Glossary

ABC (see ATP binding cassette).

Absolute bioavailability (see also Relative bioavailability): The fraction of a drug reaching systemic circulation upon extravascular administration as compared to the dose size of the drug administered intravenously. Absolute bioavailability after extravascular administration (F) can be estimated as follows:

$$F = \frac{AUC_{ex,0-\infty} \cdot D_{iv}}{AUC_{iv,0-\infty} \cdot D_{ex}}$$

where $AUC_{ex,\ 0\text{-}\infty}$ and $AUC_{iv,\ 0\text{-}\infty}$ are the AUC from time 0 to ∞after extravascular or intravenous administration of drug, respectively; and D_{ex} and D_{iv}: Extravascular or intravenous doses of drug, respectively.

Accuracy of assay (see also Precision of assay): Relative error of assay. Accuracy of assay can be assessed by determining the experimental concentrations of the control samples by substituting detector responses into the regression equation. The relative differences between the experimental concentrations and theoretical (nominal) concentrations yield the relative error.

Active metabolite: A metabolite of a drug with significant pharmacological effects.

Active transport (see also Diffusion): A mechanism of drug transport across a membrane that is carrier-mediated and saturable, and requires consumption of energy. The net movement of a drug by active transport can be against its concentration gradient.

ADME Pharmacokinetic profiles, i.e., absorption, distribution, metabolism, and excretion of a drug.

Akaiki information criterion (AIC): A statistical method of determining the appropriate pharmacokinetic model(s) for plasma exposure data of the test compound proposed by Akaike (Akaike H., A new look at the statistical model identification, *IEEE Trans. Automat. Control.* **19:** 716–723,1974). Among different models, the one yielding the lowest AIC value (highest negative in the case of negative values) is the most appropriate model for describing the data:

$$\text{AIC value} = n \cdot \ln(\text{WSS}) + 2 \cdot m$$

where n and m are the number of data points and parameters used in the model, respectively; and WSS is the weighted sum of squares.

Albumin: The most abundant plasma protein (35–50 μg/ml plasma) with molecular weight of approximately 65,000. Acidic compounds commonly bind to albumin. The liver is the body's major producer of albumin.

Allele: One of two or more alternate forms of a gene occupying the same position (locus) in a particular chromosome and containing specific inheritable characteristics.

Allometry: The study designed to establish empirical relationships between the size, shape, surface area, and/or life span of animals and their consequences in regard to physiological functions of animals or pharmacokinetics of drugs without necessarily understanding the underlying mechanisms. The most frequently used allometric relationship in drug pharmacokinetics is

$$\boxed{Y = \alpha \cdot X^{\beta}}$$

where Y is the pharmacokinetic parameter of interest, e.g., clearance or volume of distribution, and X is the physiological parameter such as body weight. Estimates for the allometric coefficient (α) and the allometric exponent (β) can be obtained from an intercept and a slope of a log–logplot of the above equation, respectively:

$$\boxed{\log Y = \beta \cdot \log X + \log \alpha}$$

Alpha(α) phase (distribution phase): The initial portion of a plasma drug concentration *vs.* time profile after rapid intravenous injection. The decrease in drug concentration in plasma during this phase is usually steeper than in the later phase pseudoequilibrium, elimination, or terminal phase) mainly due to the distribution of drug molecules from the plasma pool into other tissues and organs in the body. Drug elimination may also occur during the alpha phase.

Amorphous drug form (see also Crystalline drug form): Solid drug particles without definite crystalline structure. In general, the amorphous form of a chemical is more soluble in water than its crystalline form, which can lead to more extensive absorption after oral administration than with the crystalline compound. However, the crystalline form is thermodynamically more stable than the amorphous form, so that in time the amorphous form will convert to the more stable crystalline form. Owing to this instability of the amorphous form, the crystalline form of a compound is preferred for manufacturing and quality control.

Antagonism: The apparent total effect of two different drugs after coadministration, which is less than the addition of the individual effects obtained from each drug (the additive effect) after separate administration of drugs.

APCI: Atmospheric pressure chemical ionization.

API: Atmospheric pressure ionization.

ATP binding cassette (ABC): The ATP binding cassette (ABC) family is one of the largest superfamilies of proteins among prokaryotes and eukaryotes. In eukaryotes, this family can

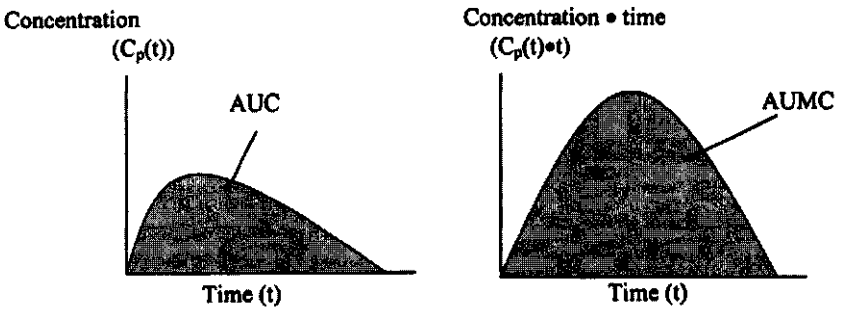

Figure G.1

be subdivided into four to six subclusters. Pharmacokinetically important ABC proteins include ATP-dependent active transporters including p-glycoprotein [multidrug resistance *(MDR)* gene products] and multidrug resistance-associated protein (MRP) responsible for active excretion of various organic cations and anions in the eliminating organs such as the liver.

AUC: The area under the plasma drug concentration *vs.* time curve. The unit of AUC is concentration multiplied by time (e.g., μg·hr/ml).

AUMC: The area under the (first)-moment of a plasma drug concentration *vs.* time curve (area under the product of plasma drug concentration and time *vs.* time curve) on a linear scale. The unit of AUMC is concentration multiplied by time^2 (e.g., μg·hr^2/ml) (Fig. G.1).

Autoinduction: A phenomenon in which a compound induces its own metabolism after single or multiple dosing. This can be due to induction and/or stabilization of the enzyme(s) metabolizing the compound. When a compound is subject to autoinduction, the extent of exposure such as AUC and/or C_{max} of the compound after multiple dosing is usually lower than that after single dosing.

BBB (see Blood Brain Barrier).

