which relate to any matter under the jurisdiction of the Food and Drug Administration.

(D) **SECRETARIAL ACTION.**—The action referred to in subparagraphs (B) and (C) is—

(i) in the case of a person other than an individual—

(I) terminating the debarment immediately, or

(II) limiting the period of debarment to less than one year, and

(ii) in the case of an individual, limiting the period of debarment to less than permanent but to no less than 1 year,

whichever best serves the interest of justice and protects the integrity of the drug approval process.

(e) **PUBLICATION AND LIST OF DEBARRED PERSONS.**—The Secretary shall publish in the Federal Register the name of any person debarred under subsection (a) or (b), the effective date of the debarment, and the period of the debarment. The Secretary shall also maintain and make available to the public a list, updated no less often than quarterly, of such persons, of the effective dates and minimum periods of such debarments, and of the termination of debarments.

**(f) TEMPORARY DENIAL OF APPROVAL.—**

(1) **IN GENERAL.**—The Secretary, on the Secretary's own initiative or in response to a petition, may, in accordance with paragraph (3), refuse by order, for the period prescribed by paragraph (2), to approve any abbreviated drug application submitted by any person—

(A) if such person is under an active Federal criminal investigation in connection with an action described in subparagraph (B),

(B) if the Secretary finds that such person—

(i) has bribed or attempted to bribe, has paid or attempted to pay an illegal gratuity, or has induced or attempted to induce another person to bribe or pay an illegal gratuity to any officer, employee, or agent of the Department of Health and Human Services or to any other Federal, State, or local official in connection with any abbreviated drug application, or has conspired to commit, or aided or abetted, such actions, or

(ii) has knowingly made or caused to be made a pattern or practice of false statements or misrepresentations with respect to material facts relating to any abbreviated drug application, or the production of any drug subject to an abbreviated drug application, to any officer, employee, or agent of the Department of Health and Human Services, or has conspired to commit, or aided or abetted, such actions, and

(C) if a significant question has been raised regarding—

(i) the integrity of the approval process with respect to such abbreviated drug application, or

(ii) the reliability of data in or concerning such person's abbreviated drug application.

Such an order may be modified or terminated at any time.

**(2) APPLICABLE PERIOD.—**

(A) **IN GENERAL.**—Except as provided in subparagraph (B), a denial of approval of an application of a person under paragraph (1) shall be in effect for a period determined by the Secretary but not to exceed 18 months beginning on the date the Secretary finds that the conditions described in subparagraphs (A), (B), and (C) of paragraph (1) exist. The Secretary shall terminate such denial—

(i) if the investigation with respect to which the finding was made does not result in a criminal charge against such person, if criminal charges have been brought and the charges have been dismissed, or if a judgment of acquittal has been entered, or

(ii) if the Secretary determines that such finding was in error.

(B) **EXTENSION.**—If, at the end of the period described in subparagraph (A), the Secretary determines that a person has been criminally charged for an action described in subparagraph (B) of paragraph (1), the Secretary may extend the period of denial of approval of an application for a period not to exceed 18 months. The Secretary shall terminate such extension if the charges have been dismissed, if a judgment of acquittal has been entered, or if the Secretary determines that the finding described in subparagraph (A) was in error.

(3) **INFORMAL HEARING.**—Within 10 days of the date an order is issued under paragraph (1), the Secretary shall provide such person with an opportunity for an informal hearing, to be held within such 10 days, on the decision of the Secretary to refuse approval of an abbreviated drug application. Within 60 days of the date on which such hearing is held, the Secretary shall notify the person given such hearing whether the Secretary's refusal of approval will be continued, terminated, or otherwise modified. Such notification shall be final agency action.

**(g) SUSPENSION AUTHORITY.—****(1) IN GENERAL.—If—****(A) the Secretary finds—**

(i) that a person has engaged in conduct described in subparagraph (B) of subsection (f)(1) in connection with 2 or more drugs under abbreviated drug applications, or

(ii) that a person has engaged in flagrant and repeated, material violations of good manufacturing practice or good laboratory practice in connection with the development, manufacturing, or distribution of one or more drugs approved under an abbreviated drug application during a 2-year period, and—

(I) such violations may undermine the safety and efficacy of such drugs, and

(II) the causes of such violations have not been corrected within a reasonable period of time following notice of such violations by the Secretary, and

**(B)** such person is under an active investigation by a Federal authority in connection with a civil or criminal action involving conduct described in subparagraph (A),

the Secretary shall issue an order suspending the distribution of all drugs the development or approval of which was related to such conduct described in subparagraph (A) or suspending the distribution of all drugs approved under abbreviated drug applications of such person if the Secretary finds that such conduct may have affected the development or approval of a significant number of drugs which the Secretary is unable to identify. The Secretary shall exclude a drug from such order if the Secretary determines that such conduct was not likely to have influenced the safety or efficacy of such drug.

**(2) PUBLIC HEALTH WAIVER.—**The Secretary shall, on the Secretary's own initiative or in response to a petition, waive the suspension under paragraph (1) (involving an action described in paragraph (1)(A)(i)) with respect to any drug if the Secretary finds that such waiver is necessary to protect the public health because sufficient quantities of the drug would not otherwise be available. The Secretary shall act on any petition seeking action under this paragraph within 180 days of the date the petition is submitted to the Secretary.

