CPG Sec. 120.100 Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities

BACKGROUND:

The House Subcommittee on Oversight and Investigations began an investigation of wrongful acts involving some manufacturers of generic drugs and some employees of the Food and Drug Administration (FDA) during July 1988. As a result of those investigations and investigations conducted by FDA, four FDA employees were found to have accepted illegal gratuities from generic drug companies, and to date, eleven generic drug companies were found to have falsified data submitted in premarket applications to FDA.

In FDA's investigations, which began as inquiries into illegal gratuities and questionable data submissions, the agency discovered broad patterns and practices of fraud in the applicants' abbreviated new drug applications. The discovery of this extensive pattern of fraudulent data submissions prompted FDA to develop a program (1) to ensure validity of data submissions called into question by the agency's discovery of wrongful acts such as fraud, untrue statements of material fact, bribery, and illegal gratuities and (2) to withdraw approval of, or refuse to approve, applications containing fraudulent data. This guide sets forth the agency's general approach to applications that have been called into question by such wrongful acts and applications found to contain fraudulent data.

TERMINOLOGY:

The terms "applicant" and "application" are used broadly in this policy statement. References to the "applicant" include 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 to market an FDA-regulated product. Actions by an applicant's employees or agents are considered actions by the applicant.

References to the "application" include 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. These review processes include, but are not limited to, new drug and new animal drug approvals, biological product and establishment licensing, premarket

notification, classification, and premarket approval of medical devices, food additive petitions, and color additive petitions. 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.

POLICY:

Validity Assessment

Actions on the part of an applicant to subvert the integrity of an FDA review process through acts such as submitting fraudulent applications, making untrue statements of material facts, or giving or promising bribes or illegal gratuities may call into question the integrity of some or all of the applicant's submissions to the agency. In such cases, FDA will conduct an investigation to identify all instances of wrongful acts and to determine the extent to which the wrongful acts may have affected approved or pending applications. The scope of FDA's investigation will be determined based on the nature of the offense and will focus on the reliability of the applicant's research and manufacturing data. If the wrongful acts have raised a significant question regarding reliability of data in some or all of the applicant's pending applications, FDA ordinarily will conduct validity assessments of those applications.

FDA generally intends to defer substantive scientific review of the data in a pending application undergoing a validity assessment until the assessment is complete and questions regarding reliability of the data are resolved. To approve an application, FDA generally must determine that the applicant is capable of producing a safe and, for some types of applications, an effective or functional product based on, among other things, testing and other data provided by the applicant and the adequacy of the applicant's manufacturing processes and controls. The principle basis for this determination is the data in the application; therefore, the reliability of data is of critical importance.

If the agency determines that the criteria for approval cannot be met because of unresolved questions regarding reliability of data, the agency will not approve the application.

When FDA finds, based on fraudulent data in an application, that the data in the application are unreliable, the agency intends ordinarily to exercise its authority, under applicable statutes and regulations, to refuse to approve the application (in the case of a pending application) or to proceed to withdraw approval (in the case of an approved application), regardless of whether the applicant attempts to replace the unreliable data with a new submission in the form of an amendment or supplement. Thus, if the applicant wishes to replace the false data with a new submission, the new submission should be in the form of a new application. The new application should identify the parts of the original application that were found to be false. The truthfulness and accuracy of the new application should be certified by the president, chief executive officer, or other official most responsible for the applicant's operations.

FDA also may seek recalls of marketed products and may request new testing of critical products. For drugs, for example, retesting may be requested for products that are difficult to manufacture or that have narrow therapeutic ranges. FDA may pursue other actions, including seizure, injunction, civil penalties, and criminal prosecution, under the act or other applicable laws, as necessary and appropriate.

Corrective Actions

The corrective actions an applicant will be expected to take will depend upon the facts and circumstances of each case, the nature of the wrongful acts, the nature of the data under consideration, and the requirements of the particular review process.

Applicants who engage in wrongful acts ordinarily will need to take the following corrective actions to establish the reliability of data submitted to FDA in support of pending applications and to support the integrity of products on the market:

1. Cooperate fully with FDA and other Federal investigations to determine the cause and scope of any wrongful acts and to assess the effects of the acts on the safety, effectiveness, or quality of products;
2. Identify all individuals who were or may have been associated with or involved in the wrongful acts and ensure that they are removed from any substantive authority on matters under the jurisdiction of FDA;
3. Conduct a credible internal review designed to identify all instances of wrongful acts associated with applications submitted to FDA, including any discrepancies between manufacturing conditions identified in approved applications and manufacturing conditions during actual production. The internal review is intended to supplement FDA's ongoing, comprehensive investigation to identify all instances of wrongful acts. The internal review should involve an outside consultant or a team of consultants who are qualified by training and experience to conduct such a review. All oral or written reports related to the review that are provided by the consultant to the applicant should be made available simultaneously to FDA for independent verification;
4. Commit, in writing, to developing and implementing a corrective action operating plan to assure the safety, effectiveness, and quality of their products. This commitment ordinarily will be in the form of a consent decree or agreement, signed by the president, chief executive officer, or other official most responsible for the applicant's operations, and submitted to FDA. The corrective action operating plan will, as appropriate, address procedures and controls to preclude future instances of wrongful acts and noncompliance with regulatory requirements for approved applications, as well as procedures and controls to preclude any recurrences of other violations which may have been found (e.g., a comprehensive ethics program).

FDA intends to reinspect the applicant to determine that the internal review has been satisfactorily completed and that the applicant's written corrective action operating plan has been satisfactorily implemented. Such inspections should disclose positive evidence (e.g., effective management controls, standard operating procedures, and corroborating documentation) that the applicant's data are reliable and that the applicant can be expected to manufacture products in compliance with current good manufacturing practices and application requirements. In addition, FDA may request an applicant to commit in writing to retest any product (including, in the case of drugs, bioequivalence and bioavailability retesting), as FDA deems appropriate. An applicant also may be requested under existing regulatory procedures to recall products affected by the wrongful acts, or otherwise lacking adequate assurance of safety, effectiveness, or quality.

Issued: 7/1/91

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