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Protecting the Public's Health Through the Application Integrity Policy

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There is no killing the suspicion that deceit has once begotten.
- *George Eliot,* Romola

Imagine the following scenario: your client, a major generic drug manufacturer with numerous pending Abbreviated New Drug Applications (ANDAs), has just been visited by FDA for a pre-approval inspection. At the close of the inspection, the investigator issued a multiple-observation FDA Form-483 noting numerous repeated deviations from Current Good Manufacturing Practices (CGMP) in the facility's manufacturing processes. The facility in question has a thorny inspectional history, which, of course, is part of the reason why the client has you on retainer. The compliance history includes FDA Form-483s from inspections over the past few years, Import Alerts, and previous Warning Letters for CGMP violations. You and your client have been back and forth with the Agency about the adequacy of the client's responses and corrective actions, often without reaching a satisfactory conclusion.

This time, however, the client indicates that there might be a new issue. During the inspection, investigators found that batch records your client had previously submitted in support of a pending ANDA contained the signatures of employees who were not present in the facility on the dates documented in the batch records. You and the client agree that this discovery portends yet another Warning Letter.

At this point, you might also begin preparing your client for the arrival of a different kind of letter, one that does more than indicate violations noted in an inspection. The firm's repeated failures to address Warning Letter deficiencies have probably eroded its credibility with FDA. With the discovery of falsified batch records in the latest inspection, the Agency has evidence that your client submitted fraudulent data in support of a marketing approval application, and the discovery of these falsified batch records may have tipped the scales. The Agency's next move may well be to invoke the Application Integrity Policy (AIP).[1]

FDA invokes the AIP when a company's actions raise significant questions about the integrity of data in drug applications.[2] When the AIP is implemented, FDA stops all substantive scientific review of new or pending drug approval applications that contain data generated by the facility in question.[3] The basic logic is that if an applicant engages in practices that raise significant doubts about the reliability of data used to support one or more applications, FDA must pause to assess whether the data in any of the applicant's submissions are reliable. Thus, under the AIP, the Agency's review divisions halt the review of pending applications until the agency has been able to determine the validity of the data in those applications and all questions regarding data reliability are resolved.

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[1] "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities: Final Policy." 56 FR 46191 (Sept. 10, 1991). (Issued as Compliance Policy Guide (CPG) 7150.09.) (hereinafter "AIP CPG")

[2] The Application Integrity Policy applies to all Centers across FDA.

[3] AIP CPG, supra note 1.

FDA's drug approval program seeks information about the safety and efficacy of products. This assessment depends heavily on the reliability of data and information submitted in support of applications for approval and manufacturing controls documentation. The Agency's experience with broad-scale unreliability of data in records submitted to support marketing approval applications, particularly fraudulent data submitted in premarket approval applications during the generic drug scandal, led FDA to establish the AIP in the early 1990s.

Although the AIP was once called "the fraud policy," the AIP is better understood as the Agency's approach to reviewing applications that may be affected by unreliable data.[4] The policy has two enumerated goals: first, "to ensure validity of data submissions called into question by the Agency's discovery of wrongful acts," and, second, "to withdraw approval of, or refuse to approve, applications containing fraudulent data."[5] Under the policy, if FDA determines that the criteria for approval cannot be met because of unresolved data integrity issues, it will not approve the application. Further, if the data integrity questions relate to approved applications, the AIP provides for withdrawal of approval, as well as recalls, additional testing, and other measures. Accordingly, the AIP is a powerful tool for protecting the health of the public because it prevents products affected by wrongful acts from reaching consumers, and it can reduce exposure when such products are already on the market.

The AIP is a directive to FDA staff in furtherance of the agency's mission to protect the health of the public.[6] It establishes a framework for investigating wrongful acts that may call into question the integrity of some or all of an applicant's submissions to the agency, and hence, that call into question the integrity of the products marketed by the companies that commit such wrongful acts. For the purposes of the AIP, a wrongful act is any act or conduct that subverts the integrity of the review process.[7] These "wrongful acts" include, but are not limited to, the following: submitting fraudulent applications; offering or promising bribes or illegal gratuities; making untrue statements of material fact (*e.g.* a false statement, a misstatement or an omission of a fact); and submitting unreliable data that results from system-wide or firm-wide behavior.[8]

Submitting data that lacks integrity, such as data that is untrue, false, inaccurate, or lacks a source in an actual event, is a wrongful act under the AIP. This type of data is unreliable and may affect the agency's actions in reviewing an application, resulting in the marketing of products that do not meet the Agency's requirements for safety and efficacy. The omission of information that could affect the evaluation of a product's safety and efficacy is also a wrongful act under the AIP. For example, a firm might find that a first round of analysis yields data that fails manufacturing specifications. If the firm retests to obtain passing results but fails to conduct a lab investigation, and later submits only the retest data in an application, omitting the initial failing results from the application could be a wrongful act under the AIP.

