APPLICATION INTEGRITY POLICY

1-1-1 Background

This section provides procedures for Food and Drug Administration (FDA) employees to carry out the Agency policy commonly known as the Application Integrity Policy (AIP). The policy focuses on the integrity of data and information in applications submitted for Agency review and approval. On September 10, 1991, the FDA published the Notice of this policy formally entitled, "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities; Final Policy" (Federal Register, 56 FR 46191). The AIP described the Agency's approach regarding the review of applications that may be affected by wrongful acts that raise significant questions regarding data reliability. FDA published the Federal Register (FR) Notice and a companion document, "Points to Consider for Internal Reviews and Corrective Action Operating Plans," in Compliance Policy Guide (CPG) 7150.09 (see Sec. 120.100 of the Compliance Policy Guides publication).

1-1-2 Purpose

The purpose of this section is to:

1. provide clear and consistent instruction to FDA staff on the elements of the AIP, particularly, the deferral of scientific review. AIP decisions and the criteria on which they are based should not be arbitrary or vary dramatically from Center to Center;

2. stress the importance of consistent application of the procedures set out in this section, FR Notice, CPG 7150.09, and the Center policy or procedure statements to carry out the policy, and

3. emphasize the importance of following up on observations or concerns about the integrity of the applicant or its application. The Center makes the AIP decision based upon input from the Office of Compliance (OC), the Center's reviewing unit, the Field office or Center investigating unit, and, as appropriate, other parts of the Agency.

Although this guidance document does not create or confer any rights for or on any person and does not operate to bind FDA or the public, it does represent the Agency's current thinking on consistent implementation of the AIP.

This section is intended to supplement any Center policy or procedure statement on the AIP. This section is effective immediately.

1-1-3 Definitions

1. Applicant. The term “applicant” includes any person within the meaning of

section 201(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(e)) who submits to FDA data or other information to influence or support an agency decision regarding approval [or clearance] to market an FDA-regulated product. Actions by an applicant's employees or agents are considered actions by the applicant.(56 *FR* 46191, at 46199).

2. Application Integrity Policy Committee (AIP-C). The AIP-C is an Agency committee comprised of members, one of whom is a chairperson, from each Center, and the Office of Regulatory Affairs (ORA). The Office of Chief Counsel (OCC) advises on legal matters. Each member is known as an "AIP contact person." The purpose of the AIP-C is to meet regularly to discuss the AIP, including consistent implementation. The AIP-C prepared this section.

3. Application. The term "application" includes "any application, petition, amendment, supplement, or other submission made by an applicant to an agency review process in support of the approval or marketing of a regulated product.... References to data in an application include all data and other information submitted in or in relation to, or incorporated by reference in the application." (56 *FR* 46191, at 46199). For purposes of this section, an application includes any submission of any type to the Agency, such as pending and approved applications or petitions, amendments, supplements, supplemental amendments, premarket notifications (510k's), annual reports, investigational new drug applications (IND's), investigational new animal drug applications (INAD's), and investigational device exemption applications (IDE's) upon which the application is based. An application also includes a drug, device, or food master file, correspondence, and any submission by any person to support the approval or marketing of a regulated product.

4. Corrective action operating plan (CAP). The "corrective action operating plan" (CAP) is the applicant's written operating plan that describes its commitment, procedures, actions, and controls to ensure data integrity. The CAP should include, but not be limited to, an explanation of the circumstances surrounding the conduct of the wrongful act, information set out in the section below, "REVOKING THE AIP AS IT APPLIES TO A FIRM'S APPLICATIONS," CPG 7150.09, and the "Corrective Actions" section of the AIP (56 FR 46191, at 46200).

5. Deferral of scientific review. The term "deferral of scientific review" indicates that the Center's review unit will not expend scientific review resources on an application until the Center is satisfied that the data or information in the application is reliable.

6. Pattern or practice. The term "pattern" means more than one instance of errors or acts involving subject matter important to the evaluation of an application. The term "practice" means an act or process of doing something affecting subject matter important to the evaluation of an application. A practice can be one or

more acts or processes. A pattern or practice can occur in one or more applications.

7. Untrue statement of material fact. An "untrue statement of material fact" is a false statement, misstatement, or omission of a fact. A determination that an untrue statement is material is necessary for purposes of invoking the AIP. The Center should make a written determination. This determination may involve discussions with OCC.

