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Guidance for Industry

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

REFERENCE GUIDE

FOR THE NONCLINICAL TOXICITY STUDIES OF ANTIVIRAL DRUGS INDICATED FOR THE TREATMENT OF NON-LIFE THREATENING DISEASES: EVALUATION OF DRUG TOXICITY PRIOR TO PHASE I CLINICAL STUDIES

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INTRODUCTION

This document discusses the nonclinical toxicity studies of antiviral drugs intended for the treatment of non-life threatening diseases in humans. This document also applies to other classes of drugs under development for non-life threatening diseases that fall under the reviewing responsibility of the Division of Antiviral Drug Products (DAVDP). A similar document prepared as part of DAVDP's Pre-IND Program for AIDS drugs applies only to the preclinical research and development of AIDS drugs and should be considered as a separate document specific for that drug class.

The purpose of this document is to help guide drug developers in the research and development of new pharmaceuticals, specifically in the area of nonclinical toxicology. This "Reference Guide" contains concepts that drug developers should keep in mind when planning the preclinical development of their new drugs. The guidance given herein is applicable to drugs studied under an Investigational New Drug Application (IND) or a New Drug Application (NDA), as regulated by 21 CFR 200 to 500. All data submitted to FDA in support of an IND or NDA is considered confidential according to 21 CFR 314.430.

The recommendations given below are not intended to be all-inclusive of the many issues related to the preclinical development of new drugs, specifically the issues related to drug toxicity. The development of each new drug requires that toxicity studies be designed so as to characterize the toxicity of the drug specifically as it is proposed to be used by humans. This might require modification of "standard" toxicity protocols in order to address novel characteristics associated with either the drug or the manner in which it is to be used in humans. Therefore, this "Reference Guide" is meant to reinforce the scientific judgment of the investigators during the design and conduct of toxicity studies and not deter the drug developer from undertaking additional studies should they be necessary. The goal is to conduct toxicity studies that are well designed, relevant to the specific manner in which the drug is to be used in humans, and which produce the maximum amount of useful information.

Additionally, the recommendations in this guide are a product of the scientific and regulatory information available at the time of its publication. Modifications might be made in the future as a result of advances in any of the biomedical disciplines associated with drug development or changes in regulatory policy. Drug developers are advised to consult DAVDP to insure that this Reference Guide is the most current.

TERMINOLOGY

a. Nonclinical toxicity studies include all in vitro and in

vivo laboratory studies that help to characterize the toxicity of the drug. These studies are usually conducted over a period of time that starts before the drug is used clinically and continues throughout the drug's clinical development. Therefore, nonclinical toxicity studies can be conceptually divided into two groups:

1. Those studies conducted prior to Phase I clinical studies: preclinical studies

2. Those studies conducted after the initiation of clinical studies: post-Phase I studies.

In this document, "preclinical" is intended to specify only those studies which are, in fact, conducted prior to the first clinical use of the drug in Phase I trials.

b. Acute toxicity studies refers to single-dose toxicity studies and not the classical "LD-50" studies (Lethal Dose in 50% of the animals). The LD-50 study is neither required nor routinely recommended by DAVDP or the FDA (Federal Register, Vol. 53, No. 196). Single-dose acute toxicity studies should characterize the spectrum of toxicity, not just the lethality, that results from a single administration of the drug to animals. Typically, animals are given a single dose of the drug in a 24 hour period and then observed for 14 days. Measurements usually include clinical signs, clinical pathology, gross pathology and limited histopathology.

c. Repeat-dose toxicity studies: Sub-acute or sub-chronic toxicity studies, as well as chronic or long-term toxicity studies all fall into the general category of repeat-dose toxicity studies. The terms "sub-acute", "sub-chronic" and "chronic" are vague and often the source of confusion about the precise length and purpose of the study. It is more informative to refer to a repeat-dose toxicity study by the duration of administration of the drug and the type of study (e.g., referred to as 4-week, 3-month, 6-month or 12-month toxicity studies).

