medical organizations, including the American Society of Clinical Oncology (ASCO). The REMS took the form of listed documents, each of which was required by the FDA:

- A Dear Healthcare Provider Letter informing healthcare providers about the incidence, type, severity and management of immune-mediated adverse reactions caused by YERVOY;
- The Immune-Mediated Adverse Reaction Management Guide;
- The Patient Wallet Card;
- The Nursing Immune-Mediated Adverse Reaction Symptom Checklist;

The Management Guide, which took the form of a booklet, included the writing:

> ipilimumab … can result in severe and fatal inflammation of the skin, including Stevens– Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) … Advise patients to report skin-related changes … Monitor patients for the most common manifestations of immune-mediated dermatitis, such as rash and pruritus … Withhold YERVOY dosing in patients with moderate to severe signs and symptoms.

b. FDA's Decision-Making Process in Evaluating Vemurafenib, and Stevens-Johnson Syndrome

This is from FDA's review of *vemurafenib* (Zelboraf®), for treating melanoma. The information is from FDA's evaluation of NDA 202429, as available at July 2013 on FDA's website. The FDA reviewer stated that, "[r]ash and pruritis were common adverse events with vemurafenib … **the patient with Stevens–Johnson syndrome** that appeared 17 days after initiation of treatment … demonstrate that vemurafenib has the potential to cause severe hypersensitivity reactions. The labeling includes severe hypersensitivity reactions under Warnings & Precautions."

A view of the package insert reveals that, in the *Warnings and Precautions* section, it reads, "[s]evere dermatological reactions, including **Stevens–Johnson syndrome** and toxic epidermal necrolysis. Discontinue ZELBORAF for severe dermatological reactions" (228). Also, the *Adverse Reactions* section reads, "[m]ost common adverse reactions … are arthralgia, rash, alopecia."

The Sponsor did not propose to use any REMS, and the FDA did not require any REMS. Regarding the risks, including skin rash, the FDA reviewer wrote that, "[t]hese risks include cutaneous squamous cell carcinoma (cuSCC), QT-prolongation … rash … and fatigue. The sponsor believes that all the risks can be managed with appropriate labeling and routine pharmacovigilance." To conclude, although the adverse event of SJS did occur, it was apparently not prevalent enough to require any more than a warning in the *Warnings and Precautions* section of the package insert.

VII. DRUG-INDUCED LIVER INJURY

a. Introduction

Drug-induced liver injury has been defined by a set of criteria known as "Hy's law." Hy's law originated in an observation by Dr Hyman Zimmerman regarding elevated liver enzyme levels and drug-induced jaundice, where the drug caused hepatocellular injury and death in 10–50% of cases. Zimmerman's observation took the form of two biomarkers that were predictive of hepatocellular injury. FDA characterizes drug-induced liver injury as an idiosyncratic drug reaction, and considers Hy's law to be a biomarker-based algorithm for liver injury, where this algorithm is a surrogate for histological examination on a liver

[228]Package insert for ZELBORAF® (vemurafenib) tablet, oral; November 2014 (15 pp.).