

The Warning Letter acknowledged that the Sponsor (application holder) had used a CRO to do its adverse event reporting, but stated that this did not relieve the Sponsor of its responsibility to comply with the applicable regulations. To this point, the Warning Letter stated:

As part of your firm's corrective action plan for late reporting ... your firm voluntarily terminated its relationship with the contractor processing individual case safety reports ... and entered into an agreement with a different contractor for adverse event report processing. However, of the ... late reports noted above, [more late reports] occurred after you implemented your corrective action plan ... [a]s the holder of approved applications, [the Sponsor] has the obligation to report serious and unexpected adverse drug experiences to FDA within 15 calendar days of initial receipt of the information ... [i]f the application holder elects to out-source drug safety, [the application holder] retains the responsibility to ensure that it is done in a manner consistent with FDA regulations.

## XII. DRUGS THAT CREATE RISK FOR INFECTIONS

### a. Drugs That Inhibit the Immune System

Drugs that inhibit the immune system are used for treating autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, psoriasis, and inflammatory bowel disease. Autoimmune diseases result from pathological behaviors of T cells and other immune cells.

But it is self-evident that any drug that suppresses the immune system might increase the risk for infections. In the words of one commentator, a safety problem with therapies that inhibit the immune system and reduce pathological inflammation is that, "as flip side of the coin, treatment ... leaves the patient more susceptible to infection by inducing a certain extent of immunosuppression" (310).

### b. Drugs That Inhibit Tumor Necrosis Factor-Alpha

Drugs that inhibit tumor necrosis factor-alpha (TNF-alpha) inhibit immune response and are used to treat rheumatoid arthritis. TNF-alpha is a cytokine. These inhibitory drugs, which include, *etanercept*, *infliximab*, and *adalimumab*, have all been associated with increased risk for infections, such as tuberculosis, hepatitis B virus (311), and fungal infections. For example, immunosuppressive therapy with anti-TNF-alpha antibodies increases the risk for *Pneumocystis* fungus (312).

In fact, the package label for *etanercept* (Enbrel<sup>®</sup>) includes a black box warning regarding infections (313). Although the drug is for treating an autoimmune disease (psoriatic arthritis), the drug also increases the risk for infections. The black box warning reads:

SERIOUS INFECTIONS. Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.

<sup>310</sup>De Keyser F. Choice of biologic therapy for patients with rheumatoid arthritis: the infection perspective. *Curr. Rheumatol. Revs.* 2011;7:77–87.

<sup>311</sup>De Keyser F. Choice of biologic therapy for patients with rheumatoid arthritis: the infection perspective. *Curr. Rheumatol. Revs.* 2011;7:77–87.

<sup>312</sup>Bello-Irizarry SN, et al. MyD88 signaling regulates both host defense and immunopathogenesis during *Pneumocystis* infection. *J. Immunol.* 2014;192:282–92.

<sup>313</sup>Package label for Enbrel<sup>®</sup> (etanercept) solution for subcutaneous use; March 2015.