**(h) TERMINATION OF SUSPENSION.—**The Secretary shall withdraw an order of suspension of the distribution of a drug under subsection (g) if the person with respect to whom the order was issued demonstrates in a petition to the Secretary—

**(1) —**

**(A)** on the basis of an audit by the Food and Drug Administration or by experts acceptable to the Food and Drug Administration, or on the basis of other information, that the development, approval, manufacturing, and distribution of such drug is in substantial compliance with the applicable requirements of this Act, and

**(B)** changes in ownership, management, or operations—

(i) fully remedy the patterns or practices with respect to which the order was issued, and

(ii) provide reasonable assurances that such actions will not occur in the future, or

**(2)** the initial determination was in error.

The Secretary shall act on a submission of a petition under this subsection within 180 days of the date of its submission and the Secretary may consider the petition concurrently with the suspension proceeding. Any information submitted to the Secretary under this subsection does not constitute an amendment or supplement to a pending or approved abbreviated drug application.

(i) **PROCEDURE.**—The Secretary may not take any action under subsection (a), (b), (c), (d)(3), (g), or (h) with respect to any person unless the Secretary has issued an order for such action made on the record after opportunity for an agency hearing on disputed issues of material fact. In the course of any investigation or hearing under this subsection, the Secretary may administer oaths and affirmations, examine witnesses, receive evidence, and issue subpoenas requiring the attendance and testimony of witnesses and the production of evidence that relates to the matter under investigation.

(j) **JUDICIAL REVIEW.**—

(1) **IN GENERAL.**—Except as provided in paragraph (2), any person that is the subject of an adverse decision under subsection (a), (b), (c), (d), (f), (g), or (h) may obtain a review of such decision by the United States Court of Appeals for the District of Columbia or for the circuit in which the person resides, by filing in such court (within 60 days following the date the person is notified of the Secretary's decision) a petition requesting that the decision be modified or set aside.

(2) **EXCEPTION.**—Any person that is the subject of an adverse decision under clause (iii) or (iv) of subsection (b)(2)(B) may obtain a review of such decision by the United States District Court for the District of Columbia or a district court of the United States for the district in which the person resides, by filing in such court (within 30 days following the date the person is notified of the Secretary's decision) a complaint requesting that the decision be modified or set aside. In such an action, the court shall determine the matter de novo.

(k) **CERTIFICATION.**—Any application for approval of a drug product shall include—

(1) a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsection (a) or (b), in connection with such application, and

(2) if such application is an abbreviated drug application, a list of all convictions, described in subsections (a) and (b) which occurred within the previous 5 years, of the applicant and affiliated persons responsible for the development or submission of such application.

(l) **APPLICABILITY.**—

(1) **CONVICTION.**—For purposes of this section, a person is considered to have been convicted of a criminal offense—

(A) when a judgment of conviction has been entered against the person by a Federal or State court, regardless of whether there is an appeal pending,

(B) when a plea of guilty or nolo contendere by the person has been accepted by a Federal or State court, or

(C) when the person has entered into participation in a first offender, deferred adjudication, or other similar arrangement or program where judgment of conviction has been withheld.

(2) **EFFECTIVE DATES.**—Subsection (a), subparagraph (A) of subsection (b)(2), and clauses (i) and (ii) of subsection (b)(2)(B) shall not apply to a conviction which occurred more than 5 years before the initiation of an agency action proposed to be taken under subsection (a) or (b). Clauses (iii) and (iv) of subsection (b)(2)(B) and subsections (f) and (g) shall not apply to an act or action which occurred more than 5 years before the initiation of an agency action proposed to be taken under subsection (b), (f), or (g). Clause (iv) of subsection (b)(2)(B) shall not apply to an action which occurred before June 1, 1992. Subsection (k) shall not apply to applications submitted to the Secretary before June 1, 1992.

2



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

JUL 29 1992

Food and Drug Administration  
Rockville MD 20857

TO ALL NDA, ANDA, AADA, AND EXPORT APPLICATION HOLDERS AND APPLICANTS:

Dear Sir or Madam:

Attached for your information is a copy of a letter, from Jane E. Henney, M.D., FDA's Deputy Commissioner for Operations, sent to trade associations representing the drug manufacturing industry. The letter discusses the new certification and information requirements imposed by the Generic Drug Enforcement Act of 1992. Dr. Henney's letter provides a detailed description of what the new certification and information provisions require as well as guidance on how to comply with those provisions, pending FDA's issuance of regulations.

Please note that the certification and information provisions of the new law went into effect on June 1, 1992. Therefore, in order to avoid delays in agency action on drug product applications, I request that you amend, no later than December 1, 1992, any pending NDA's, ANDA's, and AADA's, received by FDA on or after June 1, 1992, that do not contain these documents. In addition, please, submit the appropriate documents in all of your future applications.

The agency is required to act on Export Applications in a shorter period of time than it must act on the applications discussed above. Therefore, in order to avoid delays in agency action on Export Applications, I request that you immediately amend any pending applications submitted on or after June 1, 1992, and that you submit the appropriate certification statement in all of your future applications.