Beta(β) phase (pseudoequilibrium, postdistributive, elimination, or terminal phase): The later portion of plasma drug concentration *vs.* time profiles after rapid intravenous injection. The decrease in drug concentration in plasma during this phase is mainly due to the elimination of drug molecules from the plasma pool, and is usually shallower than in the earlier phase (alpha- or distribution phase). During the beta phase, the ratio between the total amount of drug present in the plasma and tissues remains constant.

Bioassay: Determination of the amount or pharmacological effectiveness of a biologically active substance by measuring the extent of its effects on a living organism.

Bioavailability (see also Absolute bioavailability and Relative bioavailability): The fraction of a drug reaching the systemic circulation unchanged following administration by any route. Since the availability of a drug in the systemic circulation after intravenous administration is usually unity, bioavailability (F) after extravascular administration, e.g., oral dosing, can be

estimated as follows:

$$F = \frac{D_{iv} \cdot AUC_{po,0-\infty}}{D_{po} \cdot AUC_{iv,0-\infty}}$$

where D_{iv} and D_{po} are intravenous and oral doses, respectively; and AUC_{iv}, $0\text{-}\infty$ and AUC_{po}, $0\text{-}\infty$ are the areas under the plasma drug concentration *vs.* time curves after intravenous or oral administration, respectively, from time 0 to ∞.

Bioequivalence: Statistically comparable bioavailability (the extent as well as the rate of absorption) of a drug with different products or formulations at the same dose level. The same bioavailabilities after oral administration of two different formulations implies the same extent as well as the same rate of absorption. Therefore, even if two different formulations produce the same AUC after oral administration (the extent of absorption), the bioavailabilities of those formulations can be considered different (not bioequivalent), if the concentration–time profiles such as C_{max}, T_{max}, half-life, etc, are different from each other owing to the different rates of absorption.

Biophase: The site of action for the pharmacological effect of a drug in the body.

Biotransformation: The enzymatic or biochemical transformation of a drug in the body to other chemical forms, i.e., metabolites. In most cases, the biotransformation process of endogenous or exogenous compounds is irreversible. The term biotransformation is interchangeable with metabolism.

Blood brain barrier (BBB): The physiological and biochemical barrier between the blood and the brain that restricts endogenous and exogenous compounds in the blood from entering the brain by capillary endothelial cells with very tight junctions and no pinocytic vesicles. In general, lipid-soluble small molecules with a molecular weight under a 400–600 threshold are readily transported through the blood–brain barrier *in vivo* via lipid-mediated transport (Pardridge W. M., CNS drug design based on principles of blood–brain barrier transport, *J. Neurochem.* **70:** 1781–1792, 1998).

Bolus dose: An individual dose, usually given via rapid intravenous injection.

BSA: Bovine serum albumin.

Caco-2 cells: Cells originally derived from human adenocarcinoma colon cells. When grown on porous membranes, Caco-2 cells differentiate spontaneously to monolayers of polarized cells possessing the differentiated functions of intestinal enterocytes. The morphological and biochemical properties of the cells are closer to those of the small intestinal villus cells than to those of colonic cells, except for paracellular transport permeability, which is closer to that of the colonic epithelium. Owing to these characteristics, the Caco-2 cell line has been one of the most commonly used and extensively studied cell lines to assess membrane permeability of xenobiotics for intestinal absorption in humans.

Caplet: Capsule-shaped coated tablet.

Capsule: A solid dosage form in which the drug substance and other pharmaceutical adjuncts such as fillers are contained in either a soft or a hard shell, usually made of gelatin. In general, a drug substance from a capsule is released faster than from a tablet.

Cassette dosing (Cocktail dosing or N-in-1 dosing): Dosing a mixture of several compounds (N) in one dosing vehicle (1) to single animals as opposed to dosing individual compounds in one dosing vehicle to individual animals at a time.

Central compartment: The compartment representing the total plasma pool and well-perfused body organs and tissues for which drug concentration equilibrates instantaneously with that in plasma. It is assumed that any changes in the plasma drug concentration are quantitatively and qualitatively reflected by the drug concentration in the central Compartment. The volume of the central compartment multiplied by the drug concentration in plasma at a given time indicates the total amount of drug present in the central compartment at that time. For many drugs, the volume of the central compartment is usually greater than the actual volume of the body's entire plasma pool.

Chelation: Intramolecular bonding or holding of a hydrogen or metal atom between atoms of a single molecule (e.g., chelation of iron with heme or chelation of calcium with EDTA).

Chirality (see also Enantiomer): Molecules that are not superimposable on their mirror images are called chiral. Chirality of a molecule is a necessary and sufficient condition for the existence of its enantiomer.

Chiral center (see also Enantiomer): A carbon atom to which four different groups are attached.

Chronopharmacology (chronergy): Rhythmic changes in pharmacological efficacy of drug as a function of time.

Chronopharmacokinetics: Rhythmic changes in pharmacokinetics of drug as a function of time.

Cirannual rhythm: A biological rhythm with a yearly cycle.

Circadian rhythm: A biological rhythm with a 24-hr cycle.

Clearance: The most general definition of clearance is the rate of elimination of a drug from the body (systemic clearance) or organ (organ clearance) normalized to its concentration in an appropriate reference body fluid such as plasma. Clearance can be also viewed as the apparent volume of the reference fluid completely cleared of the drug per unit time.

ClogP and **MlogP:** Log P values of a compound calculated based on the methods developed by the Medicinal Chemistry Department of Pomona College, CA, or by Moriguchi *et al.* (Moriguchi I. *et al.* Simple method of calculating octanol/water partition coefficient. *Chem. Pharm. Bull.* **40:** 127–130,1992), respectively.

cMOAT [see also Multidrug resistance-associated protein (MRP)]: Canalicular multispecific organic anion transporter located in canalicular membranes of hepatocytes. cMOAT is believed to be MRP2.

Cocktail dosing (see Cassette dosing).

Compartment (see also Central compartment and Peripheral compartment): The imaginary space in the body representing a group of tissues, organs, and/or fluids that can be treated kinetically as a homogeneous unit. The kinetic homogeneity of a drug in the compartment

does not necessarily imply that the drug concentration is equal in all the tissues within the compartment at any given time, rather that the times to reach distribution equilibrium between the plasma and each organ and tissue are similar.

