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Biological evaluation of medical devices —

Part 16: Toxicokinetic study design for degradation products and leachables

Évaluation biologique des dispositifs médicaux —

Partie 16: Conception des études toxicocinétiques des produits de dégradation et des substances relargables

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 10993-16 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This second edition cancels and replaces the first edition (ISO 10993-16:1997), which has been technically revised.

ISO 10993 consists of the following parts, under the general title *Biological evaluation of medical devices*:

— *Part 1: Evaluation and testing within a risk management process*

— *Part 2: Animal welfare requirements*

— *Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity*

— *Part 4: Selection of tests for interactions with blood*

— *Part 5: Tests for in vitro cytotoxicity*

— *Part 6: Tests for local effects after implantation*

— *Part 7: Ethylene oxide sterilization residuals*

— *Part 9: Framework for identification and quantification of potential degradation products*

— *Part 10: Tests for irritation and skin sensitization*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

— *Part 13: Identification and quantification of degradation products from polymeric medical devices*

— *Part 14: Identification and quantification of degradation products from ceramics*

— *Part 15: Identification and quantification of degradation products from metals and alloys*

— *Part 16: Toxicokinetic study design for degradation products and leachables*

— *Part 17: Establishment of allowable limits for leachable substances*

— *Part 18: Chemical characterization of materials*

— *Part 19: Physico-chemical, morphological and topographical characterization of materials* [Technical Specification]

— *Part 20: Principles and methods for immunotoxicology testing of medical devices* [Technical Specification]

Introduction

Toxicokinetics describe the absorption, distribution, metabolism and excretion, with time, of foreign compounds in the body. Essential to the evaluation of the safety of a medical device is consideration of the stability of the material(s) *in vivo* and the disposition of intended and unintended leachables and degradation products. Toxicokinetic studies can be of value in assessing the safety of materials used in the development of a medical device or in elucidating the mechanism of observed adverse reactions. Toxicokinetic studies can also be applicable to medical devices containing active ingredients. The need for and extent of such studies should be carefully considered based on the nature and duration of contact of the device with the body (see Annex A). Existing toxicological literature and toxicokinetic data can be sufficient for this consideration.

The potential hazard posed by a medical device can be attributed to the interactions of its components or their metabolites with the biological system. Medical devices can release leachables (e.g. residual catalysts, processing aids, residual monomers, fillers, antioxidants, plasticizers) and/or degradation products which migrate from the material and have the potential to cause adverse effects in the body.

A considerable body of published literature exists on the use of toxicokinetic methods to study the fate of chemicals in the body (see Bibliography). The methodologies and techniques utilized in such studies form the basis of the guidance in this part of ISO 10993. Annex A provides a rationale for the use of this part of ISO 10993.

Biological evaluation of medical devices —

Part 16:
Toxicokinetic study design for degradation products and leachables

1 Scope

This part of ISO 10993 gives principles on how toxicokinetic studies relevant to medical devices should be designed and performed. Annex A describes the considerations for inclusion of toxicokinetic studies in the biological evaluation of medical devices.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 10993-12, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

ISO 10993-18, *Biological evaluation of medical devices — Part 18: Chemical characterization of materials*

ISO 14971, *Medical devices — Application of risk management to medical devices*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 10993-1 and the following apply.

3.1
absorption
process by which a substance enters the blood and/or lymph system

3.2
bioavailability
extent of systemic absorption of specified substance

3.3
biodegradation
degradation due to the biological environment

NOTE Biodegradation might be modelled by *in vitro* tests.

3.4
bioresorption
process by which a biomaterial is degraded in the physiological environment and the product(s) eliminated and/or absorbed

3.5
clearance
rate of removal of a specified substance from the body or parts of the body by metabolism and/or excretion

3.6
c_{max}
maximum concentration of a specified substance in plasma expressed in mass per unit volume

NOTE When the maximum concentration in fluid or tissue is being referred to, it should have an appropriate identifier, e.g. c_{max}, liver, and be expressed in mass per unit volume or mass.