8. Validity assessment. The AIP and its accompanying preamble in the Federal Register Notice (56 FR 46191) frequently refer to the validity assessment. That term "validity assessment" includes the Agency's determination of the scope and extent of an applicant's suspected wrongful acts, an Agency inspection of the firm, and an Agency review of the applicant's audit. The Agency may assess the validity of any applications called into question by the wrongful acts, in addition to those directly affected. An Agency inspection may be initiated before scientific review of an application is deferred.

9. Wrongful act. A wrongful act is any act that may subvert the integrity of the review process. A wrongful act includes, but is not limited to, submitting a fraudulent application, offering or promising a bribe or illegal gratuity, or making an untrue statement of material fact. A wrongful act also includes submitting data that are otherwise unreliable due to, for example, a pattern of errors whether caused by incompetence, negligence, or a practice such as inadequate standard operating procedures or a system-wide failure to ensure the integrity of data submissions. A wrongful act may be evidenced in a document, including informal documents such as correspondence or memoranda, or verbally, such as in telephone conversations or in one-on-one meetings. Regardless of the means, each suspected incident of a wrongful act should be reported and investigated to determine whether they raise significant questions regarding data integrity and reliability with respect to a regulated product. (See 56 FR 46191, at 46192).

10. Invoking AIP. The phrase "invoking AIP" as used in this section means that the Agency will apply the Application Integrity Policy to one or more applications by deferring substantive scientific review pending a validity assessment of data and information in all of the affected applications.

11. Revoking AIP. The phrase "revoking AIP" as used in this section means that the Agency will resume substantive scientific review of all of an applicant’s pending applications that have been subject to the Application Integrity Policy.

1-1-4 Education Program

The Agency has taken the steps outlined below to ensure that its employees are aware of the AIP, and that those employees who are responsible for carrying out

the AIP (see "RESPONSIBILITIES OF AGENCY PERSONNEL" below) do so in a complete and consistent manner:

1. The FDA Orientation Program for new employees will contain a written introduction to the AIP.

2. The Director, Office of Enforcement, Office of Regulatory Affairs, and the Director, Division of Ethics and Program Integrity, issued a joint memorandum dated June 4, 1997, to Agency employees describing the AIP.

3. The AIP-C is committed to identifying methods to educate Agency staff about the AIP. Each AIP contact person ensures that his or her Center or Office has a procedure for distributing information about the AIP.

1-1-5 Responsibilities Of Agency Personnel And Organization

All FDA employees are responsible for working together to ensure that the AIP is consistently applied when warranted. Agency managers, including supervisors, and directors in each Division, Office, Center, District and Region may delegate authority for carrying out the responsibilities related to the AIP. Responsibilities are set out below.

1. Each employee should:

A. be familiar with the Agency's procedures for carrying out the AIP, and the name and telephone number of the AIP contact person (Attachment A);

B. be aware of the ways in which a person might subvert the integrity of the approval process by committing a wrongful act, e.g., bribing an Agency employee, submitting false data, etc.;

C. promptly discuss observations. Each incident of a suspected wrongful act, whether evidenced by a formal submission to the Agency, an informal document, or a verbal communication, should be reported and investigated to determine whether it raises a significant question of data integrity or reliability regarding a regulated product.

If he or she suspects wrongful acts or is asked to participate in or contribute to wrongful acts, promptly discuss those observations or concerns with his/her supervisor. If the employee thinks the supervisor is involved, then he/she should go to the next higher supervisor. The Agency's Office of Internal Affairs welcomes inquiries, but will need to know what steps have been taken within his/her Office to address the issue.

Review 5 CFR Part 2635, Subpart B, to determine if acceptance of a gift is legal. The regulations, "Standards of Ethical Conduct for Employees of the Executive Branch," have been provided to each employee. If questions remain after reviewing the regulations, contact the Division of Employee Relations, Ethics Branch (HFA-22), Office of Human Resources and Management Services. (See also 18 U.S.C. 201, "Bribery--Penalties for accepting a bribe," 18 U.S.C. 209, "Dual Compensation," and 41 U.S.C. 4.23(b)(2), "Procurement."

An employee should not assume that an incident is isolated or not important. The Agency takes each observation seriously.

