Arnall Golden Gregory LLP

Client Alert

Contact Attorneys Regarding This Matter:

William H. Kitchens
404.873.8644 - direct
404.873.8645 - fax
william.kitchens@agg.com

Jennifer S. Blakely
404.873.8734 - direct
404.873.8735 - fax
jennifer.blakely@agg.com

Lanchi Nguyen
404.873.8520 - direct
404.873.8521 - fax
lanchi.nguyen@agg.com

Arnall Golden Gregory LLP
Attorneys at Law
171 17th Street NW
Suite 2100
Atlanta, GA 30363-1031
404.873.8500
www.agg.com

FDA Issues Final Rule and Draft Guidance on Safety Reporting Requirements for Investigational New Drugs and Biological Products

On September 29, 2010, the Food and Drug Administration (FDA) issued a final rule to clarify the requirements governing safety reporting requirements for human drug and biological products subject to an investigational new drug application (IND). The rule also imposes bioavailability (BA) and bioequivalence (BE) studies to safety reporting requirements (the Final Rule). 75 *Fed. Reg.* 59935 (September 29, 2010). The Final Rule, which becomes effective March 28, 2011, was concurrently published with a draft guidance for industry and investigators, entitled *Safety Reporting Requirements for INDs and BA/BE Studies* (hereinafter referred to as Guidance Document).[1]

The FDA believes the new requirements will enhance the quality of safety reporting of drugs and biological products and strengthen the agency's ability to review critical safety information, by reducing submissions of uninformative IND safety reports and clarifying the situations where certain adverse events should be reported in the aggregate (as opposed to individually). The Final Rule also revises several definitions and reporting standards to be more consistent with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use and the World Health Organization's Council for International Organizations of Medical Sciences.

This bulletin provides an overview of the more significant provisions of the Final Rule and the related FDA Guidance Document, including the new terms and definitions related to safety reporting for INDs, examples to help sponsors assess the need for reporting of new safety information and IND safety reports and the new reporting requirements for BA/BE studies for biological products.

New Terms and Definitions

The FDA requires sponsors investigating a drug pursuant to an IND to submit a written IND safety report of any adverse experience "associated with the use of the drug" that is both "serious" and "unexpected." 21 C.F.R. § 312.32(c). The agency defines the phrase "associated with the use of the drug" to mean situations where there is a reasonable possibility that the adverse experience is caused by the drug; however, sponsors often report all serious adverse experiences due to confusion or excessive caution, resulting in uninformative

1 These documents are available on the FDA's website at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm226358.htm

reports to the agency on events where it is unlikely that the drug caused the event. Because the task of processing these reports diverts the agency's resources from more important tasks without contributing to the development of the drug product's safety profile, the FDA sought by promulgating the Final Rule to clarify problematic areas in the reporting requirements.

To improve the quality and safety reporting, the Final Rule adds to the definitions in 21 C.F.R. § 312.32(a) related to safety reporting and explains when individual safety reports must be submitted on an expedited basis. Specifically, the Final Rule and the Guidance Document provide for the following:

- Substitution of two terms, "adverse event" and "suspected adverse reaction," for the definition of the phrase, "associated with the use of the drug," to help sponsors make a clear distinction regarding the degree of evidence required to suggest a causal relationship between the adverse event and the drug.

- Clarification that "adverse event" refers to any untoward medical occurrence associated with the use of a drug, regardless of whether the occurrence is considered drug-related. In contrast, "suspected adverse reaction" means any adverse event for which there is a reasonable possibility (i.e., evidence to suggest a causal relationship) that the drug caused the adverse event.

- The sponsor or investigator must make the determination of whether an adverse event or suspected reaction is "life-threatening" or "serious" for reporting purposes.

- An adverse event or suspected reaction is considered "unexpected" if the occurrence is not listed in the investigator brochure (or at the specificity or severity observed) or if the occurrence is not specifically mentioned in relation to the particular drug under investigation (i.e., mentioned as occurring with a class of drugs only). Because the term "unexpected" is defined only in context to the investigator brochure (or the general investigational plan), adverse events anticipated to occur as part of the underlying disease process are considered to be "unexpected" for the purposes of safety reporting.

