Arnall Golden Gregory LLP

Client Alert

Contact Attorneys Regarding This Matter:

Alan G. Minsk
404.873.8690 - direct
404.873.8691 - fax
alan.minsk@agg.com

Diana Rusk Cohen
404.873.8108 - direct
404.873.8109 - fax
diana.cohen@agg.com

FDA Issues New Draft Guidance on Combination Therapy Codevelopment

Combination therapy—the use of two or more dugs to treat a disease or condition—has become an increasingly important treatment option in fields such as oncology and infectious diseases. In December 2010, the Food and Drug Administration (FDA) issued a new draft guidance, *Guidance for Industry: Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination*, to assist pharmaceutical companies in developing such combination therapies.[1] The draft guidance advises combination therapy sponsors on how to address scientific and regulatory issues that will arise during codevelopment of two or more novel drug products.[2] Interested parties have until February 14, 2011 to submit comments on the guidance.[3]

I. Determining Whether Codevelopment is Appropriate

The guidance begins with guidelines for determining whether combination therapy codevelopment is an appropriate option. The agency explains that concurrent development will generally provide less information about the safety and effectiveness of individual drugs than would be obtained if each drug were developed in isolation. Thus, the FDA believes that codevelopment generally presents a higher risk than single-drug development protocols and should be reserved for situations that meet the following criteria:

- The combination is intended to treat a serious disease or condition.
- There is a compelling biological rationale for the use of the combination.
- A preclinical model or short-term clinical study on an established biomarker suggests that the combination has substantial activity and provides greater than additive activity or a more durable response (e.g., delayed resistance) compared to the individual agents alone.
- There is a compelling reason why the agents cannot be developed individually.

1 For a link to the draft guidance, please go to http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf.

2 For purposes of the draft guidance, the FDA defines "codevelopment" as the "concurrent development of two or more drug products with the intent that the products be used in combination to treat a disease or condition." FDA, *Guidance for Industry: Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination*, at 1. "Novel drug products" refers to drug products that have not been previously marketed. *Id.* The guidance is not intended to apply to development of fixed-dose combinations of already marketed drugs or to development of single new investigational drugs to be used in combination with approved drugs. *Id.*

3 The FDA's Federal Register notice about the draft guidance includes more information on the comment process. See 75 F.R. 78,259, 78,259 (Dec. 15, 2010), available at http://www.regulations.gov/#%21documentDetail;D=FDA-2010-D-0616-0001.

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

The FDA recommends that potential combination therapy sponsors review these guidelines and consult with the agency early in the process to discuss whether codevelopment is appropriate.

II. The Codevelopment Process

The FDA draft guidance describes the various studies and phases of development that will help to support a successful codevelopment process. Although a complete description of the scientific considerations relevant to drug codevelopment is beyond the scope here, we note some highlights.

- The agency states that the sponsor must adequately demonstrate the biological rationale for the combination therapy. Thus, the biology of the disease, pathogen, or tumor type should be sufficiently understood. Otherwise, sponsors will have difficulty providing a plausible biological rationale for the use of a combination therapy to treat the disease or condition.
  - o For example, in an oncology setting, the biological rationale for a combination therapy may be to intervene at different steps in the cell proliferation process.
  - o In an infectious disease setting, the rationale for a combination therapy may be to target different metabolic pathways or different steps in the pathogen replication cycle to reduce the chance of developing resistance to the therapy or increase efficacy in treating diseases caused by resistant organisms (such as multidrug-resistant atypical tuberculosis).

- The FDA advises sponsors to develop evidence to support the biological rationale for the combination. Sponsors should develop an *in vivo* (preferable) or *in vitro* model that compares the activity of the combination to the activity of the individual components. The model should demonstrate that the combination has substantial activity and provides greater than additive activity or a more durable response in a pathophysiological process considered pertinent to the drug's intended use in humans.

- With respect to nonclinical safety characterization, the agency instructs sponsors to consult the International Conference on Harmonisation (ICH) *Guidance on Nonclinical Safety Studies*. Section XVII of the ICH guidance includes a discussion of nonclinical safety studies appropriate in a combination therapy development setting.

- Early human studies (phase 1): The FDA explains that a main objective of early human studies is to characterize the safety and pharmacokinetics of (1) the individual components, and (2) the combination. Another primary objective at this phase is to provide data to support appropriate dosing for the combination in phase 2.
  (1) Safety of the individual components: Whenever possible, the safety profile of each drug should be characterized in phase 1 studies in healthy volunteers in the same manner as would be done for development of a single drug. The safety profile for each drug should include a determination of the maximum tolerated dose, the nature of the dose limiting toxicity, and pharmacokinetic parameters.

— If testing in healthy volunteers is not possible, the safety profile of the individual drugs should be evaluated in patients with the target disease.
— If it is not possible to characterize the safety of the individual drugs in humans, the sponsor should conduct nonclinical studies of the combination to support initial dosing of the combination in humans. The nonclinical data for the combination should include pharmacokinetic and toxicokinetic data and appropriate biomarker/target inhibition, if relevant.

(2) Safety and dosing of the combination: The combination starting dose, dosing escalation intervals, and doses to be used in dose-response studies should be determined based on phase 1 safety data for the individual components. If phase 1 safety data for the individual components are unavailable, nonclinical data for the combination will be needed to determine the initial combination dose in humans.

