DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 94D–0015]

International Conference on Harmonisation; Guideline on the Assessment of Systemic Exposure in Toxicity Studies; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a final guideline entitled ''Toxicokinetics: Guidance on the Assessment of Systemic Exposure in Toxicity Studies.'' This guideline was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guideline is intended to help ensure that the assessment of systemic exposure in toxicity studies to support drug registration is carried out according to sound scientific principles.

DATES: Effective on March 1, 1995. Submit written comments at any time.

ADDRESSES: Submit written comments on the guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Copies of the guideline are available from CDER Executive Secretariat Staff (HFD–8), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Roger L. Williams, Center for Drug Evaluation and Research (HFD–4), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–6740.

Regarding ICH: Janet J. Showalter, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1382.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission; the European Federation of Pharmaceutical Industry Associations; the Japanese Ministry of Health and Welfare; the Japanese Pharmaceutical Manufacturers Association; the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA; and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Association (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

Harmonization of the assessment of systemic exposure in toxicity studies was selected as a priority topic during the early stages of the ICH initiative. In the **Federal Register** of March 1, 1994 (59 FR 9755), FDA published a draft tripartite guideline entitled, ''Toxicokinetics: A Guidance on the Assessment of Systemic Exposure in Toxicity Studies.'' The notice gave interested persons an opportunity to submit comments by May 16, 1994.

After consideration of the comments received and revisions to the guideline, a final draft of the guideline was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies at the ICH meeting held in October 1994.

The guideline discusses toxicokinetics, which is the generation of pharmacokinetic data in nonclinical toxicity studies or ancillary studies to assess exposure. The objectives of toxicokinetics are: (1) To describe the systemic exposure achieved in animals, its relationship to dose level, and the time course of the toxicity study; (2) to relate the exposure achieved in toxicity studies to toxicological findings; (3) to support the choice of species and treatment regimen in nonclinical toxicity studies; and (4) to supply information which, along with the toxicity findings, will contribute to developing additional nonclinical toxicity studies.

In the past, guidelines have generally been issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but are acceptable to FDA. The agency is now in the process of revising § 10.90(b). Therefore, this guideline is not being issued under the authority of § 10.90(b), and it does not create or confer any rights, privileges, or benefits for or on any person, nor does it operate to bind FDA in any way.

As with all of FDA's guidelines, the public is encouraged to submit written comments with new data or other new information pertinent to this guideline. The comments in the docket will be periodically reviewed, and, where appropriate, the guideline will be amended. The public will be notified of any such amendments through a notice in the **Federal Register**.

Interested persons may, at any time, submit written comments on the guideline to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the guideline follows:

Toxicokinetics: Guidance on the Assessment of Systemic Exposure in Toxicity Studies

I. Introduction

This Note for Guidance concerns toxicokinetics only with respect to the development of pharmaceutical products intended for use in human subjects.

In this context, toxicokinetics is defined as the generation of pharmacokinetic data, either as an integral component in the conduct of nonclinical toxicity studies or in specially designed supportive studies, in order to assess systemic exposure. These data may be used in the interpretation of toxicology findings and their relevance to clinical safety issues (see Note 1 for definitions of other terms used in this document).

The Note for Guidance has been developed in order to provide an understanding of the meaning and application of toxicokinetics and to provide guidance on developing test strategies in toxicokinetics. The guidance highlights the need to integrate pharmacokinetics into toxicity testing, which should aid in the interpretation of the toxicology findings and promote rational study design development.

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 study.

Secondary objectives are:

- 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_{max}, and $C_{(time)}$ (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, dose-related 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-toxic-effect 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.

Concomitant toxicokinetics may be performed either in all or a representative proportion of the animals used in the main study or in special satellite groups (Notes 1 and 5). Normally, samples for the generation of toxicokinetic data may be collected from main study animals, where large animals are involved, but satellite groups may be required for the smaller (rodent) species.