3.7
degradation product
product of a material which is derived from the chemical breakdown of the original material

3.8
distribution
process by which an absorbed substance and/or its metabolites circulate and partition within the body

3.9
excretion
process by which an absorbed substance and/or its metabolites are removed from the body

3.10
extract
liquid that results from extraction of the test substance or control

3.11
half-life
$t_{1/2}$
time for the concentration of a specified substance to decrease to 50 % of its initial value in the same body fluid or tissue

3.12
leachable
chemical that can migrate from a device or component under storage conditions or conditions of use

NOTE A leachable (e.g. additives, monomeric or oligomeric constituent of polymeric material) can be extracted under laboratory conditions that simulate normal conditions of exposure.

3.13
mean residence time
statistical moment related to half-life which provides a quantitative estimate of the persistence of a specified substance in the body

3.14
metabolism
process by which an absorbed substance is structurally changed within the body by enzymatic and/or non-enzymatic reactions

NOTE The products of the initial reaction can subsequently be modified by either enzymatic or non-enzymatic reactions prior to excretion.

3.15
test substance
degradation product or leachable used for toxicokinetic study

3.16
t_{max}
time at which c_{max} is observed

3.17
volume of distribution
V_d
parameter for a single-compartment model describing the apparent volume which would contain the amount of test substance in the body if it were uniformly distributed

4 Principles for design of toxicokinetic studies

4.1 Toxicokinetic studies should be designed on a case-by-case basis.

4.2 A study protocol shall be written prior to commencement of the study. The study design, including methods, shall be defined in this protocol. Details of areas to be defined are given in 4.3 to 4.8 and in Clause 5.

4.3 The results of leaching studies should be considered in order to determine the methods to be used for toxicokinetic studies. Information on the chemical and physicochemical properties, surface morphology of the material and biochemical properties of any leachable should also be considered.

NOTE The extent and rate of release of leachables depend on the concentration at the surface, migration to the surface within the material, solubility and flow rate in the physiological milieu.

4.4 It is recommended to undertake toxicokinetic studies with a characterized leachable or degradation product that has the potential of being toxic. However, the performance of toxicokinetic studies on mixtures is possible under certain conditions. An extract liquid (see ISO 10993-12), or a ground or powdered form of the material or device, may be used in exceptional circumstances and shall be justified in the study design.

4.5 Analytical methods shall be able to detect and characterize degradation products, leachables and metabolites in biological fluids and tissues. For analytical methods, other parts of ISO 10993 shall be used as relevant. The methods shall be fully described in the study report (see 5.1.11). Quantitative analytical methods shall be specific, sensitive and reproducible, and produce data which show linearity over the range of expected analyte concentrations. Validation of the assay method shall be presented in the report.

4.6 The study design shall state the physiological fluid, tissue or excreta in which analyte levels will be determined.

NOTE Blood is convenient to sample and thus is often the fluid of choice for kinetic parameter and absorption studies. It is necessary to specify whether analysis is on whole blood, serum or plasma and to provide validation of this choice. Binding to circulating proteins or red cells can be determined *in vitro*.

4.7 The study report should contain information on analyte binding in the sample (e.g. amount and affinity) and demonstrate that this does not lead to underestimation of analyte concentration.

4.8 There should be sufficient data points with adequate time intervals to allow determination of kinetic parameters. In theory this should cover several terminal half-lives; in practice the constraints of the analytical method may necessitate a compromise.

5 Guidance on test methods

5.1 General considerations

5.1.1 The study should be performed in an appropriate sex and species. Healthy young adult animals should be acclimatized to laboratory conditions for at least 7 d. They should be transferred to individual metabolism cages, when used, for an acclimatization period of at least 24 h. The environmental conditions should be as recommended in guidelines for the care and use of animals (see ISO 10993-2). During the study, conventional animal diets and drinking water should be freely available unless otherwise specified in the protocol. Animals should be randomly selected into groups for each time period studied; group sizes of at least three for small animals and at least two for larger species should be used. At the appropriate specified times, animals should be humanely killed.

5.1.2 A non-radiolabelled test substance may be utilized provided suitable validated assay procedures for the test substance in the relevant samples exist and the metabolism of the test substance is well characterized.