- Sponsors should conduct the same clinical pharmacology studies for each of the individual drugs in the combination as would be done if the drugs were being developed separately.
  - Such studies generally include bioavailability assessments, characterization of pharmacokinetics and mass balance.
  - Sponsors should also study the individual components or the combination to evaluate how intrinsic (e.g., renal impairment) and extrinsic (e.g., drug interactions) factors affect pharmacokinetics, pharmacodynamics and exposure-response.
  - Dose-response should be evaluated for each drug of the combination, and the results of such studies should be used to determine doses to further explore for the combination. If the drug products cannot be administered alone, various doses of each drug administered in combination should be assessed.
  - Sponsors should also evaluate the response to systemic drug concentration. The FDA states that such evaluations will provide insight into efficacy and safety as a function of drug exposure. Concentration-response assessments should be done in both phase 2 and phase 3 trials.

- Proof of concept studies (phase 2): The FDA explains that phase 2 testing should accomplish the following three things (to the extent not already established by existing data):
  (1) Demonstrate the contribution of each component of the combination
  (2) Provide evidence of the effectiveness of the combination
  (3) Optimize the dose or doses of the combination for phase 3 trials.

  The agency notes that the amount and types of clinical data needed and appropriate study designs will vary depending on the nature of the combination being developed, the disease and other factors.
  - The agency notes that the study design typically used to determine the contributions of components to a combination is a four-arm factorial design comparing the combination to individual components and placebo or standard of care (SOC) therapy. However, the agency acknowledges that this design may be of minimal utility because, for the types of combinations contemplated in the draft guidance, studies involving monotherapy treatment arms will often

be inappropriate (e.g., because the components cannot be administered individually, or at least one component is inactive or minimally active in isolation).

- In light of this complication, the draft guidance offers several scenarios that illustrate possible phase 2 study designs. For example, the guidance describes a scenario where early studies suggest that one drug is inactive or minimally active and one drug is modestly active.[4] In this scenario, the agency suggests that proof of concept and the contribution of each component drug could be demonstrated using a three-arm comparison of the active drug alone, SOC, and the combination. Alternatively, where the SOC is a known effective therapy, the three-arm design could compare the combination added to the SOC, the individual drug added to the SOC, and the SOC.
- The FDA also notes that dose-finding studies could be critical to refine the combination dose (or doses) and select doses for phase 3 trials. Depending on the role of each component, it may be useful to test multiple doses of both components to establish a best dose in terms of risks and benefits.

- Confirmatory studies (phase 3): The FDA will require different showings at phase 3 depending upon what has (or has not) been shown in the earlier phases. For example, if findings from an earlier phase of development adequately demonstrate the contribution of each component to the combination, phase 3 trials comparing the combination to a placebo will generally be sufficient to establish effectiveness. However, if the contribution of individual components is not yet clear, it may be necessary to demonstrate the contribution of the components in phase 3 studies.

- The agency advises that unexpected toxicity (e.g., serious adverse events observed at higher than expected rates) in phase 2 trials is a potential complication for development of a combination that may delay progress to phase 3 trials. Appropriate steps to address unexpected toxicity will depend on whether the issue can be attributed to one component of the combination and whether it is possible to conduct phase 3 trials using a lower dose of the more toxic component. The specifics of any phase 3 design should be discussed with the appropriate FDA review division at the End-of-phase 2 meeting.

III. Regulatory Issues in Codevelopment

The draft guidance concludes with a brief overview of regulatory issues that may arise during the combination therapy codevelopment process and FDA recommendations to maximize opportunities.

- Early and Frequent Communication with the FDA: The guidance emphasizes that early interaction with the FDA is essential. The agency encourages sponsors to communicate as early as possible (e.g., before the investigational new drug meeting) with the appropriate review division when considering codevelopment of innovative combination therapy. The FDA also encourages sponsors to maintain frequent communication with the agency as codevelopment progresses.

4 The draft guidance also describes study design in the following scenarios: (1) the components of the combination cannot be administered individually; and (2) each drug alone has activity and can be administered individually.

- Investigational New Drug (IND) Submissions and Marketing Applications: In some cases, IND submissions and marketing applications will be required for each individual component of the combination therapy. In other cases, a combined submission may be sufficient. Until the FDA has more experience with codevelopment, decisions about the required submissions will be made on a case-by-case basis, depending upon the sponsor's overall codevelopment and marketing strategy.

- Labeling Issues: The FDA advises that the content of labeling for the combination and/or the components will be case-specific, depending upon the nature of the combination, the intended uses of the individual components, the marketing strategy, and other factors. The agency recommends that sponsors consult with the appropriate review division to discuss labeling concerns in greater detail.

- Pharmacovigilence: The guidance explains that sponsors should develop a pharmacovigilence plan that accounts for the additional postmarket risks presented by initial marketing of two or more previously unapproved drugs for use in combination. Such risk assessment should consider the potential that patients will use each drug individually; the potential for patients to use any component of the combination in combination with other drugs; and drugs likely to be co-administered with the combination. The FDA encourages sponsors to discuss the pharmacovigilence plan with the appropriate review division and the Office of Surveillance and Epidemiology.

The draft guidance provides potential combination therapy sponsors with an overview of the codevelopment process and insight into the FDA's current thinking. It describes important scientific considerations and highlights regulatory issues that might arise, but the guidance also leaves room for significant variability in both the scientific and regulatory areas, depending on the specific therapy that the sponsor seeks to develop. As with the single-drug development process, early communication with the agency is essential. Early communication will allow the sponsor to understand the agency's expectations and plan accordingly for a more efficient codevelopment process.