D. notify his/her immediate supervisor or appropriate Office manager, if a person debarred under the Generic Drug Enforcement Act or a person convicted of a crime related to the development or approval/certification of a FDA-regulated product is involved with an application; and

E. forward issues requiring discussion to the AIP-C through the appropriate AIP contact person.

2. Field office or other Agency investigative unit should:

A. conduct inspections to verify allegations, including the scope and extent, of suspected wrongful acts. If wrongful acts are first uncovered by Field office investigations, notify the appropriate Center AIP contact person of findings as soon as possible. If the Center issued an assignment to investigate suspected wrongful acts, notify the contact listed on the assignment with the results of the investigation;

B. submit recommendations for withdrawal for each of the affected applications, detailing all specific findings and related exhibits. If the criteria are met, submit a recommendation for invoking the AIP to the appropriate Center OC;

C. if AIP is invoked, review the firm's proposed audit plan for adequacy, and confirm the completed independent audit information;

D. evaluate the firm's CAP and provide specific comments to the firm on its adequacy when appropriate. Seek guidance from the Center's OC when needed. Verify implementation and/or completion of the CAP; and,

E. submit to the appropriate Center, the Field's/investigating unit's recommendation and supporting documentation for revoking the AIP.

3. Reviewing Office Director should:

A. ensure that the Office has a procedure to alert the Center's Office of Compliance (OC) when the Center suspects wrongful acts;

B. notify the Office staff in writing when the Center has either invoked or revoked the AIP. Review should be deferred when the Center invokes the AIP and resumed when the Center either has granted an exception to or revoked the AIP. Ensure that the Office doesn't communicate to the firm observations of suspected wrongful acts or request further information to correct the suspected wrongful acts unless directed by the Center's OC;

C. ensure that the Office has a mechanism to identify those applications under the AIP so that substantive scientific review is appropriately deferred unless either an exception has been granted to the AIP, or the AIP is revoked;

D. if authority is delegated by the Center Director, grant or deny an applicant's request for an exception to the AIP and notify the Office staff; and,

E. transmit a copy of the firm's written request for an AIP exception (see "GRANTING AN EXCEPTION TO DEFERRAL OF SCIENTIFIC REVIEW AFTER THE AIP IS INVOKED") to the AIP contact person. The firm's documentation should describe the basis for the request.

4. Immediate review supervisors, including division directors should:

A. defer secondary (supervisory) review of an application subject to AIP when so notified by the reviewing Office Director; and,

B. resume or begin secondary review of an application subject to the AIP when notified by the reviewing Office Director.

5. Reviewers or Center consumer safety officers should:

A. defer primary review of an application subject to AIP when so notified by the reviewing Office Director; and,

B. resume or begin primary review of an application subject to the AIP when notified by the reviewing Office Director.

6. Center Compliance Office Director should:

A. ensure that the Office has a mechanism to alert the Field Office and ORA's Office of Enforcement when the Center suspects wrongful acts;

B. review the Field Office/investigating unit's recommendation for invoking

or revoking the AIP and provide guidance to the Field Office/ investigating unit on the adequacy of the firm's CAP;

C. prepare, for the Center Director's signature, the letter to the firm advising it that the Center either has invoked or revoked the AIP. Consistent language in the letters should be used where appropriate (see Attachment B for "model" letters). Notify appropriate headquarters and Field office personnel when the signed letter issues;

D. when the AIP is invoked, coordinate with the Reviewing Office/divisions to obtain a list of the firm's applications, including those affected by the AIP, and attach it to the letter notifying the firm;

E. maintain a liaison with the OCC to obtain legal consultation, as needed;

F. ensure that the scientific review units have verified the number of applications that have been identified by the firm as withdrawn;

G. notify the appropriate Agency Offices, such as the Office of Criminal Investigations, and the OCC, to: (1) share discovered facts and observations, (2) request facts and information that they are authorized to disclose that may assist the Center in its AIP decision, and (3) discuss the relevance, if any, of "milestones" in court proceedings (56 *FR* 46191, at 46194, comment 9). An example of a "milestone" is an order issued in a civil proceeding or a criminal conviction, when the order or conviction is based upon a finding of fact that establishes a wrongful act related to the approval process; and,

H. initiate and monitor administrative and legal action(s), where appropriate, in conjunction with relevant FDA and non-FDA government offices.