Compartmental model: A pharmacokinetic approach to interpret the plasma drug concentration *vs.* time profile following drug administration, assuming that the body can be viewed as one or several different compartments. The number of compartments equals the number of exponential terms in a differential equation describing the plasma concentration–time profile. For instance, if the plasma concentration–time profile data are best fitted with a biexponential equation, a two-compartment model such as one shown in Fig. G.2 can be used.

Controlled-release dosage form (see also Sustained-release dosage form): A solid dosage form designed to release a drug substance over an extended period of time at a precisely controlled rate, usually zero-order rate, compared to the sustained release product. The advantage of controlled-release dosage forms is that they require less frequent drug administration than ordinary forms, yet maintain therapeutic drug concentrations, which leads to better patient compliance.

Creatinine (see also GFR): The endogenous muscle breakdown substance, which is produced in the body at a constant rate. Concentration of creatinine in plasma in humans is about 15 μg/ml. Owing to its negligible protein binding and almost exclusive excretion via glomerular filtration, the renal clearance of creatinine is considered to be the same as the glomerular filtration rate (GFR).

Crossover study: The study in which comparison treatments in animals (or humans) follow in a counterbalanced sequence, so that each animal (or human subject) receives both treatments, and thus serves as its own control.

Crystalline drug form (see also, Amorphous drug form and Polymorphism): Solid drug materials with definite identifiable crystalline shape. Some chemicals can exist in more than one crystalline form (polymorphism), depending on the conditions (temperature, solvent, time, pressure, etc) under which crystallization is induced.

CSF Cerebrospinal fluid.

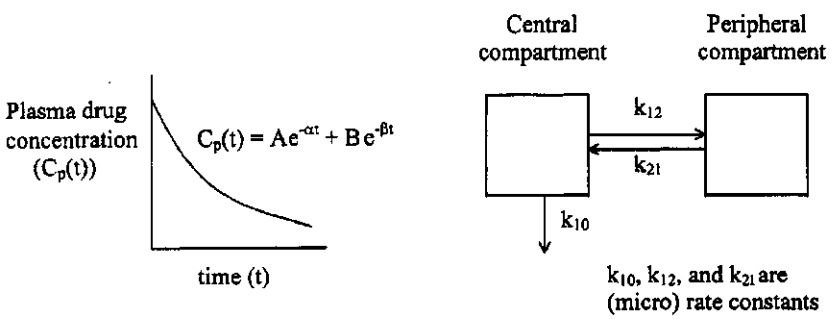

Figure G.2

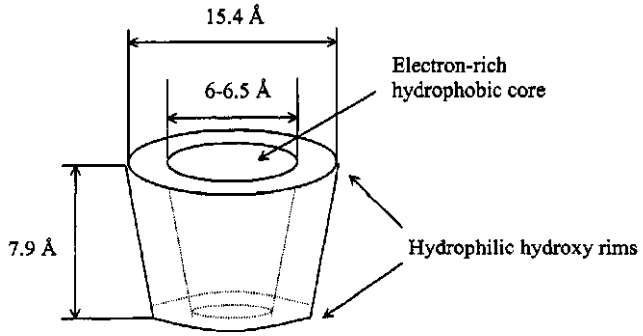

Figure G.3

Cyclodextrin (CD): Cyclic oligosaccharide. Natural cyclodextrins, i.e., α-, β-, and *y*-cyclodextrins, are cyclic oligosaccharides of 6, **7,** and 8 glucopyranose units, respectively, with aqueous solubility ranging from 150 to 230 mg/ml. Chemical substitution at the 2, 3, and 6 hydroxyl groups of the glucopyranose units of cyclodextrin, e.g., 2-hydroxypropyl β-cyclodextrin, can significantly increase the aqueous solubility of natural cyclodextrin up to more than 500 mg/ml. A three-dimensional structure of cyclodextrin resembles a truncated cone with a nonpolar electron-rich hydrophobic interior and a hydrophilic exterior (see Fig. G.3). Owing to these structural characteristics, cyclodextrins can enhance the aqueous solubility and stability of hydrophobic molecules and even biological macromolecules such as peptides and proteins by trapping the hydrophobic moiety of the compounds within their hydrophobic cores, reducing hydrophobic interactions between the compounds and the surrounding water molecules.

Deep compartment (see also Peripheral compartment): The compartment representing certain organs or tissues to which distribution of a drug from plasma is significantly slower than to other regions in the body. The prolonged drug elimination half-life often found with sensitive assay or following administration of a radiolabeled compound can be due to the slow release of a drug from the deep compartment. Identification of organs or tissues responsible for a deep compartment can be important because of the potential toxicity of a drug associated with its accumulation in those organs or tissues after multiple dosing.

Diastereomers (see also Chiral center and Enantiomers): Stereoisomers that are nonsuperimposable mirror images of each other, i.e., enantiomers. In general, diastereomers have more than one chiral center. A molecule can have only one enantiomer, but may have several diastereomers. The maximum number of possible stereoisomers of a molecule is equal to 2n, where n is the number of chiral centers in the molecule. Diastereomers have similar chemical properties, but different physical properties such as solubility, melting points, and densities.

Diffusion (see also Active transport): Diffusive transport of a drug across a membrane. Facilitated diffusion is distinguished from simple diffusion by an enhanced rate and saturability of transport. Although facilitated diffusion is carrier-mediated transport, it is different from active transport in that the net movement of a substance is not against a concentration gradient, i.e., at equilibrium the concentration of the substance in the inside and on the outside of a cell is equal, and energy is not required for transport of the substrate.

Disposition: Disposition of a drug generally implies both distribution and elimination (metabolism and excretion) processes.

Distribution coefficient (also see Partition coefficient): Distribution coefficient (D or log D as generally described) is defined as the overall ratio of a compound, ionized and un-ionized, between organic and aqueous phases at equilibrium:

$$D = \frac{[\text{Un-ionized drug}]_{\text{organic phase at equilibrium}}}{[\text{Un-ionized drug}]_{\text{aqueous phase at equilibrium}} + [\text{Ionized drug}]_{\text{aqueous phase at equilibrium}}}$$

Distribution equilibrium: Condition at which the rate of change in the amount of a drug in the peripheral compartment is zero after intravenous bolus injection, when drug disposition can be adequately described with a two-compartment model. The volume of distribution of the drug at this time point is the so-called "apparent volume of distribution at steady state."

Distribution phase [see Alpha (α) phase].

DDS (see Drug delivery system).

