inoculated at the periphery can establish lethal infection and systemic disease. While mortality and viremia can be used as therapeutic endpoints, the cause of death in these models is likely organ failure caused by replication of the virus at these sites and not 'toxemia' as was described for human smallpox. It is likely that a combination of validated animal models will be required to provide robust data sets for establishing PK–PD relationships that can be used in conjunction with human PK data to provide justification for human dose selection.

4.4 Development of OPV Therapeutics

Three clinical stage compounds, cidofovir (CDV), CMX001 and ST-246, are currently being considered for use in the treatment of OPV infections. Their discovery and development paths are unique and represent different approaches for development of OPV therapeutics.

CDV and CMX001 are acyclic nucleoside phosphonate analogs which belong to a class of compounds that have been developed into potent, clinically significant antiviral drugs.[49,50] The antiviral potency of nucleotide and nucleoside analogs is dependent upon their metabolic activation to the diphosphate and triphosphate form, respectively, and their resistance to metabolizing enzymes (Figure 4.1). For acyclic nucleoside phosphonates, the diphosphate form is the active inhibitor of viral replication typically targeting the viral polymerase. The process of activation through metabolism is determined by cellular permeability, efficiency as a substrate for host and/or viral kinases required for phosphorylation to the diphosphate form, metabolic stability of the diphosphate, efflux from the cell, activity against the viral polymerase and selectivity relative to host polymerases. These factors can determine the efficacy and target tissue specificity of acyclic nucleoside phosphonate analogs.

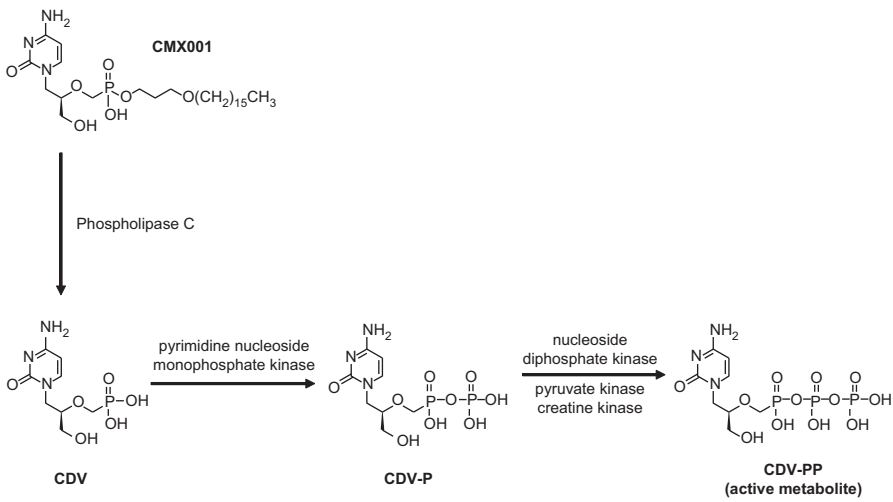

Figure 4.1 Metabolism of CMX001 and CDV.