7. Center Director should:

A. sign the letter to the firm advising it that the Center has either invoked or revoked the AIP;

B. ensure that the Center has a procedure to implement the AIP, which includes granting or denying an applicant's request for an exception to the AIP; and,

C. designate a Center AIP contact person(s).

8. AIP contact person(s) (see Attachment A) should:

A. as a member of the AIP-C, participate regularly and actively to discuss

and participate in consensus-building when confronted with an issue that will promote the goal of consistent implementation of the AIP across the Agency;

B. if a Center contact person, maintain a current list of applications subject to the AIP by each Center;

C. distribute the Agency policy and appropriate Center procedure statements on AIP to personnel it represents within the Agency; and,

D. The AIP-C chairperson should: (1) prepare an agenda for each AIP-C meeting, and (2) ensure that the AIP contact persons receive the agenda and minutes for each AIP-C meeting, and based on the information provided by the AIP contact persons, an updated list of all firms whose applications are subject to the AIP.

1-1-6 Administrative Considerations

1. Communication among the Agency's Offices involved in decision-making about AIP issues should be open, clear, accurate, complete, and prompt.

2. Managers of Offices routinely involved in AIP decision-making should develop and document procedures for delegating authority for these decisions.

3. The time it takes to investigate the issues on which decisions are based will vary. To reach AIP decisions in a timely manner, managers involved in AIP decision-making should:

A. assign AIP-related responsibilities to Agency personnel in a manner that promotes timely decisions that are consistent and of high quality;

B. establish processes to monitor the progress of activities related to AIP decisions; and,

C. expedite the flow of AIP-related documents and information.

4. Each Center should establish a procedure to maintain a file system to contain the facts, circumstances, and rationale to support its AIP decision. Examples of other documentation include the memorandum from the district office (see "REVOKING THE AIP AS IT APPLIES TO A FIRM'S APPLICATIONS," item 4), and the supporting summary and analysis. Documentation serves the following two purposes:

A. it becomes part of an administrative record; and,

B. it provides carefully developed criteria that should be applied in subsequent cases with similar facts. The reasons for deviations from such precedent should be consistent both with the AIP and with prior instances of deviation, if any. Consider consulting the AIP-C or the OCC before finalizing the decision to deviate from precedent.

GENERAL CONSIDERATIONS BEFORE A CENTER INVOKES THE AIP

Generally, the procedure set out below should be followed when the Agency suspects an applicant of committing wrongful acts that raise significant questions about data integrity.

1. No application, during or after investigation, should be approved or cleared if the data are unreliable, or there are data integrity, safety, or efficacy concerns, until the Center is satisfied that the issues in question are resolved, or, (if the AIP is invoked) an exception to deferral of scientific review is granted.

2. After suspected wrongful acts come to the Agency's attention, the Field Office/ investigating unit should investigate to determine the scope and extent of the wrongful acts.

INVOKING THE AIP

1. Generally, there should be evidence of a pattern or practice of wrongful conduct that raises a significant question about the reliability of data in an AIP application before the Center defers scientific review and invokes the validity assessment process under the AIP. When invoked, the AIP may cover one, some, or all the applications, including all applications from one or more facilities, that are affected, either directly or indirectly, by the wrongful acts that raise significant questions regarding reliability.

A wrongful act includes, but is not limited to, submitting a fraudulent application, offering or promising a bribe or illegal gratuity, or making an untrue statement of material fact. A wrongful act also includes submitting data that are otherwise unreliable due to, for example, a pattern of errors whether caused by incompetence, negligence, or a practice such as inadequate standard operating procedures or a system-wide failure to ensure the integrity of data submissions. Usually, when the AIP is invoked, there are two or more applications affected.

2. When the criteria in item 1 are met, the Center should be guided by the information set out below when deciding whether and to what extent to invoke the AIP.

A. The Center should invoke the AIP on all of a firm's applications affected by a wrongful act, that is, whenever the wrongful act raises a significant question regarding the reliability of data in those applications. A wrongful

act is any act that may subvert the integrity of the review process.