Dose-dependent pharmacokinetics (see also Nonlinear kinetics): The phenomenon that the pharmacokinetic behaviors of a drug during absorption, distribution, metabolism, and excretion differ at different dose levels. The dose-dependent plasma concentration–time profiles of a drug at different dose levels are indicative of nonlinear kinetics of the drug in the body.

Doseproportionality (see Superposition).

Drug delivery system (DDS): The technology utilized to direct a drug substance to the desirable body site for release and absorption. For instance, a transdermal patch is a drug delivery system.

E (see Extraction ratio).

ED_{50}: The dose level of a drug that is efficacious in 50% of animals following administration.

EDTA Ethylenediaminetetraacetic acid ($C_{10}H_{16}N_2O_8$, molecular weight 292.24), a chelating agent for heavy metals or divalent cations such as Ca^{+2}. EDTA can be also used as an anticoagulant or antioxidant in foods.

EHC (see Enterohepatic circulation).

Electrospray ionization: Ion formation from samples in solution by the use of electrospray. In an electrospray interface, the liquid chromatography (LC) effluent (a sample solution) is nebulized into small electronically charged aerosols into the atmospheric pressure region by applying an electric field (usually 3-kV potential difference) in a narrow-bore capillary or electrospray needle. Electrospray ionization is most suited to compounds that exist as preformed ions in the LC effluent or can be readily ionizable by altering the pH or to polar neutral molecules that can be associated with small ions such as NH_4^+.

Elimination phase (see Beta phase).

EM (see Extensive metabolizer).

Emulsifying agent: A chemical used to promote and maintain the dispersion of finely subdivided particles of a liquid in an immiscible liquid vehicle (e.g., polyoxyethylene 50 stearate, Cremophor El).

Emulsion: A dispersion dosage form in which small globules of a liquid-containing drug substance are distributed throughout an immiscible liquid vehicle. For instance, oil-in-water (o/w) emulsions refer to oil globules (internal phase) containing a drug dispersed in a water medium (external phase). Conversely, emulsions with an aqueous internal phase dispersed in an oily external phase are termed water-in-oil (w/o) emulsions.

Enantiomers: Two stereoisomers that exhibit nonsuperimposabl!e mirror images of each other. For instance, two enantiomers of lactic acid are shown in Fig. G.4. Enantiomers have the same physicochemical properties such as solubility, boiling point, melting point, and retention time on nonchiral analytical columns but not the ability to rotate the plane of polarized light, i.e., dextrorotatory *(d* or +, rotating right) or levorotatory *(l* or −, rotating left).

Encapsulating agent: A chemical used to form thin shells to enclose a drug substance or drug formulation for ease of administration.

Enteric coating: Coatings applied to a solid dosage form of drug substances such as tablets or capsules to permit safe passage of the dosage form through the acidic environment of the stomach to the intestine where dissolution of the dosage form takes place. The enteric coated tablets or capsules are suitable for drugs unstable at low pH or for targeting intestinal absorption sites or lesions.

Enterohepatic circulation (EHC): The phenomenon in which part of a drug excreted into the bile is reabsorbed from the intestine and becomes subject to the continuous recirculating process of excretion into bile and subsequent reabsorption from the intestine.

Extensive metabolizer (EM, see also Poor metabolizer): An individual with normal metabolizing activities for a certain drug.

Extracellular fluid: The fluid that lies outside of the cells, which consists of intravascular and interstitial fluids. There are about 14 liters of extracellular fluid in an average 70-kg man, which is approximately 20% of the total body weight or 33% of the total body fluid (42 liters in a 70-kg man).

Extraction ratio (E): The fraction of a drug extracted from each unit volume of blood per pass through the eliminating organ such as the liver or the kidney from inlet to outlet of blood flow. The extraction ratio (E) relates the organ clearance (Cl) to the blood flow rate (Q) into the organ, i.e., $Cl = Q \cdot E$.

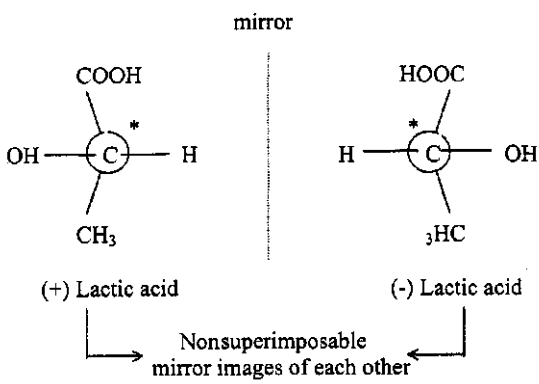

Figure G.4

Extravascular fluid: The fluid that lies outside the blood vessels, which is composed of interstitial and intracellular fluids.

Extravascular administration: All routes of administration of a drug other than those in which the drug is injected directly into the vascular blood stream, such as intraarterial or intravenous injection.

Ex vivo: Experiments conducted with biological samples such as blood or urine obtained from animals that have been pretreated with the compound(s) of interest.

FIM: First in man (see also Phase I study).

First-order kinetics: A kinetic process in which the rate of change in concentration [C(t)] or in the amount of drug with time is directly proportional to the drug concentration, i.e.,

$$\text{Rate of change of drug concentration} = k \cdot C(t)$$

where k is the first-order rate constant.

First-pass effect (presystemic elimination): Drug loss prior to reaching systemic circulation for the first time during absorption after oral administration, which is due to drug metabolism in the enterocytes (gastrointestinal membranes), drug metabolism and biliary excretion in the liver, and/or drug metabolism in the lung.

Flavin-containing monooxygenase (FMO): In addition to the cytochrome P450, hepatic microsomes contain a second class of monooxygenase, the flavin-containing monooxygenase (FMO). FMOs are present mainly in liver, kidney, and lung, and are considered to be important for metabolizing heteroatom-containing compounds, along with cytochrome P450. FMOs require NADPH and 0, for oxidation of the nucleophilic nitrogen (N), sulfur (S), and phosphorus (P) heteroatoms of xenobiotics rather than direct oxidation at a carbon atom. FMOs are heat-labile and can be inactivated in the absence of NADPH by warming microsomes at 50°C for 1 min.