5.1.3 If necessary, the test substance should be radiolabelled in a metabolically stable position, preferably with ^{14}C or ^{3}H, and of a suitable radiochemical purity (> 97 %). When using ^{3}H, the possibility of tritium exchange should be considered. The radiolabelled compound should be diluted, when appropriate, with a non-radiolabelled substance.

5.1.4 When using a radiolabelled compound, the specific activity and radiochemical purity of the test substance shall be known.

5.1.5 The test substance should be administered by an appropriate route. This route should be relevant to the use of the medical device. The test substance should be prepared in a suitable vehicle taking into account the physicochemical properties of the test substance (leachable or degradation product) using appropriate route and dose of administration. The stability of the sample under the proposed condition's administration should be known and reported.

NOTE The study design might require the inclusion of other route(s) for comparison of percent absorption.

5.1.6 In dose balance studies, animals should be housed only in metabolism cages.

5.1.7 Urine and faeces should be collected in low temperature vessels (or in vessels containing preservative that does not interfere with the analysis) to prevent post-elimination microbial or spontaneous modification. Blood for whole-blood or plasma analysis should be collected in the presence of a suitable anticoagulant.

5.1.8 Controls should, wherever possible, be collected prior to dosing. In some studies collection of controls (e.g. tissues) is not possible from the test animals and these should be obtained from a control group.

5.1.9 Collection times should be appropriate to the type of study being performed, and may be carried out, as necessary, over periods of minutes, hours, days, weeks or even months. For studies involving excreta, this is usually 24 h periods over at least 96 h. Where blood sampling is required, blood is collected according to a specified schedule ranging from minutes to hours over a period up to 72 h.

5.1.10 Toxicokinetic studies should be performed in accordance with good laboratory practice.

5.1.11 The study report shall include the following information, where relevant:

a) strain and source of animals, age, sex, environmental conditions, diet;

b) test substance and sample, purity, stability, formulation, amount administered;

c) test conditions, including route of administration;

d) assay methods, extraction, detection, validation;

e) overall recovery of material;

f) tabulation of individual results at each time point;

g) quality standard or good laboratory practice compliance statement;

h) discussion of results;

i) interpretation of results.

5.2 Guidance on specific types of test

5.2.1 General

5.2.1.1 The study should be designed to provide the necessary information for risk assessment, and therefore it is usually not necessary to examine all aspects.

5.2.1.2 Absorption, distribution, metabolism and excretion studies are a range of studies capable of being performed either individually, examining one of these aspects, or collectively, examining several aspects in one study.

5.2.1.3 Depending on the design of the study, a number of kinetic parameters may be determined including absorption rate, area under the plasma concentration versus time curve, area under the first moment plasma concentration versus time curve, volume of distribution, c_{max}, t_{max}, half-life, mean residence time, elimination rate and clearance.

5.2.1.4 Kinetic parameters can only be determined for a particular molecular species and hence the assay needs to be specific and sensitive to this molecular species. True kinetic parameters of a relevant compound can only be determined following intravenous administration. It may therefore be necessary to include a limited intravenous administration study in the design of the kinetic parameter studies. This allows the fraction of the dose absorbed to be calculated and this serves as a correction in estimating parameters in other studies.

5.2.1.5 The appropriate kinetic model should be used in determining the kinetic parameters. A number of computer programs exist for estimating kinetic parameters. The software should be validated prior to use and this validation should be documented. The assumptions entered into the program and the choices in modelling should be documented.

5.2.2 Absorption

Absorption depends on the route of administration, the physicochemical form of the test substance and the vehicle. It can be estimated from blood, serum, excreta and tissue concentrations. Complete bioavailability studies may be considered. The choice of the appropriate type of study depends on the other information required, availability of radiolabelled material and assay method. In a kinetic parameter study, the absorption rate constant can be estimated reliably only if sufficient samples are taken in the absorption phase.

NOTE *In vitro* methods exist which can give important information on gastrointestinal and dermal absorption of chemicals.

5.2.3 Distribution

5.2.3.1 Distribution studies generally require radiolabelled compounds.

Studies may be

— quantitative, determining levels in dissected tissues;

— qualitative, using whole-body autoradiography (WBA);

— semiquantitative, using graded WBA reference doses.