B. When the pattern or practice of wrongful acts raises a significant question regarding the reliability of data in only a single application, the Center should continue to resolve the data integrity issues of that application through the review process (e.g., denial or withdrawal of approval). The Center need not invoke the AIP, as to that single application, unless the review process is inadequate to deal with the data integrity issues raised by the wrongful act. Generally, the review process alone is inadequate to deal with a single application when, for example, the firm's problems are either:

> (1) system-wide, such as failure to have and implement: (A) systems or procedures to ensure the quality and accuracy of submissions, (B) standard operating procedures (SOP's) that will ensure compliance with the regulations or relevant court decisions, or otherwise ensure the integrity of the data; or,
> (2) firm-wide, such as evidence that the firm's personnel are inadequately trained, perform work incompetently, repeatedly fail to follow the firm's SOP's, or are untrustworthy as it relates to the application or the approval process.
>
> These are examples of problems that undermine the Agency's confidence in the integrity of any application submitted by the applicant. As it relates to a single application, AIP, along with the review process, is better suited than review of the application alone, to address these types of data integrity problems.

C. A Center may decide that the questions raised about the reliability of data in a single application can be resolved through the review process without invoking the AIP because the criteria in item 2.B. have not been met (also see "GENERAL CONSIDERATIONS BEFORE THE CENTER INVOKES THE AIP"). Such a decision does not preclude the Center from invoking an AIP action if the Center finds additional or new evidence that meets the criteria set forth in item 2.B., or if the firm submits other applications and the Center concludes that the wrongful conduct raises a significant question regarding the reliability of such data.

D. A determination that an untrue statement (false statement, misstatement, or an omission) is material is necessary for purposes of invoking the AIP. The Center should make a written determination. This determination may involve discussions with OCC.

E. A court order after either a civil finding of fact or a criminal conviction, each about a wrongful act related to the approval process, may be the basis for invoking the AIP. However, before the Center invokes the AIP, a

determination about the extent to which the wrongful act affected approved or pending applications must be made.

GRANTING AN EXCEPTION TO DEFERRAL OF SCIENTIFIC REVIEW AFTER THE AIP IS INVOKED

It may be appropriate to continue or resume substantive scientific review of an application in certain limited circumstances even though the AIP remains in effect as to that application. This situation is referred to as an "exception" to AIP. Generally, review may continue, with appropriate documentation of the reason and written concurrence by management according to Center procedure, for the reasons set out below. A Center may have additional reasons that justify continuing or resuming review.

Submissions for which review may continue or begin after the AIP is invoked.

1. The Center may continue an ongoing review until a logical stopping point has been reached. However, the Center should not communicate with the firm about deficiencies found during the normal course of review of the application, or about the suspected wrongful acts.

2. The Center may begin review of, and approve if warranted, the following types of applications with proper management concurrence if necessary (see "Authorization..." below). Document the decisions related to the exception. The Center does not need a firm's written request for an exception to the AIP to continue or begin review of applications in items 2.A. through E.

A. Applications for products with public health significance. The application is for a product intended or expected to provide a significant scientific break-through (e.g., a product that yields important therapeutic or diagnostic gain), is medically necessary, or is otherwise critically needed. Applications relying upon a sole supplier of the product or where other firms are unable to maintain a sufficient supply of the product may also be considered for an exception.

B. Applications regarding approved products.

(1) Supplements for class labeling, or changes that enhance the labeling or are protective in nature.

(2) Supplements for changes for post-approval applications that don't require pre-approval, such as "changes being effected" supplements to human drugs applications [21 CFR 314.70(c)]. The review should ensure that the change is fully described and meets regulatory criteria.

(3) Annual reports. The review should ensure that the change is fully described, meets regulatory criteria, and/or that the firm has met application commitments.

(4) Adverse experience/event reports.

C. A protocol that is not provided as part of an application.

D. IND's, INAD's or IDE's of the applicant whose applications are subject to AIP unless the wrongful acts raise a significant question regarding data integrity of the IND, INAD, or IDE.

E. Applications not subject to the AIP even though they reference an application or a device, drug, or food master file subject to AIP. However, these applications should not be approved until the questions raised regarding data integrity in the referenced AIP file or application have been resolved. Generally, the referenced data from an AIP file or application should be replaced or, if used, audited and validated before the Agency considers approval of the non-AIP applicant's application. In some cases, where the applicant intends to rely upon the referenced AIP data, the application should not be approved until the AIP firm has submitted and substantially executed its CAP.

F. Applications for changes that are required because of international law or federal law (such as the "Clean Air" Act) other than the Food and Drug Administration's, or state law.

Authorization to either begin review or approve the application.

Each Center should develop and document the process and rationale by which management authorizes the decision to either begin review or approve an application(s) while it is still under the AIP. The procedure, including the level of authority, may vary depending on the type of submission, the significance of the change for which the firm requests review, the basis for granting the exception, or whether evidence of wrongful acts is known to exist in the application.