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[4] The AIP defines the terms "applicant" and "application" quite broadly: "applicant [includes] any person within the meaning of section 201(e) of the Federal Food, Drug, and Cosmetic Act…who submits to FDA data or other information to influence or support an agency decision regarding approval to market an FDA-regulated product." Under the AIP, "application" references 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." *Id.*

[5] *Id.*

[6] Note that the AIP was issued as Compliance Policy Guide 7150.09. Compliance Policy Guides, by definition, are *staff* directives that provide direction to FDA management on compliance and enforcement issues. They are not binding on FDA or any other parties.

[7] AIP CPG, *supra* note 1

[8] *Id.*

Once FDA discovers a wrongful act, it may opt to invoke the AIP following a thorough investigation and analysis of the evidence. The Agency must document a "pattern or practice" of wrongful conduct that raises significant questions about the reliability of data submitted to support an application or applications, and it also must make a determination that the wrongful act is material to the agency's decision-making process regarding application approval.[9]

The AIP rests on the premise that applications should not be approved if the data are unreliable, or when there are data integrity, safety or efficacy concerns, until the relevant Center is satisfied that the issues in question are resolved.[10] When FDA places an applicant on AIP, two things occur. On the one hand, the Agency ordinarily pauses all substantive scientific review of the applicant's pending applications that may be affected by data generated at the site of the wrongful acts.[11] On the other hand, the Agency shifts its resources to assess the validity of the data and information in all of the applications affected by the wrongful acts.

This "validity assessment" is considered part of the review of those applications, and ordinarily takes priority over any substantive scientific review of the applications until the data integrity issues are resolved.[12] The validity assessment includes the Agency's determination of the scope and extent of an applicant's suspected wrongful acts and an Agency inspection of the firm, as well as Agency review of an extensive internal audit conducted by the applicant.[13]

The AIP describes several corrective actions that applicants are expected to take in order to restore FDA's confidence in their integrity and permit the agency to proceed with substantive scientific review of their premarket applications.[14] The AIP requires applicants to provide full cooperation with the agency and other regulators, identify individuals associated with the wrongful acts and remove them from positions in which they exercise authority over FDA-regulated matters, and conduct an extensive internal review. The applicant is also expected to develop and implement a written corrective action operating plan submitted to FDA.[15],[16] The agency will evaluate this plan and monitor the applicant's actions and behavior during the internal review.

After the close of the applicant's internal audit, FDA will reinspect the relevant facilities to ensure the adequacy of the internal review and implementation of the corrective action operating plan. Before formally revoking the AIP as to all of the applications on which it was invoked, FDA must have written assurance from the applicant that the applicant withdrew any questionable application(s) and com-

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[9] AIP CPG, *supra* note 1

[10] Office of Regulatory Affairs, "Application Integrity Policy Procedures March 5, 1998." available at http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm072628.htm (last visited June 11, 2010) (hereinafter "AIP Procedures.")

[11] In the case of the Center for Drug Evaluation and Research (CDER), the substantive scientific review includes CMC review, labeling review, and other data.

[12] The AIP provides for exceptional circumstances in which the Agency may review and act on an application prior to completion of the validity assessment (e.g., in cases where the application is for a product of public health significance). *supra* note 10

[13] AIP CPG, supra note 1; AIP Procedures, supra note 10.

[14] AIP CPG, *supra* note 1.

[15] *Id.*

[16] 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" ("Points to Consider"), the availability of which was announced in the same issue of the Federal Register as the AIP CPG. Points to Consider is available at http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134744.htm (last visited June 11, 2010).

mitted in writing: (a) not to 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.[17] Even after successful reinspection and validation of the reliability of an applicant's data, FDA may request that an applicant further commit in writing to retesting, recalls and other monitoring requirements as a predicate for formally revoking the AIP. [18]

In the wake of the generic drug scandal, the Agency undertook a number of AIP investigations shortly after the AIP was published in 1991, and several firms were placed on the policy. Very few firms have been subject to AIP actions in recent years, but interest in the policy has recently re-emerged in light of enforcement actions against Ranbaxy Laboratories Limited, a major producer of generic drugs.