5.2.3.2 In general, sampling times in distribution studies should be between $t_{max} = 24$ h and 168 h or longer, depending on test substance elimination. Intermediate times may be used when these additional data are required. Sampling is normally more frequent in the early phase of absorption and elimination; however samples need to be obtained over as much of the elimination phase as possible (ideally three to four half-lives) to provide the best estimates of kinetic parameters. The major determinant is often assay sensitivity.

5.2.4 Metabolism and excretion

5.2.4.1 Metabolism cages should permit a separate collection of urine and faeces throughout the study. For studies of up to 14 d, the urine and faeces should be individually collected over 24 hour intervals until the end of the experiment. In some study designs, animals may be sacrificed at intermediate times. Samples may be collected prior to 24 h when it is probable that the test substance or its metabolites will be rapidly excreted. For studies of longer duration, sampling over the initial period should occur as for the short-term studies. Thereafter samples should be obtained for a continuous 24 h period per assessment period.

NOTE The use of metabolism cages for prolonged periods might be detrimental to animal welfare. Therefore at the longer times, representative discontinuous samples can be collected and these results extrapolated to continuous sampling.

5.2.4.2 The carcasses and/or target organs of the individual animals should be retained for analysis, and blood collected for analysis of plasma and whole-blood concentrations. After collection of the samples from the metabolism cages at the sacrifice time, the cages and their traps should be washed with an appropriate solvent. The resulting washes can be pooled and a representative fraction retained for analysis.

5.2.4.3 The recovery or calculated recovery of a test substance should ideally be (100 ± 10) % when a radiolabelled compound is used (see NOTE). The amount of test substance in each fraction should be analysed by suitably validated procedures for either a radiolabelled or non-radiolabelled compound in the appropriate milieu. Where a radiolabelled compound is used, both parent compound and metabolites are assessed unless a specific assay is used. If the radiolabelled compound cannot be sufficiently recovered in the excreta (faeces and/or urine) or in the body, a collection of expired air should be considered.

NOTE The recovery range specified might not be achievable in all cases, and reasons for any deviation should be stated and discussed in the report.

5.2.4.4 Levels of radioactivity in the biological milieu should be determined, for example by liquid scintillation counting; however it must be stressed that this represents a mixed concentration of compound and metabolites, and no kinetic parameters can be derived from it. Where isolation of metabolites is considered necessary, this may involve a number of extractions and chromatographic procedures (e.g. high-pressure liquid chromatography, thin layer chromatography, gas-liquid chromatography), and the resulting material should be characterized by chemical methods and a variety of physical chemistry techniques (e.g. mass spectrometry, nuclear magnetic resonance spectroscopy).

The use of tissues, cells, homogenates and isolated enzymes for the study of metabolism *in vitro* is well documented. These methods identify potential metabolism which may not occur *in vivo* unless the compound is available at the appropriate site. The extents and rates of metabolism *in vitro* compared to *in vivo* will often differ.

Annex A
(normative)

Circumstances in which toxicokinetic studies shall be considered

A.1 Potential hazards exist in the use of most medical devices. Chemical characterization identifies chemical hazards (potential risks) (see ISO 10993-18 and ISO 14971) and should precede toxicokinetic considerations. However, it is neither necessary nor practical to conduct toxicokinetic studies for all identifiable intended and unintended leachables and degradation products, nor for all medical devices.

A.2 The need for toxicokinetic studies as part of the biological evaluation of a medical device shall be considered taking into account the final product and its constituent chemicals, intended and unintended leachables and degradation products in combination with the intended use of the device.

Possible toxicokinetic interaction between active ingredients and leachables and/or degradation products should also be considered.

A.3 *In vitro* methods, which are appropriately validated, reasonable and practically available, reliable and reproducible, shall be considered for use in preference to *in vivo* tests (ISO 10993-1). Where appropriate, *in vitro* experiments (e.g. tissue, homogenates or cells) should be conducted to investigate probable rather than possible degradation products. ISO 10993-2 applies to any *in vivo* testing being considered.

