also correspond to the mechanism of action of the treatment in humans. Regarding the need for mechanisms in the animal model to track mechanisms in humans, the FDA refers to the example of treatment of pneumonic plague caused by *Y. pestis*. The FDA states that infection by this bacterium can occur by way of flea bites, which causes bubonic plague, while infection by inhalation of the bacterium causes pneumonic plague. Thus, for obtaining regulatory approval for a drug against pneumonic plague, the animal model must use an inhalation route (not a flea bite route) for the bacterium (134). To provide one more example of the need for the mechanisms in the animal model to track those in the human, the FDA states that, "[i]f the thresholds in humans and in the animal model differ greatly, the suitability of the animal model may be called into question and the model should be discussed with FDA" (135).

Use of the Animal Rule for gaining FDA approval for drugs for human patients has been detailed for the indications of smallpox (136,137), pneumonic plague (138), ebola virus (139), anthrax (140), and radiation (141).

i. FDA's Decision-Making Process in Evaluating Raxibacumab, for Treating *Bacillus anthracis* Infections

At the time of drug approval, the FDA publishes its *Approval Letter* along with its *Medical Review* or *Clinical Review*, *Pharmacological Review*, *Statistical Review*, and other reviews. The following is from the FDA's approval of *raxibacumab*, for treating *B. anthracis* infections. The drug is an antibody for treating anthrax.

Thus, it can be readily understood that it is rarely or never the case that any human subjects will be available for this type of clinical trial. This example is from BLA 125349, which is available from December 2012 of the FDA's website. Please note that efficacy data were collected from studies on rabbits and monkeys, while safety data were collected from studies on human volunteers. The human volunteers where healthy, and were only treated with the study drug (and not exposed to any anthrax bacteria).

The FDA reviewer stated that the animal studies indicate that the study drug shows

[134]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Product development under the animal rule; May 2014 (53 pp.).

[135]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Product development under the animal rule; May 2014 (53 pp.).

[136]Trost LC, et al. The efficacy and pharmacokinetics of brincidofovir for the treatment of lethal rabbitpox virus infection: a model of smallpox disease. Antiviral Res. 2014;117:115–21.

[137]Olson VA, Smith SK, Foster S. In vitro efficacy of brincidofovir against variola virus. Antimicrob. Agents Chemother. 2014;58:5570–1.

[138]Graham VA, et al. Efficacy of primate humoral passive transfer in a murine model of pneumonic plague is mouse strain-dependent. J. Immunol. Res. 2014;2014:807564.

[139]Sullivan NJ, et al. Correlates of protective immunity for Ebola vaccines: implications for regulatory approval by the animal rule. Nat. Rev. Microbiol. 2009;7:393–400.

[140]Williamson D. Approaches to modeling the human immune response in transition of candidates from research to development. J. Immunol. Res. 2014;2014:395302 (6 pp.).

[141]Gluzman-Poltoruk Z, et al. Randomized comparison of single dose of recombinant human IL-12 versus placebo for restoration of hematopoiesis and improved survival in rhesus monkeys exposed to lethal radiation. J. Hematol. Oncol. 2014;7:31 (12 pp.).