Reporting of New Safety Information and IND Safety Reports

Under 21 C.F.R. § 312.32(b), sponsors are required to review promptly all information, from domestic or foreign sources, that may be relevant to the safety of the drug under investigation. Literature searches should be done at least annually, or at other appropriate intervals, to locate any safety information. The Final Rule provides examples of possible sources of information, such as clinical or epidemiologic investigations, animal or in vitro studies, scientific literature, unpublished scientific papers or any other sources (i.e., presentations of safety information from professional meetings). Reports from foreign regulatory authorities or commercial marketing experience (from drugs not approved in the United States) must also be reviewed and reported, as appropriate. Sponsors must also have a process to address the periodic review and analysis of the entire safety databases to facilitate safety reporting and to update investigator brochures, as appropriate.

The Final Rule clarifies the timing for the submission of IND safety reports, as well as the format of such submissions (e.g., certain reports must be in narrative format). Whenever a potentially serious risk from a clinical trial or any other source is identified and assessed, sponsors must submit an IND safety report to notify the FDA and all participating investigators as soon as possible, but no later than 15 calendar days after such a determination is made. 21 C.F.R. § 312.32(c) (as amended by the Final Rule). Similar suspected adverse reactions previously submitted in other safety reports should be addressed and analyzed in the new safety report, in addition to any other relevant information.

IND safety reports are required when:

1. A suspected adverse reaction is identified that is serious and unexpected;
2. Findings from various studies or animal or in vitro testing suggest a significant risk in humans exposed to the drugs;[2] or
3. There is a clinically important increase in the rate of a serious suspected adverse reaction over the baseline incidence rate listed in the protocol or investigator brochure, based upon factors such as the study population, the nature and seriousness of the reaction and the magnitude of the increase in rate.

Concerning the reporting of suspected adverse reactions, the Final Rule specifies that a report should be submitted only if there is evidence to suggest a causal relationship between the drug and the adverse event. The Guidance Document discusses the type of evidence that would suggest a causal relationship:

- An individual occurrence where the serious adverse event is uncommon and known to be strongly associated with drug exposure (i.e., blood dyscrasias, rhabdomyolysis, angioedema, liver injury, anaphylaxis) would be considered a suspected adverse reaction requiring a safety report.

- An individual or small number of occurrences where the serious adverse event is uncommon in the study population but not commonly associated with drug exposure in certain circumstances may require a safety report. Factors strongly suggesting causation may support the need to submit a safety report for a single case (e.g., strong temporal association, recurrence with rechallenge); however, for most events, more than one occurrence would typically be needed before the sponsor could find that a reasonable possibility exists that the drug caused the event.

- Occurrences that are expected to be seen in the study population independent of drug exposure (i.e., cardiovascular events in the elderly population) or the known consequences of the underlying disease (i.e., non-acute death in cancer patients) will meet the definition of "unexpected," as they are not listed in the investigator brochure. However, such incidents do not warrant expedited reporting as individual cases because it is not possible, based on a single case, to determine that there is a reasonable possibility that the drug caused the event.

2 Significant risks would also typically require a safety-related amendment to the protocol, the informed consent, the investigator brochure, and possibly other aspects of the clinical investigation, in addition to the IND safety report.

For reporting serious adverse events that are study endpoints, the FDA recommends that sponsors develop a protocol for monitoring such outcomes and making related reports. For serious adverse events that are not study endpoints, the agency suggests that the number of such events be tracked and reported (in the aggregate) in an IND safety report if the analysis suggested that there is a reasonable possibility that the drug caused the adverse event. In general, sponsors should also have a systematic approach in place for safety surveillance, which includes processes for the review, evaluation, and management of safety data from the entire clinical trial database at appropriate intervals.