d. Non-life-threatening diseases are those that are not generally associated with premature mortality. However, some diseases, while rarely being fatal, may produce such severe or permanently disabling effects that they might be more appropriately developed as drugs intended to treat serious or life-threatening diseases according to procedures described for such drugs (Federal Register, Vol. 53, No. 204). The risk/benefit evaluation of the initial administration of a new drug to humans balances the potential toxicity of the drug, as demonstrated in animal toxicity studies, with the expected deleterious natural progression of the disease. Consequently, the more complete and detailed the animal toxicity profile,

the more information can be brought to bear on the judgment as to whether the toxicity of the drug is likely to be worse that the non-life-threatening condition itself.

NONCLINICAL TOXICOLOGY

a. General Information

The toxicity of a new drug must be adequately characterized in preclinical toxicity studies before the drug can be administered to humans in Phase I clinical trials Prior to the availability of human clinical data, the preclinical toxicity studies are usually the sole source of data upon which the safety assessment of a new drug can be based. These toxicity studies should be part of a multidisciplinary research and development program designed to give a broad perspective of the drug's pharmacology, toxicology and pharmacokinetics prior to human use. This information is essential to making an assessment of the potential risks and benefits associated with the proposed human use of the drug.

General background references for FDA's guidelines for nonclinical toxicity studies can be found in "Current Views on Safety Evaluation of Drugs" FDA Papers, May 1968, and in "Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use", FDA Papers, January 1966. The format for submitting nonclinical toxicology and pharmacology data in an application is described in the FDA publication "Guideline for the Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application". These references can help orient the drug developer to the general types of toxicity studies historically expected by FDA for new drugs. However, the guidance reflected by this document is meant to be an extension and update of the two references above, and the drug developer should use this document, and direct guidance from DAVDP reviewers, as specific guidance for developing drugs to be reviewed by DAVDP.

All nonclinical toxicity studies conducted for the purpose of supporting INDs or NDAs must be conducted in accordance with Good Laboratory Practices (21 CFR 58) and use drug substance prepared according to the Current Good Manufacturing Practices (21 CFR 210 and 211). The drug used in nonclinical studies should preferably be in the same form (the final formulation of the drug product) as that intended for human use, especially in those circumstances in which the effect of the final formulation of the drug is or could be a major determinant of the drug's toxicity.

b. Pharmacokinetics

The absorption, distribution, metabolism and excretion (ADME) of a drug should be adequately studied as part of its preclinical

development. In general, the sponsor should develop analytical methodology for quantifying systemic and tissue levels of the drug and its primary metabolites. The drug's ADME profile should be a primary determinant of the design and interpretation of animal toxicity studies for that drug, including the choice of test species, route of administration, dose-range and schedule of administration, histopathology and clinical pathology measurements, and the need to include additional observations in the study design. As discussed below, ADME data are important for justifying the route of administration used in animal toxicity studies when the investigator plans to use a route of administration other than that proposed for human use.

For topically applied drugs, the systemic absorption of the drug product should be determined in animals using models representative of the clinical use of the topical drug preparation.

c. Single-dose acute toxicity studies

To support first-time use of a new drug in humans the single-dose acute toxicity of the drug should be determined in at least three animal species, at least one being a non-rodent. Acute toxicity studies are intended to provide information about the toxicity produced by a single administration of the drug. As discussed above, these are not classical LD-50 or acute lethality tests.

The drug should be administered by the same route of administration as that intended for use in humans, in addition to IV administration if that is not the intended route of administration.

d. Repeat-dose Toxicity Studies

To support clinical studies in which a new drug will be given in repeated administrations for up to one month, the drug's toxicity should be evaluated in repeat-dose toxicity studies of at least 4-weeks duration. Two animal species should be tested, at least one being a non-rodent. The dose-range used in these studies should be chosen to enable each toxicity study to identify the highest non-toxic dose as well as allow a thorough qualitative and quantitative characterization of the drug's toxicity. Usually, a minimum of three doses are used for these studies, with the highest dose producing overt toxicity and the lowest showing no toxicity. The middle dose should be chosen to best facilitate calculating the dose-response relationship of the drug's toxicity.