1-1-7 Revoking The AIP As It Applies To A Firm's Application(S)

After the Center invokes the AIP, it may decide to revoke the AIP as it applies to the firm's applications and resume or begin review of those applications. Revoking the AIP is not the same as granting an exception to the AIP. The Center should not revoke the AIP for fewer than the total number of applications on which it invoked the AIP. For example, if the AIP was invoked for all of the firm's applications, the Center should revoke the AIP for no fewer than all those applications. The Center generally should consider all the criteria set out below

before it revokes the AIP. However, items 1 and 2 should be met before the Center considers revoking the AIP.

1. The applicant conducted a credible and adequate internal review designed to identify all instances of wrongful acts as a supplement to the Agency's independent investigation. The applicant's internal review involved a qualified outside consultant who was given freedom to conduct an independent and adequate audit.

2. The applicant submitted and executed a CAP, which included:

A. a commitment to assure safety, efficacy, and quality;

B. a description of corporate ethics and compliance programs;

C. procedures for effectively communicating to employees through written publications and training programs: (1) the firm's SOP's, including its ethics and quality assurance programs, and (2) the employees' regulatory responsibilities to the Agency; and,

D. the steps the applicant has taken to address current wrongful acts and to prevent future occurrences, such as**:** (1) reasonable steps to ensure implementation of the CAP (audits and reporting systems); (2) consistent enforcement of standards through appropriate disciplinary mechanisms; (3) designating a specific, high-managerial agent or equivalent to be responsible for implementation of the CAP; (4) identifying individuals who were or may have been involved in, or associated with, the wrongful acts, and removing them from positions of substantive authority on matters under the Agency's jurisdiction; and, (5) retesting or recalling products with suspected data integrity problems as appropriate.

3. The applicant withdrew any questionable application(s) and committed in writing:

A. to not refile or reactivate any application not included in the validity assessment until the Agency is satisfied with the reliability of the data/information; or,

B. when a validity assessment shows that an application contains unreliable data and the applicant wishes to replace the data, to submit a new application.

4. The Center has received a memorandum from the Field Office/investigating unit signed by the appropriate manager, such as the District Office's Director, that confirms that:

A. the applicant satisfactorily completed item 1;

B. the applicant's CAP has been submitted and executed and, where applicable, any ongoing obligations have a timetable for completion; and,

C. where applicable, questionable applications have been withdrawn.

1-2 ATTACHMENTS AND EXHIBITS

ATTACHMENTS:
A - AIP COMMITTEE MEMBERS/ AIP CONTACT PERSONS
B - "MODEL" LETTERS TO THE APPLICANT

ATTACHMENT A - AIP COMMITTEE MEMBERS/ AIP CONTACT PERSONS

See an updated list of AIP Committee Members/AIP Contact Persons at http://www.fda.gov/ora/compliance_ref/AIP_Contacts.htm.

ATTACHMENT B - "MODEL" LETTERS TO THE APPLICANT

Attached are examples of two letters that are suggested to be used as model formats: (1) to invoke the AIP, and (2) to revoke the AIP.

1. Model Letter to Applicant When the Center Invokes the AIP.

Date

Responsible Person
Title
Firm Name
Firm Address

Dear [Responsible Person]:

The Center for [applicable center] has determined that [firm name] submitted [select one or more] a fraudulent application with the Agency, or made untrue statements of material fact, or gave or promised bribes or gratuities to an Agency official. These findings are more fully described in [a letter dated...indicating our intention to withdraw approval of the NDA/ANDA/PLA/BLA for [product], and/or an FDA 483 Inspectional Observations form issued to [firm] on [date]. These findings raise significant questions regarding the reliability of data in [either all or identify the subset] applications (pending and approved) that [firm] has filed with the Agency.

In accordance with FDA policy, the Agency will assess the validity of the data and information in all of [firm(s')] affected applications. This assessment will take priority over substantive scientific data review until data integrity questions are resolved. This means that the Agency will defer substantive scientific review (including review of data and labeling) of any pending application, or of any new application or supplemental application filed after the date of this letter.

The Agency may continue or resume substantive review of an application prior to completion of the validity assessment in special circumstances where such an action is clearly in the interest of public health.