Other Safety Reporting Issues

Alternative Reporting Arrangements

Under 21 C.F.R. § 312.32(c)(3), sponsors are permitted to propose alternative reporting formats or frequencies for submitting IND safety reports; this requirement has not changed in the Final Rule. However, the Final Rule provides that the FDA may also require a sponsor to submit IND safety reports in a different format or at a different frequency than required under 21 C.F.R. §§ 312.32(c)(1) and 312.32(c)(1)(v). Previously, the language stated that the FDA "may request" rather than "may require" a sponsor to submit IND safety reports in a different format or at a different frequency. In addition, the FDA may require a sponsor to continue to report expeditiously a medically significant suspected adverse reaction that is listed in the investigator brochure as observed with the drug (i.e., expected) so that its rate can be carefully monitored.

Investigator Brochure

The Guidance Document notes that, although the most important purpose of the investigator brochure is to provide the investigator with information about the investigational product, the investigator brochure is also used by the sponsor as the basis for determining if a suspected adverse reaction is *unexpected* for purposes of IND safety reporting. In general, the investigator brochure should include the information that is important for the investigator who is administering the drug to human subjects to know and understand. The investigator brochure is also required to include information about the drug substance and formulation, pharmacological and toxicological effects of the drug in animals (and in humans, if known), pharmacokinetics and biological disposition of the drug in animals (and in humans, if known), information relating to safety and effectiveness in humans obtained from prior clinical studies, and information about possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and precautions or special monitoring to be done as part of the investigational use of the drug.

The Guidance Document provides that with respect to clinical risk information, the investigator brochure should list those adverse events that have been observed with an investigational drug and for which a casual relationship with the drug is suspected and confirmed. Additionally, the investigator brochure should list adverse events that commonly occur with the class of drugs or may be predicted to occur based on the pharmacological properties of the drug, even if not yet observed with the drug under investigation, to alert the investigator to the possibility of their occurrence.

The Guidance Document also sets forth when the investigator report should be updated. For instance, the sponsor is required to update the investigator brochure on an ongoing basis with new important safety information. Until the investigator brochure is updated to include a new serious, suspected adverse reaction, subsequent occurrences of similar serious, suspected adverse reactions must be submitted expeditiously in IND safety reports.

Unblinding

The Final Rule addresses "maintaining the blind" in a blinded clinical trial.[3] The Final Rule provides that in some situations, to determine whether a single adverse event is a serious, unexpected, suspected adverse reaction, the sponsor or investigator may need to break the blind for a patient. The FDA notes that what treatment the patient received could provide critical safety information about the drug that could have implications for the ongoing conduct of the trial (e.g., monitoring, informed consent). However, if patient safety can be assured without unblinding the patient's information, the sponsor is permitted to seek an alternative reporting arrangement from the FDA. Further, if a sponsor anticipates using an alternative reporting arrangement that will maintain the blind, that arrangement should be described in the study protocol, including identification of the serious adverse events that will not be reported on an individual basis and the plan for monitoring and reporting results to the FDA.

The FDA suggests that a Data Monitoring Committee (DMC) could be used to analyze and evaluate unblinded, aggregate adverse events to determine whether the events should be reported as serious, unexpected, suspected adverse reactions. Notably, using a DMC would allow investigators to remain blinded but would potentially greatly expand the responsibilities of many DMCs.

Investigator Reporting

The Final Rule revises the investigator reporting requirements. Under the revised regulations, investigators are required to immediately report to sponsors all serious adverse events, whether or not the events are drug-related, and whether or not they are expected. Investigators must also provide sponsors with an assessment of whether there is a "reasonable probability" that the drug caused the event.

Safety Reporting for IND Studies for Drugs Already Marketed in the United States

The Final Rule clarifies that sponsors must report suspected adverse reactions observed in a clinical study conducted under an IND, even when the drug is already marketed in the United States for another indication or population. The requirement to file an IND safety report does not eliminate the postmarketing safety reporting requirements described in 21 C.F.R. §§ 310.305, 314.80, and 600.80.

