125

A Regulatory Perspective on Preclinical Studies to Support Antiviral Drug Activity. M.A. Ussery, J.C. Ramsey, and E.C. Cooper. Division of Antiviral Drug Products, Food & Drug Administration, Rockville, MD, U.S.A.

One important function of our division at the FDA is the examination of preclinical studies submitted by sponsors to determine if sufficient safety and efficacy data have been collected to support the initiation of clinical trials. In addition, to support eventual drug approval, other nonclinical studies that may be completed while clinical trials are in progress are recommended. Preclinical studies to support antiviral drug activity generally would consider factors such as drug compartmentalization, enzyme activation or inactivation, enzyme kinetics of affected pathways, effects on substrate pool levels, and the structural relationship of the new drug to known antiviral compounds. The antiviral activity of the drug should be established in in vitro studies in primary and established cell lines that are representative of tissues infected in vivo. These studies should establish dose response curves (including the calculation of IC_{50} and IC_{90} values), the effect of multiplicity of infection on antiviral activity, the effect of timing of drug addition, and the response of viral isolates from different geographical locations to the drug. Dose response curves for antiviral agents to be used in combination should be performed at fixed ratios of the two agents to allow determination of possible synergy or antagonism. The in vitro toxicity of the drug should be determined in the same cell lines used to establish activity as well as cell lines representative of tissues likely to be sensitive to drug toxicity; both the cytostatic and cytotoxic dose should be determined in these studies. Standardized methodology should be developed for susceptibility testing of clinical isolates to the drug. When available, data on the activity of antiviral drugs in appropriate animal models can offer considerable support to the development of the rationale for and regimen to be used in subsequent clinical studies.