I hope that Dr. Henney's letter will assist you in meeting the new requirements. If you have any questions or comments about the Center for Drug Evaluation and Research's implementation of the Generic Drug Enforcement Act, I encourage you to call or write our Division of Regulatory Affairs at 7500 Standish Pl., Rockville, MD 20855 (301-295-8041).

Thank you for your timely attention to these important matters.

Sincerely yours,

Daniel L. Michels  
Director  
Office of Compliance  
Center for Drug Evaluation  
and Research

Attachment



July 27, 1992

Food and Drug Administration  
Rockville MD 20857**Drug Manufacturer/Industry Association:**

As you are undoubtedly aware, Congress recently passed the Generic Drug Enforcement Act of 1992. The law authorizes FDA to debar an individual, convicted of certain crimes or found to have engaged in certain types of conduct, from providing any services to a drug product applicant. The law also authorizes FDA to debar a firm convicted of certain crimes from obtaining or participating in certain subsequent drug approvals.

I am writing to you today about the certification provisions of the new law. These provisions require applicants for drug product approval to certify that they did not and will not use the services of debarred individuals or firms. The provisions also require that applicants for approval of certain generic drugs provide information on the criminal convictions of individuals and firms involved in the applications.

While the new certification and information provisions went into effect automatically on June 1, 1992, FDA has not yet had an opportunity to issue regulations implementing the new law. This letter is intended to provide interim guidance on how to comply with the requirements, pending the development of regulations. The information provided in this letter represents FDA's current interpretation of the new certification and information requirements. Please be aware, however, that we are open to modifying these views based on our experience implementing the law and on comments received from the industry and other interested members of the public.

**1. CERTIFICATION REQUIREMENT FOR ALL APPLICATIONS FOR APPROVAL OF A DRUG PRODUCT**

Under the new law, any application for approval of a drug product submitted on or after June 1, 1992, must include --

"a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with such application."

Section 306(k)(1) of the act (21 U.S.C 335a(k)(1)).

Under the definition of "drug product" provided by the legislation, the following drug product applications received by FDA on or after June 1, 1992, must contain the certification described above:

- \* New drug applications (NDA's),
- \* Abbreviated new drug applications (ANDA's),
- \* Antibiotic drug applications,
- \* Abbreviated antibiotic drug applications (AADA's),
- \* New animal drug applications (NADA's),
- \* Abbreviated new animal drug applications (ANADA's),
- \* Export applications for certain unapproved products, and
- \* Biological product license applications (PLA's).

(See section 201(ee) of the act (21 U.S.C. 321(ee)) (a "drug product" is a drug subject to regulation under section 505, 507, 512, or 802 of the act, or under section 351 of the Public Health Service Act).)

Please note that FDA has not yet debarred any individual or firm. Any order debaring an individual or a firm will be published in the Federal Register. The order will identify the debarred individual or firm, and specify the effective date and period of debarment. In addition, FDA's Office of Regulatory Affairs will maintain a publicly available list with similar information about all debarred individuals and firms.

**2. ADDITIONAL INFORMATION REQUIREMENT FOR ANDA'S AND AADA'S**

In addition to the certification described above, the new law requires that the following abbreviated drug applications submitted on or after June 1, 1992, contain additional information about convictions:

- \* Original ANDA's,
- \* Original AADA's, and
- \* Supplements to ANDA's or AADA's that provide for a different or additional use of a drug (i.e., supplements that provide for a new indication not covered by the listed drug).

Section 306(k)(2) of the act (21 U.S.C. 335a(k)(2)).

The additional information is a list of all convictions, for which a person can be debarred, of the applicant and affiliated persons responsible for the development or submission of the application. These convictions are described in section 306(a) and (b). The list must contain all such convictions that occurred within 5 years before the date of the application.

At this time, FDA interprets the statutory phrase "affiliated person responsible for the development or submission of an abbreviated drug application" to include any individual, partnership, corporation, or association responsible for the development or submission of records or data that (1) are used to obtain approval of an application and (2) relate to the manufacturing, processing, or testing of the active ingredient(s) or the finished dosage form(s). This includes records and data submitted to an application, original or supporting information for the submitted records and data, as well as records and data required to be maintained at a firm under current good manufacturing practice requirements (21 U.S.C. 351(a)(2)(B) and 21 CFR Parts 210 and 211).

For purposes of complying with this requirement, the manufacturing of a finished dosage form includes, but is not limited to, any of the following operations: (1) mixing, (2) granulating, (3) milling, (4) molding, (5) lyophilizing, (6) tableting, (7) encapsulating, (8) coating, (9) sterilizing, or (10) filling sterile, aerosol, or gaseous drugs into dispensing containers.

Testing includes, but is not limited to, (1) in vivo bioequivalence testing, (2) dissolution testing, (3) stability testing, (4) sterility testing, (5) any other required analytical testing, and (6) any other testing required by the agency's regulations concerning current good manufacturing practices (21 CFR Parts 210 and 211).

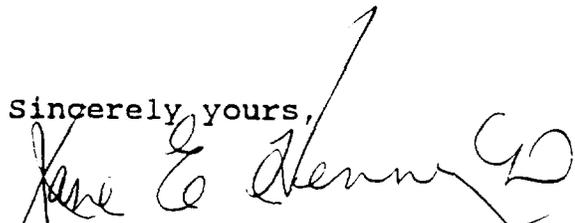
I hope that this information will assist your members in complying with the new requirements. Please convey the information to your members as soon as possible to help assure that agency action on drug product applications will not be delayed because of the absence of the certification statement and information.