A.4 Toxicokinetic studies shall be considered if

a) the device is designed to undergo bioresorption;

b) the device is a permanent contact implant, and significant corrosion (of metallic materials) or biodegradation is known or likely, and/or migration of leachables from the device occurs;

c) substantial quantities of potentially toxic or reactive degradation products and leachables are likely or known to be released from a medical device into the body during clinical use;

d) substantial quantities of active ingredients are likely or known to be released from a medical device.

NOTE The meaning of the term “substantial quantities” is dependent on the properties of the chemicals in question.

A.5 Considerations for toxicokinetic studies are not required if

a) sufficient toxicological data or toxicokinetic data relevant to the degradation products and leachables already exist;

b) sufficient toxicological data or toxicokinetic data relevant to the active ingredients already exist;

c) the achieved or expected rates of release of degradation products and leachables from a particular device have been judged (see ISO 10993-17) to demonstrate safe levels of clinical exposure;

d) clinical exposure of degradation products and leachables is documented as safe with reference to historical experience.

A.6 The release of leachables and degradation products from metals, alloys and ceramics is usually too low to justify toxicokinetic studies.

A.7 Where materials are complex and contain products which are either endogenous or they are so similar to endogenous products that they cannot be analytically distinguished, a toxicokinetic study is usually not feasible.

Bibliography

[1] AFZELIUS, L., et al., *State-of-the-art tools for computational site of metabolism predictions: Comparative analysis, mechanistic insights and future applications*. Drug. Metab. Revs., **39**, pp. 61-86, 2007

[2] BAILLIE, T.A., et al., *Contemporary Issues in Toxicology: Drug Metabolites in Safety Testing*, Toxicol. Appl. Pharmacol., **182**, pp. 188-196, 2002

[3] WINTER, M.E. (ed), *Basic clinical pharmacokinetics*, *4th edition*. Lippincott, Williams & Wilkins, 2003

[4] BEATTY, D.A. and PIEGORSCH, W.W., *Optimal statistical design for toxicokinetic studies*, Statist. Meth. Med. Res., **6**, pp. 359-376, 1997

[5] BLAAUBOER, B.J., BARRATT, M.D. and HOUSTON, J.B., *The Integrated Use of Alternative Methods in Toxicological Risk Evaluation. ECVAM Integrated Testing Strategies Task Force Report 1*, ATLA, **27**, pp. 229-237, 1999

[6] BOKKERS, B.G. and SLOB, W., *Deriving a data-based interspecies assessment factor using the NOAEL and the benchmark dose approach*, Crit. Rev. Toxicol., **37**, pp. 355-373, 2007

[7] BOOBIS, A.R., et al., *Interlaboratory comparison of the asessment of P450 activities in human hepatic microsomal samples,* Xenobiotica, **28**, pp. 493-506, 1998

[8] CLARK, D.E., (Theme ed), *Computational methods for the prediction of ADME and toxicity,* Adv. Drug. Deliv. Rev., **4**, pp. 253-451, 2002

[9] COSSON, V.F., FUSEAU, E., EFTHYMIOPOULOS, C. and BYE, A., *Mixed Effect Modeling of Sumatriptan Pharmacokinetics During Drug Development. I, Interspecies Allometric Scaling*, J. Pharmacokin. Pharmacod., **25**, pp. 149-167, 1997

[10] CROSS, D.M. and BAYLISS, M.K., *A commentary on the use of hepatocytes in drug metabolism studies during drug discovery and drug development,* Drug. Metab. Revs., **32**, pp. 219-240, 2000

[11] DIXIT, R., *Toxicokinetics: Fundamentals and applications in drug development and safety assessment*. in Biological Concepts and Techniques in Toxicology, Chapter 8, pp. 117-160, Marcel Dekker 2006

[12] DORNE, J.L., WALTON, K. and RENWICK, A.G., *Human variability in xenobiotic metabolism and pathway-related uncertainty factors for chemical risk assessment: a review*, Food Chem. Toxicol., **43**, pp. 203-216, 2005

[13] DORNE, J.L., WALTON, K., SLOB, W. and RENWICK, A.G., *Human variability in polymorphic CYP2D6 metabolism, is the kinetic default uncertainty factor adequate?* Food Chem. Toxicol., **40**, pp. 1633-1656, 2002

