

relating to the Investigational Review Board (IRB). The following letter concerns the IRB and, more specifically, the need for the Sponsor and the IRB to take into account adverse events associated with the class of drugs. This refers to the class of drugs of which the study drug is a member. The letter referred to the study drug and to its membership in a class of drugs associated with serious cardiovascular events. The letter complained that (20), “[w]ith this drug class, there is a well established association with the potential for increased risk of serious cardiovascular events. However, there is no evidence in the IRB meeting minutes ... to indicate that the IRB considered this risk in determining whether risks to subject were minimized ... it is incumbent upon the IRB to conduct a thorough, independent, systematic, non-arbitrary analysis of risks and benefits.”

VI. MOA AND DRUG COMBINATIONS

Once the mechanisms of action of various drugs are known, this knowledge can guide the design of therapies, for example, therapeutic approaches that include combinations of drugs. One particular approach is to administer two drugs, where the two drugs have different mechanisms of action, and where these two mechanisms are related in a way that would be expected to result in synergy between the two drugs.

a. Drug Combinations That Are Complementary or Synergistic

Ifosfamide in combination with *etoposide* is used in anticancer therapy. As reviewed by Grier et al. (21), ifosfamide has the effect of alkylating chromosomal DNA, while etoposide has the effect of uncoiling chromosomal DNA. When ifosfamide is administered, the result is increased alkylation of the DNA, where this is followed by the action of DNA repair enzymes, where the DNA repair enzymes cleave the tumor cell’s chromosome, thereby killing the tumor cell. When etoposide is administered, the result is increased uncoiling of the DNA of the tumor’s chromosome, which is expected to enhance the enzyme-mediated cleavage, and enhance killing of the tumor cell. The end-result of administering both drugs together is a synergistic increase in tumor killing. Miles et al. (22) describe the combination of *capecitabine* plus *docetaxel*. These two drugs have distinctly separate mechanisms of action, and their effects are synergistic. Moreover, they are both toxic, but their toxicities do not overlap. The MOA of any drug encompasses its toxicity. Piccart et al. (23) describe another example of drugs with complementary mechanisms, namely, *cisplatin* plus *gemcitabine*.

b. Drug Combinations That Avoid Inducing Cross-Resistance

Drug-resistance is a common problem in oncology, bacterial infections, and viral infections. In oncology, drug resistance can arise

²⁰Warning Letter No. 10-HFD-45-04-03 (April 26, 2010) from Dr Leslie K. Ball, MD, Office of Compliance, CDER, U.S. Food and Drug Administration.

²¹Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing’s sarcoma and primitive neuroectodermal tumor of bone. *New Engl. J. Med.* 2003;348:694–701.

²²Miles D, von Minckwitz G, Seidman AD. Combination versus sequential single-agent therapy in metastatic breast cancer. *Oncologist* 2002;7(Suppl. 6):13–9.

²³Piccart MJ, Lamb H, Vermorken JB. Current and future potential roles of the platinum drugs in the treatment of ovarian cancer. *Ann. Oncol.* 2001;12:1195–203.