FDA prefers that only one dictionary be used (293). But note, that the FDA does not require the use of MedDRA for reporting of adverse events in any study or for spontaneous reporting of adverse events (294).

While CTCAE was designed for use in oncology clinical trials it has, on occasion, been used for trials on other diseases, such as HIV and hypertension (295).

The CTCAE dictionary fits into the MedDRA dictionary. Where a clinical trial is funded by NCI, the investigator is always required to send adverse event reports to NCI, using CTCAE, for example, CTCAE version 4.0 (296). All of the CTCAE version 4.0 terms are MedDRA terms, that is, CTCAE version 4.0 is a subset of MedDRA. For clinical trials used for gaining FDA-approval, the FDA will likely accept data on adverse events that use only CTCAE terminology (297).

c. Examples of Missing Data in Documents Submitted to the FDA

Missing information can prevent or delay regulatory approval of any drug. This provides an example where missing data was an issue. The example is from the approval process for *cetuximab* (Erbitux®), an antibody used for treating cancer. At an earlier part of the approval process, the FDA complained that, "[t]he review team identified several major clinical and scientific deficiencies including ... missing data ... the totality of the deficiencies rendered the application unacceptable for filing and a Refuse to File letter was issued on December 28, 2001" (298,299). But at a later part of the approval process, the FDA wrote that, "[m]inor protocol deviations as per applicant (5.3.5.1.1) are as follow [sic] ... patient did not provide 2 consents" (300,301). Thus, a fair amount of missing data, during an early part of the approval process, delayed the approval process for the drug. But when the drug was finally approved, the fact that two consent forms were missing did not prevent the FDA from approving the drug.

d. Writing Style in Case Report Forms

The case report form (CRF) is the instrument used for reporting adverse events in

[293]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Premarketing risk assessment; March 2005.

[294]Mozzicato P. E-mail of April 4, 2011.

[295]National Cancer Institute. CTCAE FAQ. (<https://cabig-kc.nci.nih.gov/Vocab/KC/index.php/CTCAE_FAQ#> What is the rationale and purpose of CTCAE.3F) [accessed 25.11.10].

[296]Till B. Investigational Drug Branch, Cancer Therapy Evaluation Program Technical Resources International, Inc. E-mail of November 30, 2010.

[297]Till B. Investigational Drug Branch, Cancer Therapy Evaluation Program Technical Resources International, Inc. E-mail of November 30, 2010.

[298]Keegan P. Memorandum of February 12, 2004 in administrative and correspondence documents (35 pp. total).

[299]United States Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Application No. STN/BLA 125084; ERBITUX (Cetuximab). All of the correspondence documents are incorporated by reference in an approval letter dated February 12, 2004.

[300]Clinical Review Section of Application No. STN/BLA 125084 (p. 51 of 149 pp. total, no date provided).

[301]United States Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Application No. STN/BLA 125084; ERBITUX (Cetuximab). All of the correspondence documents are incorporated by reference in an approval letter dated February 12, 2004.