[14] DORNE, J.L., *Human variability in hepatic and renal elimination: implications for risk assessment*. J. Appl. Toxicol., **27**, pp. 411-420, 2007

[15] DORNE, J.L., *Impact of inter-individual differences in drug metabolism and pharmacokinetics on safety evaluation*, Fundam. Clin. Pharmacol., **18**, pp. 609-620, 2004

[16] *Drug discovery and evaluation: safety and pharmacokinetic assays.* VOGEL, H.G., et al. (eds), Springer Verlag, Berlin, 2006

[17] EKINS, S., et al., *Present and future in vitro approaches for drug metabolism,* J. Pharmacol. Toxicol. Methods, **44**, pp. 313-324, 2000

[18] ENGLISH, J.C., DEISINGER, P.J. and GUEST, D., *Metabolism of 2-ethylhexanoic acid administered orally or dermally to the female Fischer 344 rat,* Xenobiotica, **28**, pp. 699-714, 1998

[19] FDA guideline for industry. *Pharmacokinetics: Guidance for repeated dose tissue distribution studies.* Federal Register, **60** (40), pp. 11274-11275, 1995

[20] FORKERT, P.-G., *Mechanisms of 1,1-dichloroethylene-induced cytotoxicity in lung and liver.* Drug Metab. Revs., **33**, pp. 49-80, 2001

[21] FRANTZ, S.W., et al., *Pharmacokinetics of ethylene glycol II. Tissue distribution, dose dependent elimination, and identification of urinary metabolites following single intravenous, peroral or percutaneous doses in female Sprague-Dawley rats and CD-1® mice,* Xenobiotica, **26**, pp. 1195-1220, 1996

[22] FUHR, U., *Induction of Drug Metabolising Enzymes: Pharmacokinetic and Toxicological Consequences in Humans,* Clin. Pharmacokin., **38**, pp. 493-504, 2000

[23] GOTT, D., *Biodegradation and toxicokinetic studies*, in BRAYBROOK, J.H. (ed)., *Biocompatibility assessment of medical devices and materials,* John WILEY, Chichester 1997

[24] GUNDERT-REMY, U. and SONICH-MULLIN, C., *IPCS Uncertainty and Variability Planning Workgroup and Drafting Group (International Program on Chemical Safety). The use of toxicokinetic and toxicodynamic data in risk assessment: an international perspective.* Sci. Total Environ., **288**, pp. 3-11, 2002

[25] KWON, Y. (ed), *Handbook of essential pharmacokinetics, pharmacodynamics and drug metabolism for industrial scientists*, Springer Verlag, 2001

[26] HANSCH, C., MEKAPATI, S.B., KURUP, A. and VERMA, R.P., *QSAR of Cytochrome P450,* Drug Metab. Revs., **36**, pp. 105-156, 2004

[27] *Harmonised Tripartite Guideline — Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies,* ICH S3A, 1994

[28] *Harmonised Tripartite Guideline — Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies,* ICH S3B, 1994

[29] HEDAYA, M.A., *Basic pharmacokinetics*. *CRC Press pharmacy education series*, CRC Press, Boca Raton, FL, 2007

[30] HEINONEN, M., OILA, O. and NORDSTRÖM, K., *Current issues in the regulation of human tissue-engineering products in the European Union*, Tissue Eng., **11**, pp. 1905-1911, 2005

[31] HENGSTLER, J.G., et al., *Cryopreserved primary hepatocytes as a constantly available in vitro model for the evaluation of human and animal drug metabolism and enzyme induction*. Drug Metab. Revs., **32**, pp. 81-118, 2000

[32] HOUSTON, J.B. and GALETIN, A., *Progress towards prediction of human pharmacokinetic parameters from in vitro technologies,* Drug Metab. Revs., **35**, pp. 393-415, 2003

[33] GUENGERICH, F.P. and RENDIC, S., (eds), *Human cytochrome P450 enzymes, a status report summarizing their reactions, substrates, inducers and inhibitors – 1st update. Special issue on Human cytochromes P450 (Human CYPs)*, Drug Metab. Revs., **34**, pp. 1-450, 2002

[34] *Human cytochrome P450s: assessment, regulation and genetic polymorphisms*, Xenobiotica (special issue), **28**, pp. 1093-1291, 1998

[35] ICH S3A *Toxicokinetic guidance reference — Note for Guidance on Toxicokinetics: A Guidance for Assessing Systemic Exposure in Toxicity Studies* (CPMP/ICH/384/95.)

