conversion table also includes a factor of 0.1, where the dose arrived at by the calculation is multiplied by 0.1, in order to ensure that the dose in humans will not be toxic (153). The resulting dose, as found with the FDA's table, is expected to be the dose that results in no observed adverse effect, where higher doses or concentrations would result in an adverse effect. The table provides separate conversion factors, for converting animal doses to human doses, for the mouse, rat, rabbit, dog, monkey, and pig. After the investigator applies the scaling factor, the resulting number is called the human equivalent dose (HED) (154). The species that generates the lowest HED is called the most sensitive species. After arriving at the HED, the HED is further modified by applying a safety factor. Thus, according to the FDA's Guidance for Industry (155), "[a] safety factor should then be applied to the HED to increase assurance that the first dose in humans will not cause adverse effects."

e. Examples From Clinical Study Protocols of Using Animal Studies to Arrive at Appropriate Human Dose

1. *Drug for Non-small Cell Lung Cancer*

A Clinical Study Protocol for a cancer clinical trial detailed how animal studies were used to arrive at an appropriate dose for humans. The drug, LDK378, also known as ceritinib, was subsequently FDA-approved for the indication of non-small cell lung cancer (NSCLC) (156). The term "GLP" means "Good Laboratory Practice," which is a set of standards relating to the care and handling of laboratory animals. The concepts in the quoted excerpt include:

- *STD_{10}.* The term "STD_{10}" means "severely toxic dose 10 (the dose causing severe toxicity in approximately 10% of all animals)."
- *AUC.* Area under the curve. This refers to a value, determined by integration, of blood plasma concentration of the drug over a given period of time. Plasma AUC_{0-24} refers to integration from time zero to 24 h.
- *Safe starting dose.* The safe starting dose for humans was calculated using data from rat studies.
- *Efficacious dose.* The efficacious dose in humans was calculated using PK data from animals. This textbook refrains from providing background information on these calculations.
- *HNSTD.* HNSTD means, "highest nonseverely toxic dose" (157).
- *BSA.* BSA is body surface area.

[153]Ochoa R, Rousseaux C. The role of the toxicologic pathologist in risk management. Toxicol. Pathol. 2009;37:705–7.

[154]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers; July 2005 (27 pp.).

[155]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers; July 2005 (27 pp.).

[156]Khozin S, Blumenthal GM, Zhang L, et al. FDA approval: ceritinib for the treatment of metastatic anaplastic lymphoma kinase-positive non-small cell lung cancer. Clin. Cancer Res. 2015;21:2436–9.

[157]Saber H, Leighton JK. An FDA oncology analysis of antibody-drug conjugates. Regul. Toxicol. Pharmacol. 2015;71:444–52.