added or subtracted to the overall score depending on the responses to the questionnaire. These calculations yield a total score that informs the drug safety scientist whether the cause was "highly probable," "probable," "possible," or "doubtful." In detail, Naranjo scores of 9 or 10 indicate that an event was "definitely" an adverse drug reaction; scores of 5–8 rate the likelihood as "probable"; scores of 1–4 are "possible"; and scores of less than 1 are "doubtful" (124). To summarize, the Naranjo algorithm, or a similar decision-making process, bridges the gap between raw data taking the form of a documented AE, and data that are classified as an adverse drug reaction. An additional scale, that is, a scale that is an alternative to the Naranjo scale, is the RUCAM scale (125).

Bright (126) reveals issues that can impair discovery of a cause, that is, of a connection between the drug and the AE, as follows. Recognition of a relationship between a drug and an AE can be impaired where the AE is a common condition in the population of study subjects, where there is a time delay between drug use and the AE, and where the AE occurred in a different organ in the body than the organ that was being treated by the drug.

III. PARADOXICAL ADVERSE DRUG REACTIONS

An interesting aspect of adverse drug reactions is that they can take the form of a paradox. For example, a drug for preventing nausea may cause nausea, an anti-depressant can increase depression, drugs used to treat bronchial spasms can induce bronchial spasms, and an anti-cancer drug can cause a new type of cancer.

Regarding nausea, drugs that are used to prevent nausea and vomiting may also cause nausea and vomiting. For example, aprepitant is used to prevent chemotherapy-induced nausea and vomiting. Although detailed information is not available on this matter, one source expressly states that this drug may induce vomiting (127) while another source clearly states that it may induce nausea (128). Aprepitant is also known by the trade name Emend®.

The existence of these paradoxical adverse drug reactions can influence the clinician's decision to classify the adverse event as either expected or unexpected.

[124] Kelly WN. How can I recognize an adverse drug event. Medscape CME Pharmacists (February 12, 2008).
[125] Miljkovic MM, Dobric S, Dragojevic-Simic V. Consistency between causality assessments obtained with two scales and their agreement with clinical judgments in hepatotoxicity. Pharmacoepidemiol. *Drug Saf.* 2011;20:272–285.
[126] Bright RA. Strategy for surveillance of adverse drug events. *Food Drug Law J.* 2007;62:605–615.
[127] Package insert. Aprepitant. Cigna Pharmacy Coverage Policy (December 15, 2009).
[128] Package insert. Emend. Merck (March 2010).