The Agency's policies regarding validity assessments and corrective actions that companies may take are described more fully in the Agency's policy entitled "Fraud, Untrue Statements of Material Facts, Bribery and Illegal Gratuities; Final Policy," which was published in the Federal Register of Tuesday, September 10, 1991. Guidance for firms (regarding audits) and the Agency in conducting validity assessments is also contained in a document entitled "Points to Consider for Internal Reviews and Corrective Action Operating Plans", the availability of which was announced in the same issue of the Federal Register. Enclosed are copies of both documents.

The local FDA District Office is available to meet with you to discuss resolution of the data integrity and reliability questions raised in the above-mentioned applications. To arrange a meeting with the District Office, please write to or call:

District Director's name, title
District name
U.S. Food and Drug Administration
Address
Phone:

To discuss the Agency's finding that a validity assessment is warranted, please contact:

U.S. Food and Drug Administration
Center for [applicable Center]
Division of [applicable division name]
[Applicable branch, mail stop]
[Address]
Phone:

Alternatively, you may withdraw the application based on [applicable Center regulation]. A listing that identifies all the firm's currently approved and pending applications filed with the Agency, including those applications for which the Agency invoked the AIP is enclosed. Please inform the Agency of the action you intend to take with regard to each of the applications within ten days of the date of issuance of this letter.

Sincerely yours,

Center Director's name
Title
Center
Food and Drug Administration
[Address]
Enclosures

cc:

DO NOT CC LAWYERS WITHOUT A CURRENT WRITTEN STATEMENT FROM THE FIRM REQUESTING THE AGENCY TO CC THE LAWYER ON ALL CORRESPONDENCE.

[AIP CONTACT PERSONS NEED TO PROVIDE MAIL CODES FOR ALL IN

THEIR CENTER (AREA) WHO SHOULD BE CC'D ON LETTERS FROM OTHER CENTERS THAT INVOKE THE AIP]

2. Model Letter to Applicant When the Center Revokes the AIP.

Date

Responsible Person
Title
Firm name
Firm Address

Dear [Responsible Person]:

The Center for [applicable center] advised [firm] in a letter dated [insert date] that the Agency deferred substantive review of [all or identify the subset] approved and/or pending applications submitted by [firm] until questions regarding the reliability of the data were resolved. Since that date, [firm] has advised the FDA that it conducted an internal review to identify and correct the circumstances which gave rise to the submission of fraudulent applications or untrue statements of material fact, which caused the Agency to question the validity and reliability of data in the applications. Furthermore, [firm] has submitted to [Center] and substantially executed a Corrective Action Operating Plan (Plan) applicable to all of [firm] products that contain adequate safeguards and procedures designed to preclude future wrongful acts and noncompliance with regulatory requirements. The FDA's [_____] District Office [or identify the applicable Center investigating unit] has conducted a validity assessment inspection of your firm and has determined that [firm] appears to have implemented the commitments made in the Plan. Therefore, I have directed my staff to resume substantive scientific review of the affected applications.

For an application that was withdrawn by the firm and that was not included in the validity assessment, the firm has committed to not refile or reactivate that application until the Agency is satisfied with the reliability of the data/information. If the validity assessment found that the data in the withdrawn application were unreliable, the applicant who wishes to replace the data should submit a new application according to the AIP (56 *FR* 46191, at 46200).

Resumption of substantive scientific review by the FDA of [firm's] applications is not to be construed as approval of any conditions that may be found in the future. Please be advised that the FDA expects [firm] to adhere to the commitments made in its Corrective Action Operating Plan, and the Agency will monitor the firm's operations to verify continued compliance. Should it be determined at any time in the future that [firm] has failed to comply with its commitments, the FDA will not hesitate to take appropriate action.

If you have any questions, you may contact [Center Discretion], at [telephone].

Sincerely yours,

Center Director's name
Title
Center
Food and Drug Administration
[Address]]

cc:

DO NOT CC LAWYERS WITHOUT A CURRENT WRITTEN STATEMENT FROM THE FIRM REQUESTING THE AGENCY TO CC THE LAWYER ON ALL CORRESPONDENCE.

[AIP CONTACT PERSONS NEED TO PROVIDE MAIL CODES FOR ALL IN THEIR CENTER (AREA) WHO SHOULD BE CC'D ON LETTERS FROM OTHER CENTERS THAT INVOKE THE AIP]

March 5, 1998
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