We also welcome your comments on the guidance in this letter or other aspects of the new legislation. If you have questions or comments about the agency's implementation of the Generic Drug Enforcement Act, please call or write the following offices as appropriate:

- \* For human drug products other than biological products:  
The Division of Regulatory Affairs (HFD-360), Center  
for Drug Evaluation and Research, 7500 Standish Pl.,  
Rockville, MD 20855; 301-295-8041.
- \* For biological drug products: The Division of  
Regulations and Bioresearch Monitoring (HFB-130),  
Center for Biologics Evaluation and Research,  
7564 Standish Pl., Rockville, MD 20855; 301-295-8188.
- \* For animal drug products: Petitions and Regulations  
Branch (HFV-238), Division of Compliance, Center for  
Veterinary Medicine, 7500 Standish Pl, Rockville, MD  
20855; 301-295-8737.
- \* For information on the list of debarred persons:  
Division of Compliance Policy (HFC-230), Office of  
Regulatory Affairs, 5600 Fishers Ln., Rockville, MD  
20857; 301-443-1500.

Again, my appreciation for your attention to these important matters.

Sincerely yours,

  
Jane E. Henney, M.D.  
Deputy Commissioner for Operations





Food and Drug Administration  
Rockville MD 20857

April 8, 1994

TO ALL ANDA AND AADA APPLICANTS

Dear Sir or Madam:

The purpose of this letter is to provide you with information on a variety of generic drug topics that the Office of Generic Drugs (OGD) believes are important to you and the generic drug industry.

1. INCOMPLETE ABBREVIATED APPLICATIONS

The Office checks abbreviated applications for completeness and acceptability prior to accepting them for review (filing). This letter provides an update of the reasons why the Office refuses to file certain abbreviated applications. This topic was previously discussed in the Office Director's letters to industry dated November 8, 1991, and July 1, 1992.

Attachment A is a checklist of the elements used by the Office for determining if a new abbreviated application is acceptable for filing/receiving. While this checklist doesn't cover all possible filing issues, it provides guidance on the information that is required in a complete application.

The Office continues to refuse to file over 30 percent of applications submitted. Attachment B summarizes the reasons for these actions. The two most frequent reasons for refusing to file/receive applications are: 1) failure to include a letter of authorization from the drug master file (DMF) holder and 2) failure to include a list of convictions required by the Generic Drug Enforcement Act (GDEA). Further information about these two common application omissions is discussed in the following sections:

A. LETTER OF AUTHORIZATION FROM DMF HOLDER

The most frequent reason for an application to be refused for filing is the failure of the applicant to provide an acceptable drug master file (DMF) authorization for the bulk drug. OGD requires authorization to be granted by the holder of the DMF, or its designee, for each source of bulk drug substance. The letter of authorization from the DMF holder must be on the DMF holder's letterhead stationery, signed with an original signature, and dated. The letter must specifically authorize the agency to review the DMF cited by the applicant, and must cite the DMF's holders name, the drug's name, and the DMF number.

Authorization from a third party designee of the DMF holder, such as another corporate entity related to the

DMF holder or a supplier, is not acceptable unless the applicant provides two letters. One letter must be from the DMF holder on the DMF holder's letterhead, signed, and dated. It must specifically grant permission for the third party designee to authorize right of reference to a DMF on the DMF holder's behalf. The second letter must be from the third party, on its letterhead with an original signature and dated. It must refer to the letter of the DMF holder, plus cite the specific applicant, drug name, and DMF number.

B. LIST OF CONVICTIONS UNDER GDEA

The second most frequent reason for refusing to file an application is failure to include a list of convictions of individuals participating in the development of information in the application, as required by the 1992 GDEA. The requirements went into effect on June 1, 1992. In a January 15, 1993, letter to industry, the Office of Generic Drugs stated that, effective February 25, 1993, it would no longer accept for filing abbreviated applications that did not contain the certification and list of convictions required in 21 U.S.C. §335a(k)(1) and (2) of the GDEA.

OGD now requests that the signed certification in the application include not only the list of convictions but also the name(s) of the persons convicted, the title and section of the federal or state statute involved, the sentencing date, the court entering judgment and the case number, if known, and a brief description of the offense. The applicant also should indicate the role of each convicted person in the development or submission of the application, and the time period of the person's involvement in the development of the application.

Beginning June 1, 1994, the Office will no longer accept abbreviated applications for filing that do not contain a signed certification that includes a list of convictions with this additional information. Any questions regarding filing requirements may be directed to the Regulatory Support Branch (301) 594-0315.

2. MULTIPLE SUPPLEMENTS TO THE OFFICE

At times a firm may wish to submit multiple supplements to cover an identical change to several different new drug applications and/or abbreviated applications. To improve the efficiency of the review process, the Center requests that applicants follow these guidelines when this occurs:

A. Prior to sending the multiple supplements, please notify

OGD, and the Offices of Drug Evaluation (ODE) I and/or II, as appropriate. For abbreviated applications, send a copy of the transmittal letter described in item 2.B. by facsimile to the attention of Mr. Robert L. West, OGD, Review Support Branch, (301) 594-0180. For new drug applications, send a copy of the transmittal letter that lists all affected new drug application numbers to Dr. Charles Kumkumian, Assistant Director (Chemistry), ODE I, HFD-102.