Flip–flop kinetics: The term describing the phenomenon observed when the rate of absorption of a drug from the site of administration is similar to or slower than the rate of its elimination from the body after it enters the systemic circulation. This can be often observed after oral administration of sustained-release drug formulations. When a drug is subject to flip-flop kinetics, the slope of the plasma concentration [$C_p(t)$] *vs.* time profile during the later phase after oral (P.O.) administration is shallower than that after intravenous (I.V.) bolus injection, as illustrated in Fig. G.5.

FMO (see Flavin-containing monooxygenase).

Free drug hypothesis: A hypothesis that the biological activity of a given hormone is governed by its unbound rather than its protein-bound concentration in plasma.

Futile cycling (see also Reversible metabolism): A phenomenon in which conjugated metabolites (glucuronide or sulfate conjugates) of endogenous or exogenous compounds undergo successive cycles of synthesis of the conjugates and hydrolysis back to the parent compounds by more than one enzyme.

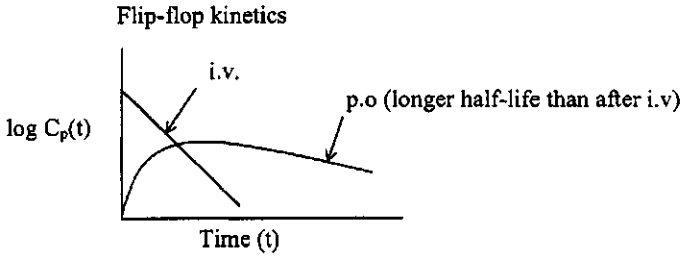

Figure G.5

GCP (see Good clinical practice).

Gene therapy: A therapeutic approach to the treatment of diseases (resulting mainly from genetic defects) by delivering a human gene to a target organ with the subsequent production of a "gene product" or protein such as an enzyme, which can act as a drug. The delivery of a gene can be achieved by, e.g., liposomes, DNA vectors, or recombinant retroviruses.

Genotype: The fundamental assortment of genetic information (genes) contained in chromosomes of an organism.

GFR (see Glomerular filtration rate).

GLP: Good laboratory practice.

Glomerular filtration rate (GFR): Glomerular filtration rate can be used as an index for a subject's renal function. In general, renal impairment causes a decrease in GFR.

Glutathione S-transferase (GST): Glutathione S-transferases represent an integral part of the phase II detoxification system. The glutathione conjugation reaction protects cells against oxidatively and chemically induced toxicity and stress by catalyzing the glutathione conjugation with an electrophilic moiety of hydrophobic and often toxic substrates. In the liver, the glutathione S-transferase accounts for up to 5% of the total cytosolic protein.

GMP: Good manufacturing practice.

Good clinical practice (GCP): Guidelines for planning and performing clinical trials.

gp170 (see P-glycoprotein).

GST (see Glutathione S-transferase).

Gunn rat: A mutant strain of Wistar rat that is genetically deficient in the conjugation of certain aglycones such as, e.g., bilirubin, planar, and bulky phenols.

Half-life: The time it takes a drug concentration in the blood or plasma (or the amount in the body) to decline to one-half of its reference value.

Heated nebulizer: A liquid chromatography (LC)–mass spectrometry (MS) interface, which consists of a pneumatic nebulizer combined with a heated desolvation tube (or chamber) for the introduction of a sample solution (LC column effluent) into an atmospheric pressure chemical ionization (APCI) source. In a heated nebulizer, the column effluent from LC is pneumatically nebulized at room temperature into a heated tube, where evaporation of the solvent in LC effluent (desolvation process) takes place. Owing to the heat required to volatilize a sample solution prior to APCI, a heated nebulizer is not suitable for thermolabile compounds.

Hematocrit: The fraction of the blood composed of red blood cells. Hematocrit can be determined by centrifuging blood in a "hematocrit tube," until the red blood cells become tightly packed in the bottom of the tube. The hematocrit values in healthy men and women are roughly 0.4 and 0.36, respectively.

Henderson–Hasselbalch equation: An equation elucidating the relationship between pH and pKa of acids and bases:

$$\text{Acid (HA)}: \quad pH = pK_a + \log([A^-]/[HA])$$

$$\text{Base (B)}: \quad pH = pK_a + \log([B]/[BH^+])$$

Heterocedacity(see Homocedacity).

Homocedacity: When calculated residuals in linear regression are independent of each other and normally distributed with equal variances, the condition of the equal variance of the data is called homocedacity. When there is unequal variance, the condition of the unequal variance of the data is called heterocedacity (Fig. G.6).

Homeostasis: The physiological processes responsible for maintaining the constancy of the internal biochemical and biological functions and conditions in living organisms.

HPLC: High-pressure (or performance) liquid chromatography.

Hybrid rate constant (see also Compartment model): Apparent rate constant consisting of more than one microconstant. For instance, α and β, the exponents in a biexponential equation describing biphasic plasma concentration–time profiles of a drug after intravenous injection, i.e., $C_p(t) = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$, are hybrid constants, because those are functions of k_{10}, k_{12}, and k_{21}, the microconstants in a two-compartment model.

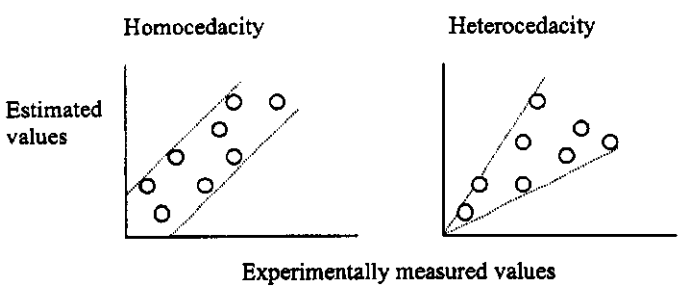

Figure G.6

Hypertonic solution: A solution with a higher osmolarity compared to the reference solution. For instance, solutions with more than 0.9% sodium chloride are considered hypertonic to the intracellular fluid with osmolarity of 280 mOsm/liter, which is equal to that of a 0.9% sodium chloride solution.

Hypotonic solution: A solution with a lower osmolarity compared to the reference solution. For instance, solutions with less than 0.9% sodium chloride are considered hypotonic to the intracellular fluid with osmolarity of 280 mOsm/liter, which is equal to that of a 0.9% sodium chloride solution.