[36] *International Programme On Chemical Safety. Environmental Health Criteria 57: Principles of toxicokinetic studies*, World Health Organization, Geneva, 1986

[37] TOZER, T.N. and ROWLAND, M. (eds)., *Introduction to pharmacokinetics and pharmacodynamics: the quantitative basis of drug therapy,* Lippincott, Williams & Wilkins, 2006

[38] KEEGAN, G.M., LEARMONTH, I.D. and CASE, C.P., *Orthopaedic metals and their potential toxicity in the arthroplasty patient. A review of current knowledge and future strategies,* J. Bone Joint Surg. [Br], **89-B**, pp. 567-573, 2007

[39] KIRMAN, C.R., SWEENEY, L.M., CORLEY, R. and GARGAS, M.L., *Using physiologically-based pharmacokinetic modeling to address nonlinear kinetics and changes in rodent physiology and metabolism due to aging and adaptation in deriving reference values for propylene glycol methyl ether and propylene glycol methyl ether acetate,* Risk Anal., **25**, pp. 271-284, 2005

[40] KRISHNAN, K. and JOHANSON, G., *Physiologically-based pharmacokinetic and toxicokinetic models in cancer risk assessment,* J. Environ. Sci. Health, Part C: Environ. Carcinogen. Ecotox. Rev., **23**, pp. 31-53, 2005

[41] LEWIS, D.F.V. and DICKINS, M., *Baseline lipophilicity relationships in human cytochromes P450 associated with drug metabolism*, Drug Metab. Revs., **35**, pp. 1-18, 2003

[42] LINHART, I., *Stereochemistry of styrene biotransformation*. Drug Metab. Revs., **33**, pp. 353-368, 2001

[43] LUU, H.M.L., HUTTER, J.C. and BUSHAR, A., *Physiologically based pharmacokinetic model (PBPK) model for 2,4-toluenediamine leached from polyurethane foam-covered breast implants,* Envir. Health Perspectives **106(7)**, pp. 393-400, 1998

[44] MAHMOOD, I., GREEN, M.D. and FISHER, J.E., *Selection of the first-time dose in humans: comparison of different approaches based on interspecies scaling of clearance,* J. Clin. Pharmacol., **43**, pp. 692-697, 2003

[45] MEEK, B., RENWICK, A. and SONICH-MULLIN, C., *International Programme on Chemical Safety: Practical application of kinetic data in risk assessment — an IPCS initiative*. Toxicol. Lett., **138**, pp. 151-60, 2003

[46] MIZUTANI, T., *PM frequencies of major CYPs in Asians and Caucasians*, Drug Metab. Revs., **35**, pp. 99-107, 2003

[47] NESTOROV, I., *Whole Body Pharmacokinetic Models: Review Article*, Clin. Pharmacokin., **42**, pp. 883-908, 2003

[48] OECD Guideline for Testing of Chemicals, 417: *Toxicokinetics*, Adopted: 4 April 1984

[49] ÖRN, U. and KLASSON-WEHLER, E., *Metabolism of 2, 2', 4, 4'- tetrabromodiphenylether in rat and mouse*, Xenobiotica, **28**, pp. 199-211, 1998

[50] POULIN, P. and THEIL, F-P., *Prediction of pharmacokinetics prior to In Vivo studies. II. Generic physiologically based pharmacokinetic models of drug disposition*, J. Pharm. Sci., **91**, pp. 1358-1370, 2002

[51] RENWICK, A.G. and LAZARUS, N.R., *Human variability and noncancer risk assessment — An analysis of the default uncertainty factor,*. Regul. Toxicol. Pharmacol., **27**, pp. 3-20, 1998