- B. Send a separate supplement, plus a duplicate copy, for each application affected by the change. Send all the generic supplements in one package to OGD's document control room. Send all the new drug supplements in one package to the appropriate ODE I and/or II Reviewing Divisions. Each package should contain a transmittal letter that provides the date of the supplements, the purpose of the changes, and the file number of each application affected for that Office, i.e., OGD or ODE I/II. Each supplement for a common change should have the same date. Also include the file number of any applications for which similar supplements are being sent to the other Office(s).

Unless the supplements require the review of stability data for approval, OGD intends to assign the review of all the supplements to one chemist. If possible, OGD will coordinate the review of the similar OGD and ODE I/II supplements.

### 3. ANNUAL REPORTS FOR BULK ANTIBIOTIC DRUGS

Under Section 507 of the Federal Food, Drug, and Cosmetic Act (act), the Office uses an approval mechanism for bulk antibiotic drug substances that is similar to that used to approve antibiotic finished dosage forms. Approval letters issued to all applicants of abbreviated antibiotic drug applications (AADA), including bulk antibiotic drugs, specify that post-marketing reporting requirements are set forth in 21 CFR §314.81. Annual reports must be submitted each year within 60 days of the anniversary date of the approval of the application. However, some bulk substance applicants have not been diligent in submitting these reports. OGD reminds applicants that failure to file the annual reports under section 314.81 and section 507(g) of the act can result in the approval of the application being withdrawn.

Beginning June 1, 1994, all annual reports for bulk AADA's must be accompanied by Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use). The form must be completed and signed with an original signature by the applicant or, if the applicant is not a resident in the United States (U.S.), by the applicant's U.S. agent. The forms are available from

the Consolidated Forms and Publications Distribution Center, Washington Commerce Center, 3222 Hubbard Road, Landover, MD 20785. Form FDA 2252 contains sections which may not be applicable for bulk applications (i.e., nonclinical laboratory studies, clinical data), and these sections can be marked as "not applicable--bulk drug." However, all other sections on this form should be addressed.

4. MINIMUM BATCH SIZE FOR TRANSDERMAL PRODUCTS

The Office has established a tentative policy for a minimum test batch size requirement for transdermal delivery systems. The Office believes this requirement is reasonable based on its discussion with a number of manufacturers with approved abbreviated applications for this dosage form. The test batch size should be at least one tenth of the proposed commercial production batch or 25,000 units for each strength, whichever is greater, all of which are to be fully packaged. OGD will consider, on a case-by-case basis, protocols to package less than the entire test batch.

New biostudies may be required for scale-up beyond ten-fold of the abbreviated application test batches.

5. BIOEQUIVALENCE PROTOCOLS

The Office recommends that before starting bioequivalence studies on a drug product for which a guidance is unavailable, the firm submit the proposed study protocol(s) to the Office. Effective June 1, 1994, protocols submitted for which a bioequivalence guidance exists will not be reviewed unless the proposed protocol differs from the guidance and the cover letter clearly outlines the differences. The protocol should be addressed to the Director, Division of Bioequivalence, for review (21 CFR §320.30) at the address listed in this letter. Protocols submitted for review should be complete and include any supporting references or scientific reprints from the literature which would facilitate the review process.

6. RESEARCH

The Office's research program continues to provide answers to scientific questions and address scientific issues related to the drug approval process. The following is a summary of important initiatives underway or planned in this program.

The results of three extramural contracts with the Universities of Michigan, Uppsala (Sweden), and Maryland were presented at the Generic Drugs Advisory Committee (GDAC) meeting on January 11-12, 1994. The focus of the meeting was

on *in vitro* dissolution. These Universities are conducting the following research on solid, oral immediate-release dosage forms.

A. University of Michigan and University of Uppsala

The fundamental properties which define oral drug bioavailability in humans are solubility and permeability. These properties are being determined at the Universities of Michigan and Uppsala to identify classes of drugs to allow an assessment of the impact of changes in formulation, manufacturing and site on drug product performance. This effort is expected to lead to rational and potentially differing judgments, depending on the drug class, about physicochemical, *in vitro* dissolution and *in vivo* bioequivalence test requirements in the presence of a given change. The drug classification system will be based on *in vitro* and *in vivo* studies of the biopharmaceutical properties of 24 model drugs. All of the drugs being investigated under the manufacturing research contract at the University of Maryland (below) are also being studied under this contract.

B. University of Maryland

Studies involving five model drugs are underway to examine the links between critical manufacturing variables, *in vitro* dissolution, and *in vivo* bioavailability and bioequivalence. This information will assist the Office in better defining minor and major changes in manufacturing and clarifying the role of *in vitro* dissolution in assessing the impact of these changes on bioavailability.

