pustules, which then form scabs causing the discrete pocks that are the hallmark of OPV infections. Virus can be cultured from the scab material and the patient remains infectious until the scabs fall off and the skin heals. Mortality in humans has been attributed to toxemia, associated with immune complexes and hypotension. Toxemia is a poorly defined clinical condition thought to be caused by an excessive inflammatory immune response similar to septicemia associated with systemic bacterial infections.

4.3 Antiviral Discovery and Development

4.3.1 Regulatory Path to Developing OPV Therapeutics

The regulatory path for approval of therapeutics to treat smallpox is complicated by the lack of human disease. Since it is not possible to conduct human efficacy trials with new therapeutics that target variola virus, it is difficult to define pharmacokinetic–pharmacodynamic (PK–PD) relationships for human dose selection. Biomarkers based upon virological endpoints are not available for predicting disease outcome since current molecular markers and techniques used to describe human disease had not been developed prior to smallpox eradication.

The US Food and Drug Administration (FDA) proposed guidance (FDA regulation 21 CFR 314 Subpart I) designed to evaluate new drug products when human efficacy studies are not ethical or feasible. The intent of this guidance was to provide a mechanism for approval of drugs to treat diseases caused by pathogens considered to be potential bioweapon threats. Drug candidates would follow the normal regulatory path for approval through Phase 1 and modified Phase 2 safety evaluations in healthy volunteers. However, in place of human efficacy trials, the guidance proposed the use of validated animal models to establish PK–PD relationships to facilitate human dose selection (Table 4.1). Although there are numerous models of OPV infection, none of these models recapitulates all aspects of human disease. Therefore, interpretation of this guidance has been challenging for companies developing therapeutics in this area. A recent FDA advisory committee meeting addressing this topic will hopefully bring clarity to this issue.[34] Alternative regulatory paths, such as conditional approvals or emergency use authorization, may allow the distribution of therapeutics in the event of an outbreak. The development of appropriate validated animal models will be essential for approval of smallpox therapeutics.

4.3.2 Animal Models of OPV Infection

The current CDC clinical case definition for smallpox is given as 'An illness with acute onset of fever >101 °F (38.3 °C) followed by a rash characterized by firm, deep seated vesicles or pustules in the same stage of development without other apparent cause.'[35] Polymerase chain reaction (PCR) using primers specific for variola virus is used to confirm the diagnosis. The CDC case