

## **HYPOTHETICAL CASE STUDY 2: PRODUCT APPLICATIONS THAT ARE ABANDONED OR WITHDRAWN BY THE APPLICANT BEFORE APPROVAL.**

Company X is developing a drug for both acute and chronic treatment of a serious disease. The Company conducts two relatively short-term, randomized controlled clinical trials of the drug for the acute indication. A small percentage of the study subjects report mild side effects, but there is no statistically significant difference in the rate or severity of adverse events between the drug and control groups.

Based on the results of its first two clinical studies, Company X submits a new drug application (NDA 1) to FDA for the acute indication, while continuing to conduct long-term trials to support a chronic indication for the same disease.

Company X then merges with Company Y and Company Y acquires NDA 1. Shortly after the merger, Company Y withdraws NDA 1. SEC filings indicate that Company Y had submitted an NDA (NDA 2) for a similar drug for the same acute and chronic indications.

### **Issues for Discussion:**

(Note: Because the purpose of the discussion is to elucidate the policy considerations that should be weighed in deciding whether changes to current practice, laws, or regulations are warranted, the issues should be discussed without regard for current practice, laws, or regulations.)

Fact of withdrawal: Should FDA disclose the fact that Company Y has withdrawn NDA 1? What are the factors that should be considered in deciding whether to do so? Should FDA consider affirmative disclosure (i.e., posting on FDA.gov) or only disclose the information in response to a request?

Reason for withdrawal: Should FDA disclose why Company Y has withdrawn NDA 1? It appears that this was for business reasons because the new company does not want to pursue two drugs for the same indication. However, FDA may not know the real reason why the application was withdrawn. Applicants are not required to tell FDA why they are withdrawing an application. How does this affect the analysis? Should FDA consider affirmative disclosure or only disclose the information in response to a request?

Summary of FDA reviews: Should FDA disclose a summary of its review of NDA 1? What are the factors that should be considered in deciding whether to do so? Does the reason for the withdrawal matter? If the application is withdrawn early in the review, not much information would be available for a summary. Does the timing of the withdrawal in the course of the review matter? Should FDA consider affirmative disclosure or only disclose the information in response to a request?

Disclosure of data from the application: Should any data from NDA 1 be disclosed? What factors should be considered in deciding whether to do so? What information should be disclosed (e.g., toxicology data, safety and efficacy data, raw data, summary reports)? Should the information be affirmatively disclosed or only disclosed in response to a request? Who should be responsible for disclosing this information, FDA or the applicant?

## **HYPOTHETICAL CASE STUDY 2: PRODUCT APPLICATIONS THAT ARE ABANDONED OR WITHDRAWN BY THE APPLICANT BEFORE APPROVAL.**

FDA analysis of the data in Company Y's NDA 2 reveals a small number of cases of slightly elevated liver enzymes in study subjects in the short-term trials. FDA notifies Company Y and asks the company to look at the data in the long-term trials which have not yet been submitted. Company Y stops the trials, notifies FDA of a safety concern, and then withdraws NDA 2 because it determines that both short-term and long-term use of the drug could be associated with liver toxicity.

### **Issues for Discussion:**

(Note: Because the purpose of the discussion is to elucidate the policy considerations that should be weighed in deciding whether changes to current practice, laws, or regulations are warranted, the issues should be discussed without regard for current practice, laws, or regulations.)

Do these facts affect the analysis in response to the questions above? If so, how?

Fact of withdrawal: Should FDA disclose the fact that Company Y has withdrawn NDA 2? How does the fact that NDA 2 was withdrawn for safety reasons affect the analysis of the factors that should be considered in deciding whether to do so? Should FDA consider affirmative disclosure or only disclose the information in response to a request?

Reason for withdrawal: Should FDA disclose why Company Y has withdrawn NDA 2? It appears that the reason for withdrawing the application was based on a safety concern but a link between the adverse events and drug use was not definitively established. FDA may not know the real reason why the application was withdrawn. How does this affect the analysis?

Summary of FDA reviews: Should FDA disclose a summary of its review of the application? How does the fact that NDA 2 was withdrawn for safety reasons affect the analysis of the factors that should be considered in deciding whether to do so? Does the timing of the withdrawal in the course of the review matter?

Disclosure of data from the application: Should any data from NDA 2 be disclosed? What factors should be considered in deciding whether to do so? What information should be disclosed (e.g., toxicology data, safety and efficacy data, raw data, summary reports)? Should the information be affirmatively disclosed or only disclosed in response to a request? Who should be responsible for disclosing this information, FDA or the applicant?

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FDA issues Company Y a complete response letter for NDA 2 describing FDA's concerns about liver toxicity associated with this class of drug. Company Y voluntarily suspends all studies of the drug and does not respond to the complete response letter. Several years pass. The application is considered abandoned.

Another company, Company Z, submits an investigational new drug application (IND) for another molecule in the same drug class which is very similar in chemical structure and has the same mode of pharmacological action as those in NDAs 1 and 2. Based on its knowledge of the potential for liver toxicity that it acquired through the review of Company Y's applications, FDA places the IND on clinical hold. A clinical hold means that a study may not proceed until deficiencies in the study are addressed. FDA may place an IND on clinical hold because the drug poses a risk to study subjects, or for various other reasons. Company Z wants to know why FDA put the study on hold.

**Issues for Discussion:**

(Note: Because the purpose of the discussion is to elucidate the policy considerations that should be weighed in deciding whether changes to current practice, laws, or regulations are warranted, the issues should be discussed without regard for current practice, laws, or regulations.)

**This scenario assumes that the withdrawal of NDA 2 and the reason for the withdrawal are not publicly disclosed.**

Disclosure to Company Z: Should FDA disclose the reason for the clinical hold to Company Z? How much information about the safety problem should be disclosed?

Other request for disclosure: A researcher is conducting research on liver toxicity and requests nonsummary preclinical and clinical information from any applications withdrawn or abandoned because of liver toxicity. Should FDA disclose the fact that Company Y's NDA 2 was abandoned and/or any data from the application? What about data from Company Y's NDA 1 or NDA 2? Who should be responsible for disclosing this information, FDA or the applicant?

Since Company Y abandoned NDA 2, it has discovered that the active metabolite of the drug is a promising treatment for a disease and preliminary studies indicate that the liver toxicity concerns are mitigated. Company Y is considering developing the drug. FDA may not know Company Y's business plans. Does this affect the analysis, and if so, how?