[52] ROFFEY, S.J., OBACH, R.S., GEDGE, J.I. and SMITH, D.A., *What is the objective of the mass balance study? A retrospective analysis of data in animal and human excretion studies employing radiolabelled drugs*, Drug Metab. Revs., **39**, pp. 17-44, 2007

[53] ROSSO, F., MARINO, G., GIORDANO, A., BARBARISI, M., PARMEGGIANI, D. and BARBARISI, A., *Smart materials as scaffolds for tissue engineering,* J. Cell Physiol., **203**, pp. 465-470, 2005

[54] SCARFE, G.B., et al., *^{19}F-NMR and directly coupled HPLC-NMR-MS investigations into the metabolism of 2-bromo-4-trifluoromethylaniline in rat: a urinary excretion balance study without the use of radiolabelling*, Xenobiotica, **28**, pp. 373-388, 1998

[55] SHEINER, L.B. and STEIMER, J-L, *Pharmacokinetic/pharmacodynamic modelling in drug development*. Ann. Rev. Pharmacol. Toxicol., **40**, pp. 67-95, 2000

[56] SKORDI, E., WILSON, I.D., LINDON, J.C. and NICKOLSON, J.K., *Characterization and quantification of metabolites of racemic ketoprofen excreted in urine following oral administration to man by ^{1}H-NMR spectroscopy, directly coupled HPLC-MS and HPLC-NMR, and circular dichroism,* Xenobiotica, **34**, pp. 1075-1089, 2004

[57] SLATTER, J.G., et al., *Pharmacokinetics, toxicokinetics, distribution, metabolism and excretion of linezolid in mouse, rat and dog,.* Xenobiotica, **32**, pp. 907-924, 2002

[58] SMITH, D.A., WALKER, D.K. and VAN de WATERBEEMD, H., *Pharmacokinetics and metabolism in drug design. Methods and principles in medicinal chemistry,* **31**, Wiley-VCH, Weinheim, 2006

[59] SMITH, D.A., HUMPHREY, M.J., and CHARUEL, C., *Design of toxicokinetic studies*, Xenobiotica, **20**, pp. 1187-1199, 1990

[60] SMITH, D.A., *Pharmacokinetics and pharmacodynamics in toxicology*, Xenobiotica, **27**, pp. 513-525, 1997

[61] SUN, H.F., MEI, L., CUNXIAN, S., CUI, X., and WANG, P., *The in vivo degradation, absorption and excretion of PCL-based-implant*, Biomaterials, **27**, pp. 1735-1740, 2006

[62] LIPSCOMB, J.C. and OHANIAN, E.V. (eds.),*Toxicokinetics and risk assessment*, Informa, 2006

[63] CLAYSON, D.B., et al. (eds.), *Toxicology,* Elsevier, New York, 1996

[64] TOZER, T.N. and ROWLAND, M., *Introduction to Pharmacokinetics and Pharmacodynamics — The Quantitative Basis of Drug Therapy,* Lippincott, WILLIAMS & WILKINS, 2006

[65] VENKATAKRISHNAN, K., VON MOLTE, L.L. and GREENBLATT, D.J., *Human drug metabolism and cytochromes P450: Application and relevance of in vitro models,* J. Clin. Pharmacol., **41**, pp. 1149-1179, 2001

[66] WALKER, D.K., *The use of pharmacokinetic and pharmacodynamic data in the assessment of drug safety in early drug development,* Br. J. Clin. Pharmacol., **58**, pp. 601-608, 2004

[67] YACOBI, A., SKELLY, J.P., and BATRA, V.K., *Toxicokinetics and new drug development*, Pergamon Press, 1989

[68] YAN, Z. and CALDWELL, G.W., *Metabolism profiling, and cytochrome P450 inhibition & induction in drug discovery*, Curr. Top. Med. Chem., **1**, pp. 403-425, 2001

[69] YANNAS, I.V., *Synthesis of Tissues and Organs,* Chem. Bio. Chem., **5**, pp. 26-39, 2004

[70] ZHOU, S., et al., *Drug bioactivation, covalent binding to target proteins and toxicity relevance,* Drug Metab. Rev., **37**, pp. 41-214, 2005

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