Submitting an IND Safety Report and Follow-up Information

The Guidance Document provides specific guidance on the format of the IND safety reports, where to submit the IND safety reports, and reporting timeframes. With respect to format, the format for IND safety

3 A blinded study is a study where some of the participants involved are prevented from knowing certain information that might lead to conscious or unconscious bias on their part, thereby invalidating the results. Unblinding occurs when there is a disclosure, planned or unintended, of the allocation of one, a group, or all of the participants.

reports is based on the type of expedited report. For reports of individual cases, a sponsor would ordinarily use FDA Form 3500A. The FDA will accept foreign suspected adverse reaction reports on a Council for International Organizations of Medical Science (CIOMS) I Form instead of FDA Form 3500A. 21 C.F.R. § 312.32(c)(1)(v). These forms should be completed with all available information, including a brief narrative describing the suspected adverse reaction and any other relevant information. If applicable, the narrative must also include identification of similar reports and an analysis of the significance of the suspected adverse reaction. 21 C.F.R. § 312.32(c)(1).

The IND safety reports are required to be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. As to the timeframe for submitting an IND safety report to the FDA and all participating investigators, the reports must be submitted no later than 15 calendar days after the sponsor determines that the suspected adverse reaction or other information qualifies for reporting. 21 C.F.R. § 312.32(c)(1). However, if the FDA requests any additional data or information, the sponsor must submit it to the FDA as soon as possible, but no later than 15 calendar days after receiving the request. 21 C.F.R. § 312.32(c)(1)(v). Unexpected fatal or life-threatening suspected adverse reactions must be reported more rapidly to the FDA, but no later than seven calendar days after the sponsor's initial receipt of the information.

As to follow-up information, the Final Rule eliminates the requirement that sponsors report follow-up information both within 15 days and in an information amendment or the annual report. The revised regulations only require the 15-day follow-up report.

Safety Reporting Requirements for BA and BE Studies

The Final Rule contains new safety reporting requirements under 21 C.F.R. § 320.31(d)(3) that apply to persons conducting bioavailability (BA) and bioequivalence (BE) studies that are exempt from the IND requirements. Specifically, the person conducting a BA or BE study, including any contract research organization, must notify the FDA and all participating investigators of any serious adverse event observed during conduct of the study, regardless of whether the event is considered drug-related, as soon as possible but in no case later than 15 calendar days after becoming aware of its occurrence. 21 C.F.R. § 320.31(d)(3). Serious adverse events observed in the investigational drug group and in the approved drug group (e.g., reference listed drug) must be reported.

Any relevant additional information that is obtained and concerns a previously submitted safety report must be submitted to the FDA as a *Follow-up Bioavailability/Bioequivalence Safety Report* as soon as the information is available. In addition, upon request from the FDA, the person conducting the study must submit to the FDA any additional data or information that the FDA deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request. However, if the adverse event is fatal or life-threatening, the person conducting the study must also notify the Office of Generic Drugs within CDER as soon as possible, but in no case later than seven calendar days after becoming aware of its occurrence. The

Guidance Document recommends that these notifications be made by telephone or facsimile transmission.

Each report must be submitted on FDA Form 3500A. The form should be completed with all the available information, including a brief narrative describing the serious adverse event, an assessment of causality and any other relevant information. If applicable, the narrative should also include identification of other similar reports and an analysis of the significance of the serious adverse event. A summary of the study protocol should be submitted with the report. Each report must bear prominent identification of its contents. 21 C.F.R. § 320.31(d)(3).

Conclusion

While many of the requirements in the Final Rule are not new, they clarify existing requirements to promote submission of meaningful safety information. As noted in the Guidance Document, many sponsors already have processes in place for ongoing surveillance of accumulating safety information. Importantly, the FDA does not anticipate that implementation of these new requirements will require sponsors to make major changes to their current practices or ongoing clinical trials. Nevertheless, sponsors should review their ongoing clinical trials and, if a sponsor has any questions about whether changes are necessary to meet the new requirements (e.g., aggregating certain serious adverse events, not reporting study endpoints as IND safety reports), the sponsor should contact the FDA review division responsible for the IND.