Finally, the agency has awarded three new extramural contracts for FY 1994. The first contract was awarded to the University of Michigan to study the relationship between critical manufacturing variables of topical formulations relative to *in vitro* release characteristics. This study will contribute to a database for the regulatory applications of *in vitro* testing for these formulations. The second contract was awarded to Rutgers University to evaluate experimental variables associated with diffusion cells used to measure *in vitro* drug release from topical dosage forms. The third contract was awarded to the University of Iowa to evaluate the design of histamine challenge studies for documenting the bioequivalence of metered dose inhalers. This information will be considered in the future when the agency evaluates the Office's *Interim Guidance for Documentation of In Vivo Bioequivalence of Albuterol Inhalation Aerosols (Metered Dose Inhalers)* that

issued on January 27, 1994.

7. INDUSTRY COMMENTS TO AUGUST 4, 1993, LETTER TO INDUSTRY

The Office of Generic Drugs (OGD) has received certain questions from generic drug trade associations and others concerning its August 4, 1993, letter to the industry. Due to space restrictions, this section of the letter includes responses to the more significant questions posed, but does not address packaging issues. The Office is preparing a Policy and Procedure Guide on packaging issues and plans to issue it within the next several months.

Q: Specific manufacturing conditions are determined only through experience gained during the validation process, and it is not possible for the initially proposed production batch record to contain more than broad manufacturing ranges and controls. On this basis, can the blank production batch record be submitted with the first annual report? (Section 3, Batch Scale Terminology, August letter.)

A: The proposed production record cannot be submitted in an annual report because the record submitted for the production batch is the basis for evaluation and approval of the initial scale-up proposed in the application. Broad control ranges or undefined conditions, to be established during product manufacture, reduce confidence that the production scale batch is in fact representative of the test batch used to demonstrate bioequivalence. This record must be submitted and identified as the intended scale-up before such evaluation can occur.

OGD's Procedure and Policy Guide (P&PG) 22-90 thus requires that the test batch size be determined based on the proposed production batch. Additionally, 21 CFR §314.94 (58 FR 47352) requires that applications "shall contain the proposed or actual master production record,...to be used for the manufacture of a commercial lot of the drug product."

The purpose of validation with post-approval scale-up is to demonstrate that when the initial in-process controls and specifications which produced the test batch are maintained, the scale-up process reproducibly yields a production batch of equivalent quality.

Q: Can the size of the proposed production batch submitted in the application be changed? (Section 3, Batch Scale Terminology, August letter.)

A: There may be circumstances, prior to approval of the

application, under which the firm wishes to change the size of the proposed production batch. This change can be made by submitting the new proposed production record as an amendment to the application as a replacement for the production batch record originally submitted. Please note, however, that the approved batch record should be the one used to produce the post-approval validation batches.

Q: Is scale-up determined by the size of the final blend, or by the initial quantity of dosage units manufactured from each blend? (Section 6, Common Granulations, August letter.)

A: The test batch size for solid oral dosage forms is based on the quantity of drug product units manufactured. Any scale up considerations also must be determined on this basis. The total amount of in-process granulation may not necessarily correspond to the quantity of an individual strength produced and therefore cannot be used as the basis for scale up.

Q: How are the test batch size requirements of P&PG 22-90 interpreted when the proposed production batch is less than 100,000 units? (Section 3, Batch Scale Terminology, August letter.)

A: For products that are controlled substances (see P&PG #2), products with certain specialized dosage forms, or products that are expected to have extremely low market volume, a firm may wish to propose a production batch size of less than 100,000 dosage units. In these cases, the test batch and proposed production batch must be the same size. Additionally, since the minimum test batch size described by the P&PG is 100,000 dosage units, a rationale to manufacture a smaller batch must be fully justified in a presubmission protocol for acceptance by the Office.

Q: Why should there be a designation in the cover letter that the submission contains sterility assurance data? (Section 8, Microbiological Data, August letter.)

A: This designation will assist the Office in directing the submission to one of OGD's microbiologists for a sterility assurance review. The following information is provided to industry to assist the microbiologist in making the most timely, as well as consistent, review possible. The current reference document is the agency's *Sterility Assurance Guideline* published in the *Federal Register* (58 FR 63996, December 3, 1993). Please present

the appropriate information and data, as outlined in the Guideline, in the Manufacturing and Controls section of the application. The Office further requests that the topics be indexed according to the headings in the Guideline. Stability information requested in the Guideline can be presented with the other stability data, but it should be referenced in the above-mentioned index.

Q: Please clarify the reference in the August 4, 1993, letter to industry that stated, "...the agency...may require the firm to provide dissolution testing data using methods other than those in the USP, especially when an alternative method has been previously approved in the ...application." (Section 10, Dissolution Requirements, August letter.)

A: The Office may approve a dissolution testing method whether or not there is a USP method available at the time the ANDA is approved. If there is a USP method available at the time the ANDA is approved, the Office, according to the statute, may approve an alternative dissolution testing method for valid scientific reasons. The Office, may, in its discretion, determine that the alternative method should be used either instead of or in addition to the USP method. For example, this would occur if the USP method is not discriminating or uses hydro-alcoholic (or organic solvent) medium for dissolution testing. The Office expects that instances will occur only rarely where dissolution tests and specifications that differ from the USP method will be proposed.

If no USP method is available at the time the ANDA is approved, the dissolution testing method approved is generally, but not restricted to, the one used by the innovator. The Office may approve a dissolution testing method developed by the agency for the specific drug product. Subsequent to approval, if the USP establishes a dissolution testing method, acceptable to the agency, the firm must conduct post-approval quality control testing using this USP method.