The route of administration used for repeat-dose animal toxicity studies should be the same as that proposed for human use of the drug. If the human route of administration can not be

duplicated in the animal, then alternative routes can be proposed to DAVDP. As discussed above, supporting ADME data for the test species are often necessary for justifying that the ADME profile resulting from the alternative route of administration will be adequate for the purposes of studying the drug's toxicity.

Another important point to consider is the schedule of administration of the drug. If the drug is expected to be administered to humans in multiple daily doses, then the dosing schedule in animal toxicity studies should reflect this. The schedule dependency of a drug's toxicity should be a primary consideration in the design of toxicity studies since the qualitative and quantitative toxicity of a drug may change significantly according to its schedule of administration during repeated dosing. If single daily dosing in animals does not allow an adequate characterization of the drug's toxicity to be made, then such studies might not support clinical studies in which the drug is to be used in multiple daily administrations since the toxicity study did not adequately describe the potential toxicity of the drug under conditions similar to its proposed clinical use. Additionally, an accurate description of the drugs's schedule-specific toxicity greatly facilitates choosing the starting dose and schedule for clinical trials.

To support repeated administration of the drug to humans for longer than one month, the sponsor should evaluate the drug's toxicity in repeat-dose animal toxicity studies of at least 3 months duration in at least two animal species, with at least one being a non-rodent. The same general considerations discussed above for the 4-week repeat-dose toxicity studies also apply to 3-month repeat-dose toxicity studies.

For topical drug preparations, toxicity studies specifically addressing the drug's potential to produce dermal irritation and sensitization should be conducted. Additionally, because of the potential for topically applied drugs to get into the eyes, ophthalmic irritation studies should also be conducted. The overall design of dermal toxicity studies should reflect the manner in which the drug will be used in humans.

e. Immunotoxicology

An evaluation of the drug's effects on the immune system may be necessary as part of the preclinical development of the new drug. To evaluate the immunotoxicity of a drug, a tiered approach such as that developed by the National Toxicology Program (NTP) can be used (Luster et al., Fundamental and Applied Toxicology 10:2-19 1988). The NTP's tiered approach for evaluating immunotoxicity uses a battery of assays in which the first-tier assays constitute a preliminary screen for detecting functional and pathologic effects on the major components of the mammalian immune system.

It is expected that for most new drugs only the first-tier studies would be needed prior to Phase I studies.

f. Genetic Toxicology

The genetic toxicity of the drug should be evaluated in a battery of genetic toxicity tests. Because of ongoing developments in the field of genetic toxicology, drug developers are urged to contact DAVDP reviewers for specific guidance concerning genetic toxicity studies for a particular drug so that the current state of scientific knowledge can be applied. In general, however, it is anticipated that no single test will be sufficient to adequately characterize the potential genetic toxicity or carcinogenicity of a new drug. The drug should be tested in a battery of short-term assays that are relevant to the various mechanisms by which genetic damage can occur.

g. General Pharmacology

An evaluation of the drug's general pharmacological or physiological activity should be performed. This evaluation can be accomplished using established in vitro and in vivo assays that screen for the major types of pharmacological or physiological responses that can be produced as side effects of drugs, such as effects on the central nervous system, autonomic nervous system and cardiovascular system. Because the general pharmacology studies measure drug-induced effects which may not be detected in the other toxicity studies, they are needed to complete the overall profile of the drug's potential toxicity and are intended to complement the animal toxicity studies described above.

HUMAN CLINICAL DATA

In certain instances, data from prior human use of the drug may exist. Whenever possible these data should be submitted for review by FDA by inclusion in the IND or NDA. Depending on the scientific quality of the data and its relevance to the proposed clinical use, DAVDP may modify the nonclinical toxicology requirements on a case by case basis.