The number of animals to be used should be the minimum consistent with generating adequate toxicokinetic data. Where both male and female animals are utilized in the main study it is normal to estimate exposure in animals of both sexes unless some justification can be made for not so doing.

Toxicokinetic data are not necessarily required from studies of different duration if the dosing regimen is essentially unchanged (see also 4.3).

3.6 Complicating factors in exposure interpretation

Although estimating exposure as described above may aid in the interpretation of toxicity studies and in the comparison with human exposure, a few caveats should be noted.

Species differences in protein binding, tissue uptake, receptor properties, and metabolic profile should be considered. For example, it may be more appropriate for highly protein bound compounds to have exposure expressed as the free (unbound) concentrations. In addition, the pharmacological activity of metabolites, the toxicology of metabolites, and antigenicity of biotechnology products may be complicating factors. Furthermore, it should be noted that even at relatively low plasma concentrations, high levels of the administered compound and/or metabolite(s) may occur in specific organs or tissues.

3.7 Route of administration

The toxicokinetic strategy to be adopted for the use of alternative routes of administration, for example, by inhalation, topical, or parenteral delivery, should be based on the pharmacokinetic properties of the substance administered by the intended route.

It sometimes happens that a proposal is made to adopt a new clinical route of administration for a pharmaceutical product; for example, a product initially developed as an oral formulation may subsequently be developed for intravenous administration. In this context, it will be necessary to ascertain whether changing the clinical route will significantly reduce the safety margin.

This process may include a comparison of the systemic exposure to the compound and/or its relevant metabolite(s) (AUC and C_{max}) in humans generated by the existing and proposed routes of administration. If the new route results in increased AUC and or C_{max}, or a change in metabolic profile, the continuing assurance of safety from animal toxicology and kinetics should be reconsidered. If exposure is not substantially greater, or different, by the proposed new route compared to that for the existing route(s) then additional nonclinical toxicity studies may focus on local toxicity.

3.8 Determination of metabolites

A primary objective of toxicokinetics is to describe the systemic exposure to the administered compound achieved in the toxicology species. However, there may be circumstances when measurement of metabolite concentrations in plasma or other body fluids is especially important in the conduct of toxicokinetics (Note 9).

- When the administered compound acts as a ''pro-drug'' and the delivered metabolite is acknowledged to be the primary active entity.
- When the compound is metabolized to one or more pharmacologically or toxicologically active metabolites which could make a significant contribution to tissue/organ responses.
- When the administered compound is very extensively metabolized and the measurement of plasma or tissue concentrations of a major metabolite is the only practical means of estimating exposure following administration of the compound in toxicity studies (Note 10).

3.9 Statistical evaluation of data

The data should allow a representative assessment of the exposure. However, because large intra- and inter-individual variation of kinetic parameters may occur and small numbers of animals are involved in generating toxicokinetic data, a high level of precision in terms of statistics is not normally needed. Consideration should be given to the calculation of mean or median values and estimates of variability, but, in some cases, the data of individual animals may be more important than a refined statistical analysis of group data.

If data transformation (e.g., logarithmic) is performed, a rationale should be provided.

3.10 Analytical methods

Integration of pharmacokinetics into toxicity testing implies early development of analytical methods for which the choice of analytes and matrices should be continually reviewed as information is gathered on metabolism and species differences.

The analytical methods to be used in toxicokinetic studies should be specific for the entity to be measured and of an adequate accuracy and precision. The limit of quantification should be adequate for the measurement of the range of concentrations anticipated to occur in the generation of the toxicokinetic data.

The choice of analyte and the matrix to be assayed (biological fluids or tissue) should be stated and possible interference by endogenous components in each type of sample (from each species) should be investigated. Plasma, serum, or whole blood are normally the matrices of choice for toxicokinetic studies.

If the drug substance is a racemate or some other mixture of enantiomers, additional justification should be made for the choice of the analyte (racemate or enantiomer(s)).