Hysteresis: The time-related changes in the apparent relationship between the plasma concentration of a drug and its observed pharmacological effect. When the plasma drug concentration is plotted against the corresponding observed effect of the drug, and the points are connected in time sequence, the intensity of the observed effect at the same drug concentrations is sometimes different. If the effects are less pronounced during the later time points than those during the earlier time points at the same plasma concentrations, this concentration–effectrelationship as a function of time is known as "clockwise hysteresis (or proteresis)." If the intensity of the effect is higher at the later time points than at the earlier ones for the same plasma concentrations, this phenomenon is known as "counterclockwise hyteresis (or hysteresis)."

I.A. injection: Intraarterial injection.

Investigator's brochure (IB): A document containing all pertinent information such as pharmacological and toxicological effects in animals and humans, if any data exist, known about the investigational new drug (IND) provided by the sponsor to all clinical investigators.

ICH: International committee of harmonization.

I.M. injection: Intramuscular administration (injection).

IND: Investigational new drug (see also Phase I).

Inducer: A compound that increases the concentration of metabolizing enzymes in tissues and thus enhances the rates of metabolism of endogenous or exogenous substrates.

Induction (or enzyme induction): The increase in enzyme content or activities. Induction of metabolizing enzymes usually results in faster metabolism of a drug, which can be due to the enhanced synthesis of enzymes and/or the stimulation of preexisting enzymes by inducers. Enhancement of enzyme synthesis by xenobiotics is known to be the most common mechanism for enzyme induction. If a drug stimulates its own metabolism, it is referred as autoinduction.

Inhibition: The decrease in enzyme content or activities. Inhibition of metabolizing enzymes usually results in slower metabolism of a drug, which can be due to the suppressed synthesis of enzymes and/or the inactivation of preexisting enzymes by inhibitors. Depending on the patterns of inhibitor interaction with the enzyme, there are three different types of inhibition, i.e., competitive, noncompetitive, and uncompetitive inhibition. (a) *Competitive inhibition:* Inhibitor competing for the same binding site of the enzyme with substrates: this type of

inhibition causes an increase in K_m, the Michaelis–Mentenconstant, but no change in V_{max}, the maximum rate of enzymatic reaction, as compared to that in the absence of the inhibitor. (b) *Noncompetitive inhibition:* Inhibitor binding to both the free enzyme and the enzyme–substrate complex. This type of inhibition causes a decrease in V_{max}, but no change in K_m. (c) *Uncompetitive inhibition:* Inhibitor binding to the enzyme–substrate complex. This type of inhibition causes a decrease in both V_{max} and K_m.

In situ: Experiments conducted with intact organs or tissues.

Interstitial fluid: The fluid present in the space between cells, the so-called, interstitium (extracellular fluid minus plasma volume). There are about 11 liters of interstitial fluid in an average 70-kg man, which is approximately 16% of the total body weight or 26% of the total body fluid (42 liters in a 70-kg man). The interstitial fluid is derived from plasma by filtration and diffusion via capillary membranes and contains almost the same constituents as plasma, except for lower concentrations of plasma proteins.

Intracellular fluid: The fluid that resides within the cells. There are about 28 liters of intracellular fluid in an average 70-kg man, which is approximately 40% of the total body weight or 67% of the total body fluid (42 liters in a 70-kg man).

Intravascular fluid: The fluid that resides within blood vessels, i.e., plasma water.

Intrinsic clearance: In general, intrinsic clearance refers to the intrinsic ability of the eliminating organ, such as the liver, to eliminate drugs when there are no limitations in other physiological factors affecting *in vivo* drug clearance. For instance, intrinsic hepatic clearance implies the intrinsic ability of the liver to eliminate drugs via metabolism and/or biliary excretion, when, e.g., hepatic blood flow (supply of the drug to the liver), membrane transport (transport of the drug from the sinusoidal blood into hepatocytes), cofactor availability, and drug binding to blood components are not limiting factors for drug clearance.

In vitro: Experiments conducted in laboratory glassware.

In vivo: Experiments conducted in intact animals.

Iontophoresis: The process of transferring ionized molecules into the tissues, usually skin, by the use of a small electric current.

I.P. injection: Intraperitoneal injection.

Isoelectric point (p*I):* The pH at which the net charge of a molecule such as an amino acid, peptide, or protein is zero, i.e., at p*I,* the molecule is electronically neutral.

Isomers (structural isomer): Distinct molecular entities that have the same molecular formula and share a common characteristic in their chemical structure. There are two different kinds of structural isomers, i.e., constitutional isomers, which differ in the sequential arrangement of atoms, and stereoisomers, which have the same constitutions but differ in the spatial orientation of their atoms. For instance, 1-propranolol ($HO\text{-}CH_2\text{-}CH_2\text{-}CH_3$) and 2-propranolol ($CH_3\text{–}CHOH\text{–}CH_3$)are constitutional isomers, whereas (+)-lactic acid and (–)-lactic acid are stereoisomers (see Stereoisomers).

Isotonic solution: A solution with the same osmolarity as the reference solution. For instance, a 0.9% sodium chloride solution or a 5% glucose solution is isotonic to the intracellular fluid, since it produces the same osmolarity (280 mOsm/liter).

I.V. injection: Intravenous injection.

Lagrange method: A curve-fitting method with a cubic polynominal function to put a smooth curve through the data points such as plasma drug concentration [$C_p(t)$] *vs.* time (t) plots. Usually, the four data points around the segment of interest in the plot are fitted with the cubic function shown below:

$$C_p(t) = A + B \cdot t + C \cdot t^2 + D \cdot t^3$$

Lag time: The time elapsed between the administration of a drug and its appearance in the systemic circulation or between its appearance in the systemic circulation and the manifestation of its pharmacological effects. For instance, the lag time between drug administration and drug exposure in blood or plasma can be often observed after oral administration of solid dosage forms such as tablets, capsules, and especially enteric-coated tablets. The delay is due to the slow disintegration and/or dissolution of dosage forms in the gastrointestinal tract before the drug is actually absorbed and can be anywhere from a few minutes to several hours.

LC: Liquid chromatography.

LD_{50}: The dose level of a drug that is lethal to 50% of animals after administration.

Linear conditions (see also Linear kinetics and Superimposibility): Conditions in which pharmacokinetic processes of a drug such as absorption, distribution, metabolism, and excretion can be properly described by the first-order kinetics. The linearity of the system can be recognized when the dose-normalized plasma concentration *vs.* time profiles of a drug at different dose levels are superimposible and can be properly described by the same first-order kinetics.

