and relate the data to patient exposure, summarize market authorization status in different countries, and indicate whether changes should be made to safety information supplied with the product (201). Ordinarily, all dosage forms and formulations as well as indications for a given pharmacologically active substance should be covered in one PSUR. Separate presentations of data for different dosage forms, indications, or populations, for example children versus adults, may be used. The PSUR may contain safety information acquired from a number of sources, including spontaneous notifications from health care professionals, spontaneous notifications from consumers, sponsored clinical studies, the published medical literature, and from adverse drug reaction reporting systems used by regulatory agencies (202).

The following compares safety reporting by way of two different formats, the PSUR and the individual case safety report (ICSR). According to Michael Klepper (203) the majority of individual case safety reports (ICSRs) are based on single subjects and is used for expedited reporting (IND reports during pre-marketing and 15-day alert reports during post-marketing), whereas the Periodic Safety Update Report (PSUR) is an aggregate report of both expedited and non-expedited ICSRs (as well as other information) that was received by the sponsor, primarily on the marketed drug. Therefore periodic reports (PSUR) are bigger and more inclusive than ICSRs (204).

Once a drug is approved the sponsor has to send in a Periodic Adverse Drug Experience Report (PADER; 21 CFR 314.80) quarterly for the first 3 years after drug approval, then annually thereafter. The PSUR is used in Europe and elsewhere and may eventually replace the PADER. The FDA will accept the PSUR in lieu of the PADER upon request, but the PSUR must also be submitted quarterly for the first 3 years, then annually (205).

VII. RISK MINIMIZATION TOOLS

a. Introduction

The following mainly concerns *Dear Healthcare Professional* letters. These letters are issued in the post-marketing context.

The *Dear Healthcare Professional* letter fits into a broader context, namely, that of risk minimization tools. These tools include: (1) patient package insert; (2) medication

[201] U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for Industry. E2C. Clinical safety data management: periodic safety update reports for marketed drugs. November 1996 (21 pages).
[202] U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for Industry. E2C. Clinical safety data management: periodic safety update reports for marketed drugs. November 1996 (21 pages).
[203] Klepper M. E-mail of April 6, 2011.
[204] Klepper M. E-mail of April 6, 2011.
[205] Klepper M. E-mail of April 6, 2011.