"potential survival benefit" to humans suffering from anthrax. Also, the reviewer described the animal models as, "two representative animal models of inhalation anthrax in NZW rabbits (35–44% survival) and cynomolgus macaques (69% survival) when treatment was initiated postexposure at the time when all animals were toxemic/febrile."

Please note that the study design was a stringent one, in that the study drug was administered after infection, rather than prior to infection. The study with human subjects was only for assessing safety and in referring to these studies, the FDA reviewer pointed out that, "[s]afety of raxibacumab … single intravenous infusion was established in … 326 healthy human volunteers."

V. ESTIMATING HUMAN DOSE FROM ANIMAL STUDIES

a. Introduction

The most appropriate dose of a drug for humans can be derived from animal studies. The FDA provides guidance on converting effective doses from animal studies, to corresponding doses that are likely to be effective in human subjects (142). Two approaches with animals are in common use. The first is to arrive at the highest drug dose that is not toxic. This approach is commonly used for small-molecule drugs for cancer. The second is to arrive at the dose of a drug that is optimally effective, as determined by tests sensitive to efficacy. With the information of the dose in hand, investigators then scale up the dose derived from animal studies, and then calculate a dose for first use in humans. Lowe et al. (143), Reigner and Blesch (144), Contrera et al. (145), and Sharma and McNeill (146) review methods for using animal studies to arrive at doses for humans. These methods include methods based on body surface area, and methods based on pharmacokinetic (PK) data. Sawyer and Ratain (147) and Kouno et al. (148) discuss the common formulas used to calculate body surface area.

b. NOAEL Approach

The No Adverse Effect Dose Level (NOAEL) is determined in animal safety

[142]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for Industry. Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers. U.S. Department of Health and Human Services, Food and Drug Administration. 2002; 24 pp.

[143]Lowe PJ, Hijazi Y, Luttringer O, Yin H, Sarangapani R, Howard D. On the anticipation of the human dose in first-in-man trials from preclinical and prior clinical information in early drug development. Xenobiotica 2007;37:1331–54.

[144]Reigner BG, Blesch KS. Estimating the starting dose for entry into humans: principles and practice. Eur. J. Clin. Pharmacol. 2002;57:835–45.

[145]Contrera JF, Matthews EJ, Kruhlak NL, Benz RD. Estimating the safe starting dose in phase I clinical trials and no observed effect level based on QSAR modeling of the human maximum recommended daily dose. Regul. Toxicol. Pharmacol. 2004;40:185–206.

[146]Sharma V, McNeill JH. To scale or not to scale: the principles of dose extrapolation. Br. J. Pharmacol. 2009;157:907–21.

[147]Sawyer M, Ratain MJ. Body surface area as a determinant of pharmacokinetics and drug dosing. Invest. New Drugs 2001;19:171–7.

[148]Kouno T, Katsumata N, Mukai H, Ando M, Watanabe T. Standardization of the body surface area (BSA) formula to calculate the dose of anticancer agents in Japan. Jpn J. Clin. Oncol. 2003;33:309–13.