Linear kinetics (see also First-order kinetics): Pharmacokinetic processes, that can be described by first-order kinetics.

Liposome: A stable microscopic vesicle composed of one bilayer (unilamellar liposome) or a number of bilayers (multilamellar liposome) of various phospholipids and similar amphipathic lipids concentrically oriented around an aqueous core. Liposomes are spontaneously formed when certain phospholipids are dispersed in excess water. Liposomes have been utilized as drug delivery systems to carry lipophilic compounds within their lipid bilayers.

Loading dose: The one-time dose administered at the beginning of therapy in conjunction with a regular dose regimen, to achieve therapeutic drug concentration faster than the regular dose regimen alone.

Locus: Any genetically defined site.

Log D (see also Distribution coefficient): Logarithm of the distribution coefficient. A rough estimate of log D of a compound at any given pH can be obtained by subtracting one unit from log P for every unit of pH above (for acids) or below (for bases) the pK_a:

$$\log D \approx \log P - \Delta|pK_a - pH|$$

Log $D_{7.4}$: Log D measured at pH 7.4 in an aqueous phase.

Log P (see Partition coefficient): Logarithm of the partition coefficient.

MAD: Maximum absorptive dose.

MA0 (see Monoamine oxidase).

Mass balance study: Study performed in humans or animals, usually small laboratory animals such as rats or mice, using a radiolabeled compound to elucidate the pharmacokinetic profiles of the compound. Mass balance studies in small animals are conducted in metabolic cages, which enable the collection of urine and feces samples for estimating the degree of drug recovery during the experiments. Levels of radioactivity in various tissues and organs can be determined by sacrificing animals at various time points. The main purposes of such studies are to investigate the routes and extent of elimination of a drug and its metabolites from the body after administration and to understand tissue distribution profiles of a drug and its metabolites when needed. The information from these studies can be useful for the interpretation of potential organ-specific toxicity. Mass balance studies with radiolabeled compounds in humans involve many regulatory and ethical issues, and there are many different guidelines in various countries. In general, a mass balance study is performed using a limited number of (usually male) volunteers, e.g., three or four, and women at the age of procreation are excluded.

MAT (see Mean absorption time).

MDR (see Multidrug resistance gene product and P-glycoprotein).

Mean absorption time (MAT): The average time it takes for a drug molecule to be absorbed into the systemic circulation from the site of administration, e.g., into the gastrointestinal tract after oral dosing. The MAT of a drug can be determined from the difference between the mean residence time (MRT) values after oral and intravenous bolus administration.

Mean input time (MIT): The average time it takes a drug molecule to reach the systemic circulation from the site of extravascular administration. The MIT of a drug following extravascular administration can be determined as the difference in the mean residence time (MRT) values between extravascular and intravenous bolus administration.

Mean residence time (MRT): The average time after administration that a drug molecule spends in the body before being eliminated.

Mechanism-based inhibitor: A compound inhibiting the activity of metabolizing enzymes, such as cytochrome P450s, by forming covalent bonds with the enzymes as a result of its own metabolism by the enzyme(s). For instance, 1-aminobenzotriazole (ABT) is a mechanism-based inhibitor of various cytochrome P450 isozymes. To be activated, ABT undergoes a P450-catalyzed oxidation to form benzyne, a reactive intermediate, which covalently binds to the prosthetic heme group of cytochrome P450 and thereby causes an irreversible loss of enzyme activity.

Membrane: Cell membranes are basically composed of two different kinds of molecules, i.e., lipids and proteins. There are three types of lipids, i.e., phospholipids, cholesterol, and glycolipids. Phospholipids, which have both hydrophilic and lipophilic groups in their

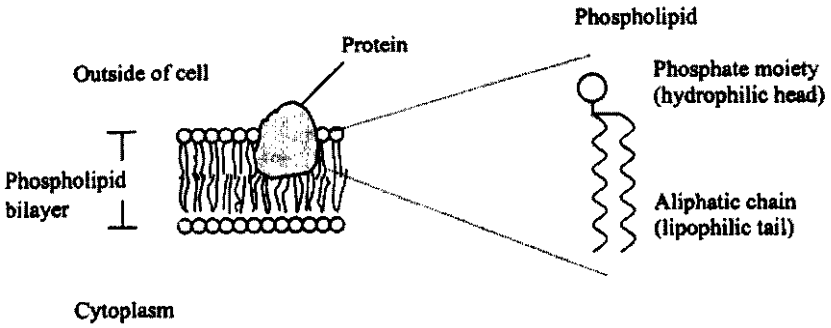

Figure G.7

structures, form a bilayer (ca. 70 Å in thickness) such that their polar groups constitute the outer surfaces of the membrane, whereas nonpolar groups are buried within the interior region of the membrane. Protein molecules may lie at or near the inner or outer membrane surface or penetrate partially or entirely through the membrane (Fig. G.7).

Metabolic ratio (MR, see also Polymorphism): A ratio between the amount of parent drug and its particular metabolite(s) excreted in urine. When MR values are measured for metabolites known to be produced by polymorphic enzyme(s), they can be used for polymorphic phenotype screening for drugs subject to polymorphic metabolism:

$$\text{MR} = \frac{\text{Amount of parent drug excreted in urine}}{\text{Amount of metabolite excreted in urine}}$$

Metastable form (see also Polymorphism): Various types of less stable crystalline forms of a chemical than its most stable crystalline form at a given temperature and pressure. The metastable forms of a compound convert in time to the stable crystalline form.

MFO: Mixed function oxidase.

MIC (see Minimum inhibitory concentration).

Michaelis–Menten equation: An equation, shown below, that characterizes certain concentration–dependent biological or pharmacokinetic processes such as, e.g., protein binding, metabolism, and active transport:

$$\boxed{\frac{dC}{dt} = \frac{V_{max} \cdot C}{K_m + C}}$$

where C is the concentration of substrate, K_m is the Michaelis–Menten constant (concentration of substrate at which the rate of the process is one half of V_{max}), and V_{max} is the maximum rate of the process. At substrate concentrations well below K_m, the rate of change in concentration is a function of the concentration [$dC/dt = (V_{max}/K_m) \cdot C$], i.e., the first-order kinetics), whereas at concentrations well above Km, it becomes constant ($dC/dt = V_{max}$, i.e., the zero-order kinetics).

