CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

Additional copies are available from:
Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

Points to Consider in the Preclinical Development Of Antiviral Drugs*

This document addresses the considerations involved in establishing the preclinical antiviral activity of drugs, with particular emphasis on those drugs intended for the treatment of human immunodeficiency virus (HIV) infection. For general comments on the chemistry, manufacturing and controls, preclinical pharmacology and toxicology, and clinical considerations pertaining to these drugs, as well as other drug classes reviewed by the Division of Antiviral Drug Products, refer to the document entitled "Points to Consider in the Preparation of IND Applications for New Drugs Intended for the Treatment of HIV-Infected Individuals". Separate documents that address the assessment of the preclinical activity of immunomodulators and drugs for the treatment of opportunistic infections associated with HIV infection are in preparation.

The following information should be included in the microbiology/virology portion of your IND submission:

A. Antiviral Activity

Evidence of antiviral activity sufficient to provide a rationale for human use must be submitted prior to the initiation of

*This statement is an informal communication under 21 CFR 10.90 (b)(9) that represents the best judgement of the Division of Antiviral Drug Products at this time. This document does not necessarily represent the formal position of the Center for Drug Evaluation and Research or the Food and Drug Administration, and does not bind or otherwise obligate the Center or Agency to the views expressed.

clinical studies. Without a reasonable rationale, there is no context in which to assess safety risks. If *in vitro* studies are to be used to provide a rationale for Phase 1 clinical trials, we recommend that the items listed below be addressed in your IND submission.

1. For antiviral agents intended to be used as single agent therapy for viral infections, the following *in vitro* studies should be performed to provide evidence of antiviral activity:

   a. Identify primary cell cultures and established cell lines representative of tissues that are infected with the virus *in vivo*.

   b. Determine dose response curves for the antiviral agent against each virus to be tested (see f below).

   c. Determine the effects, if any, of variation in multiplicity of infection (M.O.I.) on observed antiviral activity.

   d. Determine the effects, if any, that the timing of drug addition to the cell cultures has on observed antiviral activity.

e. Calculate the concentrations of drug that inhibit viral replication by 50% (IC50), and by 90% (IC90), in each host cell type evaluated.

f. Submit IC_{50} and IC_{90} values established using low passage clinical virus isolates obtained from several geographic locations.

2. The evaluation of antiviral activity in appropriate infected animal models should be performed as early as possible after demonstration of <u>in vitro</u> antiviral activity, as information from such models can offer considerable support to a rationale for human use of new antiviral drugs and, in addition, can better guide the selection of dose levels and regimens to be investigated in subsequent clinical studies.

Animal studies may be particularly useful in helping make risk/benefit assessments for antiviral agents that have the potential to cause immunotoxic or other adverse effects in tissues that are not well represented by available tissue culture models. The optimal animal model for HIV infection would consist of a small animal infected with HIV itself. Sufficient numbers of animals should be tested (6 - 10 animals per dose group) to generate statistically meaningful data. Activity against similar ("surrogate") viruses, such as other

lentiviruses or even less closely related retroviruses, in appropriate animal models may provide useful information if the "surrogate" virus and HIV share the targeted biochemical function (e.g. reverse transcriptase, *tat* gene product, etc.). Susceptibility of the "surrogate" virus to the experimental agent should be confirmed *in vitro*, since examples of agents active against HIV alone have been reported (1). "Surrogate" virus animal models also offer the advantage of providing models of viral-induced immunodeficiency, whereas a clinical syndrome similar to AIDS in humans has not been caused by HIV in any other species.

3. For combinations of antiviral agents intended for investigational use in the treatment of viral infections, the studies described in section 1 above should be performed for each individual antiviral drug. In addition, the following combination studies should be performed:

   a. Determine the dose response curve against the virus for the drug combination (using a fixed ratio between the drug components (2)).

   b. Establish the IC_{50} for each drug and for the drug combination. Utilizing the Median Dose Effect Equation (2) or other suitable methods, determine whether the antiviral effect of the drug combination represents

antagonistic, additive or synergistic interaction between the individual antiviral drug components.

4. Drugs used concomitantly with antiviral agents to treat other underlying conditions may alter antiviral activity. When the potential for such drug interaction is suspected, the existence of antagonistic or synergistic drug interactions should be investigated as described above (see section 3).

B. Cytotoxicity

Sufficient information from cytotoxicity testing must be provided to demonstrate that any antiviral activity observed is independent of cytotoxic effects. The results of the following in vitro studies should be submitted to support Phase 1 clinical trials:

1. For antiviral drugs whose metabolism is not appreciably affected by the infecting virus, cytotoxicity should be evaluated in cell cultures representative of in vivo tissues likely to be most sensitive to drug toxicity. The following information should be provided:

   a. Determine the drug concentration that inhibits cell growth by 50% (IC_{50}) i.e. the cytostatic concentration.

Additionally, the drug concentration that results in 50% cell death (TC_{50}) should be determined.

b. Calculate the *in vitro* therapeutic index of the drug (i.e. the ratio of cytotoxicity to antiviral activiy as a function of drug concentration; cytostatic IC_{50} or cytotoxic TC_{50} divided by antiviral IC_{50}).

2. For antiviral drugs whose metabolism is appreciably affected by the infecting virus, cytotoxicity should be evaluated in both infected and non-infected cell cultures as described above.

3. For drugs that are cytostatic at concentrations significantly below the TC_{50}, the reversibility of cytostasis upon drug removal should be determined.

C. Mechanism of Action and Drug Metabolism

Results of studies elucidating the mechanism(s) through which the drug induces its biological activity should be reported as available. In addition, information should be provided concerning factors such as compartmentalization, enzyme activation/inactivation, enzyme kinetics of affected pathways, substrate pool level effects, and other metabolic parameters that may influence drug

activity. The antiviral activity and cytotoxicity of major metabolites should be examined as in Section **A** and **B** above. Particular attention should be paid to the metabolic profiles of closely related compounds previously reported in the scientific literature, as these may help to identify the potential for significant interactions with specific metabolic pathways. These studies may be conducted while clinical trials are in progress, and the results submitted to the IND as soon as available.

D. Clinical Laboratory Susceptibility Test Methods

We strongly recommend that the potential for viral resistance be evaluated during the course of the clinical development program. Results from studies utilizing standardized methodology for susceptibility testing of the antiviral agent against clinical isolates should be submitted. These reports should include evaluation of parameters such as cell type, culture conditions, inoculum size, assay procedures and statistical evaluation of results. These methods may be developed during Phase 2 or Phase 3 clinical trials if they are not available prior to Phase 1 studies.

Questions regarding this document, the preclinical development of AIDS drugs, or the Division of Antiviral Drug Products' pre-IND program, should be referred to Mr. Tony DeCicco, Pre-IND Assistant,

Division of Antiviral Drug Products, at (301) 443-9559. He will assist sponsors in contacting other members of our staff as needed.

References:

1. Pauwels, R., K. Andries, J. Desmyter, D. Schols, et al. "Potent and Selective Inhibition of HIV-1 Replication in vitro by a Novel Series of TIBO Derivatives." Nature 343: 470-4 (1990).

2. Chou, Joseph, and Ting-Chao Chou. "Dose-Effect Analysis with Microcomputers." Biosoft, Cambridge, United Kingdom (1987).

Initiated 11/90