the immune system, *glatiramer* (Copaxone®), expressly states that *increased infections have not been found*. The *Warnings and Precautions* section for the package insert reads (324):

> Because COPAXONE can modify immune response, it may interfere with immune functions ... in a way that would undermine the body's ... defenses against infection. There is no evidence that COPAXONE does this.

Dr Masha Hareli also commented on the fact that glatiramer has not been found to increase the risk for infections, explaining that, "[i]nterestingly, Copaxone does not cause immunosuppression, as you would presume, due to its short half-life" (325).

XIII. FDA'S DECISION-MAKING PROCESS ON ADVERSE EVENTS THAT APPEAR IRRELEVANT TO THE STUDY DRUG

a. Introduction

This provides examples of comments by FDA reviewers, for evaluating adverse events that seem unrelated to the study drug. Despite the apparently unrelated nature, the adverse event was recorded in the drug safety database and not ignored. In all cases, the FDA reviewer referred to reasoning or judgment on whether the adverse event was related to the drug. The take-home lesson is that study investigators and medical writers should not ignore adverse events, even when appearing to be extremely remote from the mechanism of action of the study drug.

b. Dimethyl Fumarate for Multiple Sclerosis

The example of *dimethyl fumarate* is from NDA 204063, which is available at Mar. 2013 on FDA's website. Dimethyl fumarate is metabolized in the body to fumaric acid which is a naturally occurring component of most foods and hence, at first glance, might not be expected to present any life-threatening safety issues. However, the clinical trial was for multiple sclerosis, which can be fatal. The *Medical Review* noted that the causes of death included, "traumatic brain injury following bicycle accident, motor vehicle accident, complications from MS (multiple sclerosis) relapse." The Review noted that the subject, "experienced a traumatic brain injury resulting from a bicycle accident ... as the subject attempted to avoid a collision with a driver who was under the influence of alcohol." The reasoned conclusion in the *Medical Review* was that, "there does not appear to be a meaningful difference in mortality between" the study drug and placebo.

c. Irbesartan for Hypertension

The example of *irbesartan* is from NDA 20758, at Jan. 2015 on FDA's website. The adverse event was an automobile accident. According to the *Medical Review*, the "subject ... was a 55 year old male with a 32-year history of hypertension. After 20 months on ... irbesartan ... he died in a motor vehicle accident. Relationship to study drug was considered unlikely, but no description appears to rule out sudden incapacitation of the subject prior to the accident." Although the conclusion contained no details, the FDA

[324]Package insert for COPAXONE (glatiramer acetate injection) for subcutaneous use; January 2014 (8 pp.).

[325]Kind response from Dr Masha Hareli, Ph.D., in e-mail of May 1, 2015.