On February 25, 2009, FDA announced that it had invoked the AIP for Ranbaxy's Paonta Sahib, India site because of falsified data and test results in pending and approved applications.[19] In a letter notifying Ranbaxy of the decision to invoke the AIP, CDER Director Dr. Janet Woodcock wrote that FDA "determined that [Ranbaxy] submitted untrue statements of material fact in abbreviated and new drug applications filed with the Agency."[20] The letter identified a number of observations that supported the conclusion that Ranbaxy had engaged in a pattern of submitting untrue statements of material fact. Among the patterns and practices of wrongful acts, FDA uncovered the omission of critical information regarding stability testing storage conditions; a Warning Letter response submitting test dates that differed from dates originally submitted in a marketing application; reports prepared by outside consultants that identified storage times and conditions different from those in protocols submitted to the agency; verification reports identifying errors in testing dates, data results and changes of specification limits; falsified stability test results; and submission of falsified batch records.[21]

After uncovering evidence of these wrongful acts during several years of inspections and enforcement actions, FDA's investigations ultimately revealed a pattern of questionable data raising questions about facts material to the evaluation of applications from the Paonta Sahib facility.[22] When it invoked the AIP, FDA asked Ranbaxy to cooperate with the agency to resolve the questions of data integrity and

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[17] AIP Procedures, *supra* note 10

[18] AIP CPG, *supra* note 1

[19] "FDA Takes New Regulatory Action Against Ranbaxy's Paonta Sahib Plant in India" (February 25, 2009) available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm149532.htm (last visited June 11, 2010) (hereinafter "AIP News Release.")

[20] Letter from Dr. Janet Woodcock, CDER Director, to Mr. Malvinder Mohan Singh, Ranbaxy CEO and Managing Director (February 25, 2009). available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/ucm118418.pdf (last visited June 11, 2010).

[21] *Id.*

[22] The February 25, 2009 AIP action followed several years of enforcement actions against Ranbaxy. On Sept. 16, 2008, the FDA issued two Warning Letters and instituted an Import Alert barring the entry of all finished drug products and active pharmaceutical ingredients from Ranbaxy's Dewas, Paonta Sahib and Batamandi Unit facilities due to CGMP violations. That action barred the commercial importation of 30 different generic drugs into the United States and remains in effect. In addition, the Agency has continued to investigate other Ranbaxy facilities for data integrity issues and has issued Warning Letters to the company's facilities in India and the United States, including one on December 24, 2009. *See* Jim Edwards, "Ranbaxy's Christmas Turkey: FDA Again Warns Disaster-Prone Company." (December 24, 2009) a*vailable at* http://industry.bnet.com/pharma/10005885/ranbaxys-christmas-turkey-fda-again-warns-disaster-prone-company (last visited June 11, 2010).

reliability. Among other things, Ranbaxy has withdrawn several pending ANDAs, retained a third-party consultant to audit the Paonta Sahib facility and developed a corrective action operating plan, which it submitted to FDA in May 2009.[23]

As Deborah Autor, director of CDER's Office of Compliance stated, invoking the AIP against Ranbaxy "reflect[ed] the FDA's continued vigilance and its steadfast commitment to safeguarding the public's health."[24] It also indicates a renewed interest within the agency, throughout industry and among the public in the workings of one of FDA's more powerful but lesser-known tools for protecting the health of the public. As regulated companies rely more heavily the submission of electronic data in support of marketing applications, CDER's Office of Compliance expects that the number of AIP investigations will increase as the agency develops more sophisticated tools for analyzing data integrity issues.

In conjunction with the Ranbaxy AIP action, and in light of the possibility that more AIP cases will develop, CDER's Office of Compliance is currently undertaking an initiative to raise awareness of the AIP within CDER and improve internal procedures for improving the ways to address integrity issues raised by the policy. A working group within the Office of Compliance has revised internal procedures for investigating AIP cases. The group also currently offers AIP education and training to FDA staff, including field investigators as well as reviewers and compliance staff at CDER. The training focuses on the substance of AIP cases (what types of "red flags" to report as potential data integrity problems, how to develop evidence and conduct investigations/inspections, etc.). It also provides staff with a clear understanding of the AIP procedures, and links the AIP with the agency's broader goal of protecting the public's health.

"Companies must provide truthful and accurate information in their marketing applications," said CDER Director Dr. Janet Woodcock.[25] "The American public expects and deserves no less." The Application Integrity Policy helps protect the health of the public by directing FDA to investigate wrongful acts that may call into question the integrity of some or all of an applicant's submissions to the agency, and hence, that call into question the integrity of the products marketed by the companies that commit such wrongful acts.

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[23] *Id.*

[24] AIP News Release, *supra* note 19

[25] *Id.*