#### 8. REQUESTS FOR DEVIATION FROM OGD POLICY

Applicants are encouraged to follow the policies and procedures published in the regulations, Center Guidelines, and OGD Policy and Procedure Guides. However, requests for information about deviations from Office policies can arise before or after an abbreviated application is submitted. Before an application is submitted, questions about deviating from the Office's policies and procedures should be directed to the Acting Director, OGD. After an application is

submitted, such questions that are specific to an application should be resolved through the routine application review process.

Regardless of whether the question arises before or after an application is submitted, the requester should provide the following information in the opening statement of the letter:

- A. Indicate whether the request is a general question or applies specifically to an individual or class of applications and provide the application numbers, as appropriate.
- B. Indicate the nature of the request, and provide a reference to the appropriate guideline, policy or regulation in question, clearly stating the deviation about which information is requested and/or question about the issue.
- C. Indicate the applicable dosage forms and strengths.

If the inquiry about a deviation from Office policy relates to a packaging issue, please follow the procedures stated below:

- A. If the application has been submitted and the inquiry pertains to the mechanism by which the firm is to initiate a change in the container/closure system, the firm should include the type of dosage form and information on the approved and proposed packaging components including supplier, composition, drawings and any additional testing such as incoming release testing.

The Office then will be able to determine whether the change can be submitted as a supplement or in the annual report. The Office, if requested, will provide the applicant with a list of information which should be submitted to support the change.

- B. If the application has not yet been submitted and the request is for waiver of batch packaging requirements, an applicant should provide a protocol that demonstrates that the test batch is chemically, physically and microbiologically uniform. Adequate controls should be proposed.

The protocol should provide at least the following:

- (1) a description of the dosage form and its properties, including any characteristics that may be affected by environmental factors, such as heat, light, humidity and oxygen,

- (2) a description of the container/closure system and packaging and labeling operations, and
- (3) a description of the sampling plan and analytical methodology.

Once a written response is provided by the Office, please include a copy of the response in the ANDA/AADA submission(s).

9. OFFICE PERSONNEL FOR QUESTIONS

From time to time, individuals outside the agency call several members of the Office requesting the same information. To conserve valuable Office time and resources and assure that the opinions provided to the public are uniform, the Office requests that questions be directed to the following individuals, depending on the content of the question:

- A. Questions about the chemistry review status of an application should be directed to the Branch consumer safety officer (CSO), if known, or the Regulatory Support Branch, (301) 594-0315,
- B. Questions about the bioequivalence review status should be directed to Dr. Jason Gross, (301) 594-0315,
- C. Labeling questions should be directed to Mr. Jerry Phillips, Chief, Labeling Review Branch, (301) 594-0365, or
- D. General information should be directed to the Regulatory Support Branch (301) 594-0315, unless stated otherwise in this letter.

10. MAILING ADDRESS AND TELEPHONE NUMBERS

The Office continues to get several inquiries for the following information:

- A. Submissions and other correspondence intended to be part of an abbreviated application, whether sent by the U. S. Mail, a courier service or by a parcel service should be addressed as follows:

Office of Generic Drugs, CDER, FDA  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

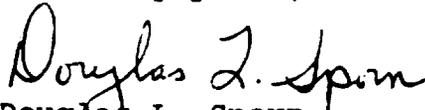
- B. Correspondence not associated with an abbreviated application should include the above address and also

include the name of the person to whom the correspondence is directed.

- C. The Office has new telephone numbers. Generally you can replace the numbers 295-8xxx with 594-0xxx and proceed. For example, the number 295-8340 has been changed to 594-0340. A few new numbers do not follow this rule, but if you have questions, please call the Regulatory Support Branch (301) 594-0315.

The Office of Generic Drugs appreciates your consideration of the issues raised in this letter. Your attention to these matters will assist us in our efforts to improve the generic drugs review process.

Sincerely yours,



Douglas L. Sporn  
Acting Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

indusltr.04





REFUSAL TO FILE LETTERS BY REASON AND FREQUENCY  
 JANUARY 1, 1993, to DECEMBER 31, 1993

REASON	FREQUENCY
NO AUTHORIZATION OF THE DMF	15
NO CONVICTION STATEMENT	14
NO ENVIRONMENTAL IMPACT ANALYSIS	9
INCOMPLETE 356h	9
NO DEBARMENT CERTIFICATION	9
FAILURE TO IDENTIFY & CHARACTERIZE THE DIFFERENCES IN THE INACTIVE INGREDIENTS	9
NO MASTER PRODUCTION RECORD	9
NO AUTHORIZATION OF AGENT	8
NO SIDE-BY-SIDE COMPARISON OF LABELING	8
NONCOMPLIANCE WITH ANDA PPG #20-90	8
INCOMPLETE BATCH RECORDS	8
NEED FOUR COPIES OF DRAFT LABELING	7
NO COMPARATIVE DISSOLUTION DATA	6
NO CGMP CERTIFICATION STATEMENT	5
INCOMPLETE ENGLISH TRANSLATION	5
NO REFERENCE BULK DRUG	4
IMPROPER PATENT CERTIFICATION	4
NO INFO ON CONTAINER CLOSURE	4
NO CERT. OF ANALYSIS FOR THE LOTS OF INTERMEDIATE DRUG SUBSTANCE	4
EXCLUSIVITY RIGHTS NOT ADDRESSED	3
NEED OF DESI UPGRADE NOTICE	3
FAILURE TO IDENTIFY SOURCE OF MICROORGANISM	3
LOT NUMBERS OF STABILITY STUDIES DO NOT CORRESPOND WITH BATCH RECORD	3
STRENGTH NOT EQUIVALENT TO ANY LISTED DRUG PRODUCT	2
NO CERTIFICATION OF FIELD COPY	2
NO DESCRIPTION OF FOREIGN MANUFACTURING FACILITIES PER PPG #26-80	2
GROSSLY INCOMPLETE SUBMISSION	2
UNAPPROVABLE AS AN ANDA/AADA	2
NO CERTIFICATE OF ANALYSIS OF INACTIVE INGREDIENTS	1