The analyte and matrix assayed in nonclinical studies should ideally be the same as in clinical studies. If different assay methods are used in non-clinical and clinical studies they should all be suitably validated.

3.11 Reporting

A comprehensive account of the toxicokinetic data generated, together with an evaluation of the results and of the implications for the interpretation of the toxicology findings, should be given.

An outline of the analytical method should be reported or referenced. In addition, a rationale for the choice of the matrix analysed and the analyte measured (see 3.8 and 3.10) should be given.

The positioning of the report within the application will depend upon whether the data are specific to any one toxicity study or is supportive of all toxicity testing.

4. Toxicokinetics in the Various Areas of Toxicity Testing—Specific Aspects

4.1 Introduction

Based on the principles of toxicokinetics outlined above, the following specific considerations refer to individual areas of toxicity testing. The frequency of exposure monitoring or profiling may be extended or reduced where necessary.

It may be appropriate to take samples from some individual animals only, where this may help in the interpretation of the toxicology findings for these animals.

4.2 Single dose toxicity studies

These studies are often performed in a very early phase of development before a bioanalytical method has been developed and toxicokinetic monitoring of these studies is therefore not normally possible. Plasma samples may be taken in such studies and stored for later analysis, if necessary; appropriate stability data for the analyte in the matrix sampled would then be required.

Alternatively, additional toxicokinetic studies may be carried out after completion of a single dose toxicity study in order to respond to specific questions which may arise from the study.

Results from single dose kinetic studies may help in the choice of formulation and in the prediction of rate and duration of exposure during a dosing interval. This may assist in the selection of appropriate dose levels for use in later studies.

4.3 Repeated dose toxicity studies

The treatment regimen (Note 11) and species should be selected whenever possible with regard to pharmacodynamic and pharmacokinetic principles. This may not be achievable for the very first studies, at a time when neither animal nor human pharmacokinetic data are normally available.

Toxicokinetics should be incorporated appropriately into the design of the studies. It may consist of exposure profiling or monitoring (Note l) at appropriate dose levels at the start and towards the end of the treatment period of the first repeat dose study (Note 12). The procedure adopted for later studies will depend on the results from the first study and on any changes in the proposed treatment regimen. Monitoring or profiling may be extended, reduced, or modified for specific compounds where problems have arisen in the interpretation of earlier toxicity studies.

4.4 Genotoxicity studies

For negative results of in vivo genotoxicity studies, it may be appropriate to have demonstrated systemic exposure in the species used or to have characterized exposure in the indicator tissue.

4.5 Carcinogenicity (Oncogenicity) studies[1]

4.5.1 Sighting or dose-ranging studies

Appropriate monitoring or profiling of these studies should be undertaken in order to generate toxicokinetic data which may assist in the design of the main studies (see 4.5.2.). Particular attention should be paid to species and strains which have not been included in earlier toxicity studies and to the use of routes or methods of administration which are being used for the first time.

Particular attention should be paid to the establishment of appropriate toxicokinetic data when administration is to be in the diet (Note 13).

Toxicokinetic data may assist in the selection of dose levels in the light of information about clinical exposure and in the event that nonlinear kinetics (Note 3) may complicate the interpretation of the study.

In principle, the ideal study design would ensure that dose levels in oncogenicity studies generate a range of systemic exposure values that exceed the maximum therapeutic exposure for humans by varying multiples. However, it is recognized that this idealized selection of dose levels may be confounded by unavoidable species-specific problems. Thus, the emphasis of this guidance is on the need to estimate systemic exposure, to parent compound and/or metabolite(s) at appropriate dose levels and at various stages of an oncogenicity study, so that the findings of the study may be considered in the perspective of comparative exposure for the animal model and humans.

A highest dose based on knowledge of probable systemic exposure in the test species and in humans may be an acceptable end-point in testing for carcinogenic potential. Historically, a toxicity end-point[1] has been often used to select the top dose level.

