Toxicokinetic measurements are normally integrated within the toxicity studies and as such are described in this document as "concomitant toxicokinetics" (Note 1). Alternatively, data may be generated in other supportive studies conducted by mimicking the conditions of the toxicity studies.

Toxicokinetic procedures may provide a means of obtaining multiple dose pharmacokinetic data in the test species, if appropriate parameters are monitored, thus avoiding duplication of such studies; optimum design in gathering the data will reduce the number of animals required.

Various components of the total nonclinical pharmacokinetics and metabolism program may be of value in contributing to the interpretation of toxicology findings. However, the toxicokinetic data focus on the kinetics of a new therapeutic agent under the conditions of the toxicity studies themselves.

Toxicokinetics is thus an integral part of the nonclinical testing program; it should enhance the value of the toxicological data generated, both in terms of understanding the toxicity tests and in comparison with clinical data as part of the assessment of risk and safety in humans. Due to its integration into toxicity testing and its bridging character between nonclinical and clinical studies, the focus is primarily on the interpretation of toxicity tests and not on characterizing the basic pharmacokinetic parameters of the substance studied.

As the development of a pharmaceutical product is a dynamic process which involves continuous feedback between nonclinical and clinical studies, no rigid detailed procedures for the application of toxicokinetics are recommended. It may not be necessary for toxicokinetic data to be collected in all studies and scientific judgment should dictate when such data may be useful. The need for toxicokinetic data and the extent of exposure assessment in individual toxicity studies should be based on a flexible step-by-step approach and a case-by-case decisionmaking process to provide sufficient information for a risk and safety assessment.

## 2. The Objectives of Toxicokinetics and the Parameters Which May Be Determined

The primary objective of toxicokinetics is: • To describe the systemic exposure achieved in animals and its relationship to dose level and the time course of the toxicity

Secondary objectives are:

study.

• To relate the exposure achieved in toxicity studies to toxicological findings and contribute to the assessment of the relevance of these findings to clinical safety.

• To support (Note 1) the choice of species and treatment regimen in nonclinical toxicity studies.

• To provide information which, in conjunction with the toxicity findings, contributes to the design of subsequent nonclinical toxicity studies.

These objectives may be achieved by the derivation of one or more pharmacokinetic parameters (Note 2) from measurements made at appropriate time points during the course of the individual studies. These measurements usually consist of plasma (or whole blood or serum) concentrations for the parent compound and/or metabolite(s) and should be selected on a case-by-case basis. Plasma (or whole blood or serum) AUC, C<sub>max</sub>, and C<sub>(time)</sub> (Note 2) are the most commonly used parameters in assessing exposure in toxicokinetics studies. For some compounds it will be more appropriate to calculate exposure based on the (plasma protein) unbound concentration.

These data may be obtained from all animals on a toxicity study, in representative subgroups, in satellite groups (see 3.5 and Note 1) or in separate studies.

Toxicity studies which may be usefully supported by toxicokinetic information include single and repeated dose toxicity studies, reproductive, genotoxicity, and carcinogenicity studies. Toxicokinetic information may also be of value in assessing the implications of a proposed change in the clinical route of administration.

### 3. General Principles to be Considered

### 3.1 Introduction

In the following paragraphs some general principles are set out which should be taken into consideration in the design of individual studies.

It should be noted that for those toxicity studies whose performance is subject to Good Laboratory Practice (GLP) the concomitant toxicokinetics must also conform to GLP. Toxicokinetic studies retrospectively designed to generate specific sets of data under conditions which closely mimic those of the toxicity studies should also conform to GLP when they are necessary for the evaluation of safety.

#### 3.2 Quantification of exposure

The quantification of systemic exposure provides an assessment of the burden on the test species and assists in the interpretation of similarities and differences in toxicity across species, dose groups, and sexes. The exposure might be represented by plasma (serum or blood) concentrations or the AUC's of parent compound and/or metabolite(s). In some circumstances, studies may be designed to investigate tissue concentrations. When designing the toxicity studies, the exposure and dose-dependence in humans at therapeutic dose levels (either expected or established) should be considered in order to achieve relevant exposure at various dose levels in the animal toxicity studies. The possibility that there may be species differences in the pharmacodynamics of the substance (either qualitative or quantitative) should also be taken into consideration.

Pharmacodynamic effects or toxicity might also give supporting evidence of exposure or even replace pharmacokinetic parameters in some circumstances.

Toxicokinetic monitoring or profiling of toxicity studies should establish what level of exposure has been achieved during the course of the study and may also serve to alert the toxicologist to nonlinear, doserelated changes in exposure (Note 3) that may have occurred. Toxicokinetic information may allow better interspecies comparisons than simple dose/body weight (or surface area) comparisons.

### 3.3 Justification of time points for sampling

The time points for collecting body fluids in concomitant toxicokinetic studies should be as frequent as is necessary, but not so frequent as to interfere with the normal conduct of the study or to cause undue physiological stress to the animals (Note 4). In each study, the number of time points should be justified on the basis that they are adequate to estimate exposure (see 3.2). The justification should be based on kinetic data gathered from earlier toxicity studies, from pilot or dose range-finding studies, from separate studies in the same animal model, or in other models allowing reliable extrapolation.

# 3.4 Contribution to the setting of dose levels in order to produce adequate exposure

The setting of dose levels in toxicity studies is largely governed by the toxicology findings and the pharmacodynamic responses of the test species. However, the following toxicokinetic principles may contribute to the setting of the dose levels.

### 3.4.1 Low dose levels

At the low dose, preferably a no-toxiceffect dose level (Note 5), the exposure in the animals of any toxicity study should ideally equal or just exceed the maximum expected (or known to be attained) in patients. It is recognized that this ideal is not always achievable and that low doses will often need to be determined by considerations of toxicology; nevertheless, systemic exposure should be determined.

### 3.4.2 Intermediate dose levels

Exposure at intermediate dose levels should normally represent an appropriate multiple (or fraction) of the exposure at lower (or higher) dose levels dependent upon the objectives of the toxicity study.

#### 3.4.3 High dose levels

The high dose levels in toxicity studies will normally be determined by toxicological considerations. However, the exposure achieved at the dose levels used should be assessed.

Where toxicokinetic data indicate that absorption of a compound limits exposure to parent compound and/or metabolite(s) (Note 6), the lowest dose level of the substance producing the maximum exposure should be accepted as the top dose level to be used (when no other dose-limiting constraint applies, Note 7).

Very careful attention should be paid to the interpretation of toxicological findings in toxicity studies (of all kinds) when the dose levels chosen result in nonlinear kinetics (Note 3). However, nonlinear kinetics should not necessarily result in dose limitations in toxicity studies or invalidate the findings; toxicokinetics can be very helpful in assessing the relationship between dose and exposure in this situation.

### 3.5 Extent of exposure assessment in toxicity studies

In toxicity studies, systemic exposure should be estimated in an appropriate number of animals and dose groups (Note 8) to provide a basis for risk assessment.