**ATTACHMENT B (CONTINUED)**

<b>REASON</b>	<b>FREQUENCY</b>
BATCH RECORD FOR THE WRONG STRENGTH	1
NO COPY OF PETITION	1
NO SAMPLE STATEMENT	1
NO RECORD OF PACKAGING THE EXHIBIT BATCH	1
NO COMPLETED BATCH RECORD	1
INCOMPLETE STABILITY DATA	1
NO CERTIFICATE OF ANALYSIS FOR BATCH USED IN THE STABILITY STUDY	1
FAILURE TO PROVIDE SUFFICIENT BATCH QUANTITY	1
NO IN-VIVO BIO STUDY	1
INCORRECT LISTED DRUG CITED	1
<b>TOTAL</b>	<b>178</b>

**NUMBER OF REASONS CITED IN A REFUSE TO FILE LETTER  
JANUARY 1, 1993 to DECEMBER 31, 1993**

<b>REASONS CITED</b>	<b>LETTERS ISSUED</b>
ONE	38
TWO	15
THREE	4
FOUR	7
FIVE	2
SIX	1
SEVEN	2
EIGHT	5
<b>TOTAL</b>	<b>74</b>





January 15, 1993

TO ALL ANDA AND AADA APPLICANTS

Dear Sir or Madam:

In a letter dated July 27, 1992, Jane E. Henney, M.D., Deputy Commissioner for Operations of the Food and Drug Administration (FDA) notified drug manufacturers and industry associations that the Generic Drug Enforcement Act of 1992 (GDEA) was enacted. The letter described new certification and information requirements for drug product applications. The requirements went into effect on June 1, 1992. The letter also provided guidance on how to comply with the new requirements.

In accordance with the new requirements of GDEA, the Office of Generic Drugs (OGD) intends to refuse to file or approve submissions that require the new information but do not contain it.

**Refusal to File**

Effective 40 days after the date of this letter, OGD will no longer accept for filing abbreviated applications that do not contain the following information:<sup>1</sup>

1. Certification About the Use of a Debarred Person

A certification "...that the applicant did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [section 306(a) or (b)], in connection with such application." [Section 306(k)(1) of the GDEA (21 U.S.C. 335a(k)(1)).]

2. List of Relevant Convictions for Persons Debarred or Not Debarred

A list of all relevant convictions of the applicant and affiliated persons responsible for the development or submission of the application. See Dr. Henney's July 27, 1992, letter for a description of affiliated persons (copy

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<sup>1</sup>Supplements to abbreviated new drug applications (ANDA's) or abbreviated antibiotic applications (AADA's) that provide for a different or additional use of a drug (i.e., supplements that provide for a use not covered by the listed drug and are supported by new clinical studies, not literature references) also require this information. However, OGD does not formally "refuse to file" any supplement.

attached). Please also note that contractors responsible for the development of data and other information used to support approval of an application are affiliated persons. Relevant convictions are those for which a person can be debarred as described in section 306(a) and (b). The list must contain all such convictions that occurred within five years before the date of the application. [See section 306(k)(2) of the GDEA.]

Firms with no convictions to list should submit a statement to that effect.

### **Refusal to Approve**

Effective immediately, OGD will refuse to approve ANDA's, AADA's, and the applicable supplements described in footnote 1 of this letter received on or after June 1, 1992, that do not have the certification and list of convictions described above.

#### 1. Submissions Pending at the Agency

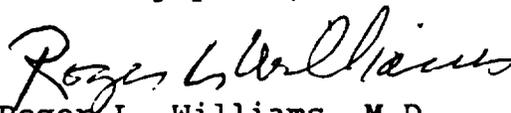
If the affected submission currently is pending with the agency and OGD reviews it before you amend with the required information, OGD will issue a not approvable letter, citing the failure to provide this information as a deficiency along with other deficiencies, if any.

#### 2. Submissions at the Firm

If the affected submission currently is with you, include this information in your amendment responding to a prior not approvable letter or telephone call notice of deficiency. Otherwise, after OGD reviews the amendment, it will issue a not approvable letter citing the failure to provide the certification and list of convictions as a deficiency, along with other deficiencies, if any.

If you have any questions or comments about the Center for Drug Evaluation and Research's implementation of the GDEA, please call (301-295-8041) or write to the Division of Regulatory Affairs at the following address: 7500 Standish Place, Rockville, Maryland 20855.

Sincerely yours,



Roger L. Williams, M.D.  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research