4.5.2 The main studies

The treatment regimen, species, and strain selection should, as far as is feasible, be determined with regard to the available pharmacokinetic and toxicokinetic information. In practice, the vast majority of these studies is conducted in the rat and mouse.

As mentioned in the ''Introduction'' to this section, it is recommended that reassurance be sought from monitoring that the exposure in the main study is consistent with profiles of kinetics established in free-standing or specific dose-ranging studies. Such monitoring will be appropriate on a few occasions during the study, but it is not considered essential to continue beyond 6 months.

4.6 Reproductive toxicity studies[2]

4.6.1 Introduction

It is preferable to have some information on pharmacokinetics before initiating reproduction studies since this may suggest the need to adjust the choice of species, study design, and dosing schedules. At this time, the information need not be sophisticated or derived from pregnant or lactating animals. At the time of study evaluation, further information on pharmacokinetics in pregnant or lactating animals may be required depending on the results obtained.

The limitation of exposure in reproductive toxicity is usually governed by maternal toxicity. Thus, while toxicokinetic monitoring in reproductive toxicity studies may be valuable in some instances, especially with compounds with low toxicity, such data are not generally needed for all compounds.

Where adequate systemic exposure might be questioned because of absence of pharmacological response or toxic effects, toxicokinetic principles could usefully be applied to determine the exposures achieved by dosing at different stages of the reproductive process.

A satellite group of female animals may be used to collect the toxicokinetic data.

4.6.2 Fertility studies

The general principles for repeated dose toxicity studies apply (see 4.3). The need to monitor these studies will depend on the dosing regimen used and the information already available from earlier studies in the selected species.

4.6.3 Studies in pregnant and lactating animals

The treatment regimen during the exposure period should be selected on the basis of the toxicological findings and on pharmacokinetic and toxicokinetic principles.

Consideration should be given to the possibility that the kinetics will differ in pregnant and nonpregnant animals.

Toxicokinetics may involve exposure assessment of dams, embryos, fetuses, or newborn at specified days (Note 14). Secretion in milk may be assessed to define its role in the exposure of newborns. In some situations, additional studies may be necessary or appropriate in order to study embryo/fetal transfer and secretion in milk.

Consideration should be given to the interpretation of reproductive toxicity tests in species in which placental transfer of the substance cannot be demonstrated.

5. Supplementary Notes

Note 1: Definitions of expressions appearing in this ''Note for Guidance:''

Analyte: The chemical entity assayed in biological samples.

Matrix: Blood, plasma, urine, serum, or other fluid or tissue selected for assay.

Concomitant toxicokinetics: Toxicokinetic measurements performed in the toxicity study, either in all animals or in representative subgroups or in satellite groups.

Exposure: Exposure is represented by pharmacokinetic parameters demonstrating the local and systemic burden on the test species with the test compound and/or its metabolites. The area under the matrix level concentration-time curve (AUC) and/or the measurement of matrix concentrations at the expected peak-concentration time C_{max}, or at some other selected time $C_{(time)}$ are the most commonly used parameters. Other parameters might be more appropriate in particular cases.

Monitor: To take a small number of matrix samples (e.g., 1 to 3) during a dosing interval to estimate $C_{(time)}$ or C_{max}.

Profile: To take (e.g., 4 to 8) matrix samples during a dosing interval to make an estimate of C_{max} and/or $C_{(time)}$ and area under the matrix concentration-time curve (AUC).

Satellite: Groups of animals included in the design and groups: conduct of a toxicity study, treated and housed under conditions identical to those of the main study animals, but used primarily for toxicokinetics.

Support: In the context of a toxicity study—to ratify or confirm the design of a toxicity study with respect to pharmacokinetic and metabolic principles. This process may include two separate steps:

(a) Confirmation using toxicokinetic principles that the animals on a study were exposed to appropriate systemic levels of the administered compound (see 3.4) and/or its metabolite(s).

