Medical Dictionary for Regulatory Activities (MedDRA)" (166). Moreover, the FDA prefers that only one dictionary be used (167). But note that FDA does not require the use of MedDRA for reporting of adverse events in any study or for spontaneous reporting of adverse events (168).

While CTCAE was designed for use in oncology clinical trials it has, on occasion, been used for trials on other diseases, such as human immunodeficiency virus (HIV) and hypertension (169).

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 (170). 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 (171).

c. Examples of missing data in documents submitted to the FDA

Missing information can prevent or delay regulatory approval of any drug. Paper trails that document decisions made during the drug approval process for hundreds of drugs can be found on the FDA's website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/). These paper trails describe FDA's reasons for approval based on safety and efficacy data, as well as issues relating to deviations from the Clinical Study Protocol, and the issue of missing data.

The following 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 wrote, "The 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" (172,173). But at a later part of the approval process, the FDA wrote, "Minor protocol deviations as per applicant

166 U.S. Dept. of Health and Human Services. Food and Drug Administration. Guidance for Industry. Providing regulatory submissions in electronic format – postmarketing expedited safety report (May 2001).

167 U.S. Dept. of Health and Human Services. Food and Drug Administration. Guidance for Industry. Premarketing Risk Assessment (March 2005).

168 Mozzicato P. E-mail of April 4, 2011.

169 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 November 25, 2010).

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

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

172 Keegan P. Memorandum of February 12, 2004 in Administrative and Correspondence Documents (35 pages total).

173 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.