and EGFR (receptor), and associated signaling pathways, are used to mediate innate immune response against infections (319,320). The behavior of FDA reviewers in documenting associations between *cetuximab* and infections is revealed below. The *Medical Review* is dated Oct. 2, 2007, long before concrete information was available on the association, or on the relevant mechanisms, of EGFR-mediated signaling and infections.

e. FDA's Decision-Making Process in Evaluating the Association of Cetuximab With Infections

This concerns FDA's review of the anti-EGFR antibody *cetuximab* for treating colorectal cancer. The information is from BLA 125084 from Mar. 2015 of FDA's website. The *Medical Review* is dated from a much earlier year, 2007, a time when it was not suspected that EGFR-mediated signaling was relevant to infections. The FDA reviewer's comments reveal how the FDA handles an adverse event, where causality is not suspected.

The FDA reviewer wrote, "Infectious events are noted to be more common in the cetuximab/arm of this and other controlled studies. **A causal link** between this patient's Gram negative sepsis [bacterial infection] and cetuximab **cannot be excluded**."

Further comments from the FDA reviewer revealed that the FDA did not suspect that EGFR-mediated pathways were used for innate immunity against infections. The FDA reviewer wrote, "[a]dministration of cetuximab causes or predisposes toward infections, possibly due to catheter use, increased number of medical procedures . . . other iatrogenic events."

The reviewer's comments about catheter use being a cause of infections was reasonable, in view of the fact that chronic catheter use does result in infections (321,322).

The take-home lesson is that the Sponsor should ensure documentation of all adverse events, even if a causal connection between the study drug and adverse event is unknown.

The package insert for *cetuximab* provides information about infections in the *Warnings and Precautions* section, the *Adverse Reactions* section, and in the *Clinical Trials Experience* section. The *Clinical Trials Experience* section reads "Infections: The incidence of infection was variable across studies, ranging from 13–35%. Sepsis occurred in 1–4% of patients" (323). (There was a black box warning, but it did not mention infections.)

f. Package Insert for a Drug That is a Potentialy Immunosuppressive Drug (Glatiramer)

Because, as a class of compounds, immunosuppressive drugs increase the risk for infections, it is interesting to point out that the package label for one drug that influences

[319]Feng Z, et al. Epithelial innate immune response to Acinetobacter baumannii challenge. Infect. Immunity 2014;82:4458–65.

[320]Yamashita M, et al. EGFR is essential for TLR3 signaling. Sci. Signal. 2012;5(233):ra50. http://dx.doi.org/10.1126/scisignal.2002581.

[321]Giare-Patel, K, et al. WO2013/070951. Novel enhanced formulations for coating medical devices. Int. Publication Date, 16 May 2013.

[322]This patent application (WO2013/070951) was drafted and submitted by Tom Brody.

[323]Package insert for ERBITUX® (cetuximab) Injection, for Intravenous Infusion; April 2015 (14 pp.).