(b) Confirmation that the metabolic profile in the species used was acceptable; data to support this will normally be derived from metabolism studies in animals and in humans.

Validate: In the context of an analytical method—to establish the accuracy, precision, reproducibility, response function, and the specificity of the analytical method with reference to the biological matrix to be examined and the analyte to be quantified.

Note 2: Symbols and definitions according to ''Manual of Symbols, Equations and Definitions in Pharmacokinetics,'' Committee for Pharmacokinetic Nomenclature of the American College of Clinical Pharmacology, Philadelphia, PA, May 1982:

C_{max}-Maximum (peak) concentration.

$C_{(time)}$-Maximum concentration at a specified time after administration of a given dose.

t_{max}-Time to reach peak or maximum concentration following administration.

$AUC_{(0\text{-}t)}$-Area under concentration-time curve from zero to time t. It should be noted that $AUC_{(O\text{-}infinity)}$ is a special case of $AUC_{(0\text{-}t)}$.

Other measurements, for example, urinary excretion, may be more appropriate for some compounds. Other derived parameters, for example, bioavailability, half-life, fraction of unbound drug, and volume of distribution, may be of value in interpreting toxicokinetic data. Thus, the selection of parameters and time points has to be made on a case-by-case basis considering the general principles as outlined in Section 3.

Note 3: Increases in exposure may arise unexpectedly as a result of nonlinear kinetics due to saturation of a clearance process. Increasing exposure may also occur during the course of a study for those compounds which have a particularly long plasma half-life. Careful attention should also be paid to compounds which achieve high C_{max} values over comparatively short time periods within the dosing interval. Conversely, unexpectedly low exposure may occur during a study as a result of auto-induction of metabolizing enzymes.

Note 4: If samples are taken from main study animals it should be considered whether samples should be taken from *all* the dosed animals and the controls in order to treat all animals on the study in the same way, or whether samples should be taken from representative subgroups of the same size.

Note 5: In this context, a ''no-toxic-effect dose level'' (deemed to be the same as ''no-observed-adverse-effect dose level'') is defined as a dose level at which some pharmacological response may be observed, but at which no adverse effect is found.

Note 6: In these circumstances it should be established that absorption is the rate limiting step and that limitations in exposure to the administered substance are not due to an increased clearance.

Note 7: The limits placed on acceptable volumes which can be administered orally to animals may constrain the dose levels achievable for comparatively non-toxic compounds administered as solutions or suspensions.

Note 8: It is often considered unnecessary to assay samples from control groups. Samples may be collected and then assayed if it is deemed that this may help in the interpretation of the toxicity findings, or in the validation of the assay method.

Note 9: Measurement of metabolite concentrations may be especially important when documentation of exposure to human metabolite(s) is needed in the nonclinical toxicity studies in order to demonstrate adequate toxicity testing of these metabolites.

Note 10: It is recognised that measurement of metabolite(s) as a part of toxicokinetic evaluation serves only to assess exposure and cannot account for possible reactive intermediate metabolites.

Note 11: Treatment regimen encompasses dosage, formulation, route of administration, and dosing frequency.

Note 12: The first repeat dose study incorporating toxicokinetic data for each species is normally of 14 day's duration or longer.

Note 13: Additional studies may be required in order to compare exposure to the compound administered in diet and by gavage or by routes different from the intended clinical route.

Note 14: It should be noted that while it is important to consider the transfer of substances entering the embryo-fetal compartment, fetal exposure is the parameter which is most often assessed in practice in separate studies and expressed as ''placental transfer.''

6. References (other ICH Guidance)

1. Code SlC ''Carcinogenicity: Guidance for Dose Selection Dose Selection for Carcinogenicity Studies of Therapeutics.''

2. Code S5A ''Detection of Toxicity to Reproduction for Medicinal Products.''

Dated: February 23, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

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