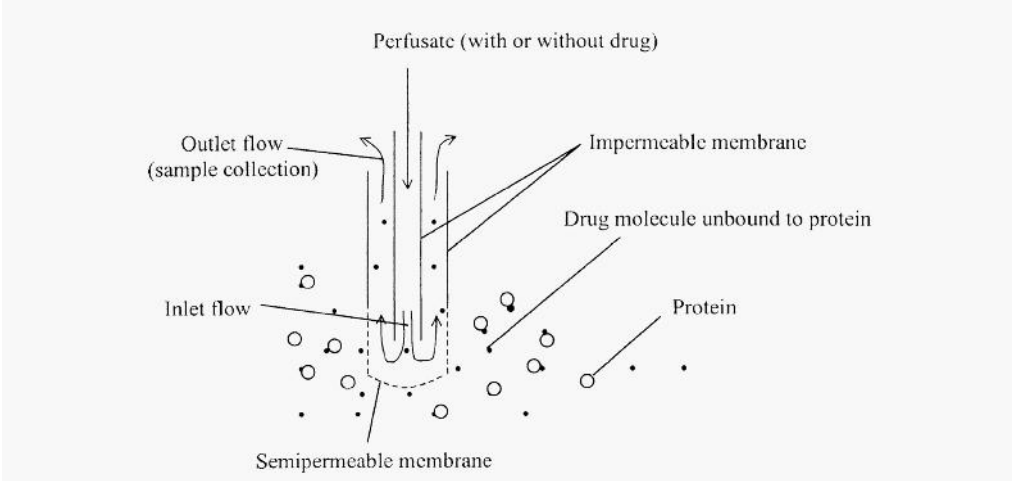

Figure *G.8*

Microdialysis: A technique for measuring the extracellular concentration of a drug(s) not-bound to proteins by implanting a semipermeable membrane probe into tissues or blood vessels in an animal (freely moving). The typical microdialysis probe consists of an impermeable tube attached to a semipermeable, hollow fiber usually 200–400μm in diameter with a molecular-weight cutoff of 10,000–30,000Da, inside of which is placed an impermeable tube for perfusate. The design of the probes can be specialized to match different tissues. The microdialysis probe is bidirectional. That is, it can collect drug-containing samples from the site of implantation by flushing the tube inside of the probe with an isotonic perfusion fluid, but also can deliver the drug by perfusing the tube with the drug solution. Microdialysis can be also used for in vitro experiments, such as, e.g., protein binding and drug metabolism in microsomes.

Middle molecules (see also Middle-molecule hypothesis): The specific uremic toxins identified in uremia with a molecular weight approximately between 300 and 12,000. Uremic retention solutes representing middle molecules include parathormone, β_2,-microglobulin, some peptides, and glucuronated conjugates among others, of which most are still without proven toxicity.

Middle-molecule hypothesis: A hypothesis that uremic syndrome (a progressive deterioration of physiological and biochemical functions of the kidneys that accompanies the development of renal failure) is the result of the retention of metabolic compounds with a molecular weight approximately between 300 and 12,000 (so-called "middle molecules") that are normally cleared by healthy kidneys.

Minimum inhibitory concentration (MIC): The lowest concentration of an antimicrobial agent that prevents the growth of microorganisms on an agar plate after incubating for a certain period of time, usually 18 to 24 hr.

MIT (see Mean input time).

Molarity (M, see also Mole): The number of moles of solute dissolved in 1 liter of solution. Solutions of 1 M, 1 mM. and 1 μM contain 1 mole, 1 mmole, and 1 μmole of drug in 1 liter

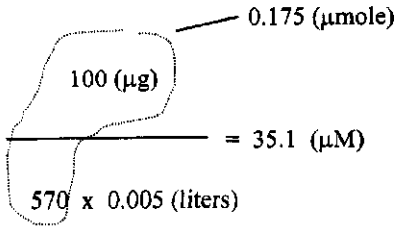

Figure G.9

of solution. Thus, molarity has the units of concentration, i.e., moles per liter:

$$\text{Molarity (M, mM or } \mu\text{M)} = \frac{\text{Number of moles of solute (mol, mmol, } \mu\text{mol)}}{\text{Number of liters of solution (liters)}}$$

For instance, a molar concentration of 100 μg of compound A with a molecular weight of 570 dissolved in 5 ml of water is 35.1 μM (Fig. G.9). If one needs 5 ml of a 10 μM of compound A in 1% DMSO and water, one dissolves 28.5 μg of the compound in 50 μl of DMSO and adds 4.95 ml of water:

$$\frac{10(\mu\text{mole}) \times 570}{1000\ \text{ml}} \times 5(\text{ml}) = 28.5(\mu\text{g})$$

Mole: A mole of any substance that contains Avogadro's number (6.022×10^{23}) of atoms or molecules. For instance, 1 mole of water molecules contains 6.022×10^{23} H_2O molecules, or 12.044×10^{23} H atoms and 6.022×10^{23} 0 atoms. The mass of 1 mole of the substance is equal to its molecular weight in grams. For instance, 1 mole, 1 mmole, and 1 μmol of water are equal to 18 g, 18 mg, and 18 μg of water, respectively:

$$\text{Mole (mole, mmole, or } \mu\text{mole)} = \frac{\text{Amount of substrate (g, mg, or } \mu\text{g)}}{\text{Molecular weight}}$$

Monoamine oxidase: Monoamine oxidase (MAO) is known to be related to the metabolism of exogenous tyramine and the "cheese effect" produced by the ingestion of large amounts of tyramine-containing foods under certain conditions. MAO catalyzes the oxidative deamination of biogenic amines. It is primarily a mitochondrial enzyme, although some of its activity has also been reported in the microsomal fraction.

MR (see Metabolic ratio).

MRM: Multiple reaction monitoring (see also SRM): Selected reaction monitoring applied simultaneously to two substances as in the case of a drug accompanied by an internal standard.

MRP (see Multidrug resistance-associated protein).

MRT (see Mean residence time).

MS: Mass spectrometry.

MTD: Maximum tolerated dose.

Table G.10. Nomenclature of MDR Gene Product

Species	Class I	Class II
Human	MDR1	MDR3
Rat, mouse, hamster	mdr1a, mdr1b	mdr2

Multidrug resistance-associated protein (MRP): A member of the ATP binding cassette (ABC) family of transporters with molecular weight of about 190 kDa, which can confer drug resistance in tumor cells with a broad spectrum of substrates. Multidrug resistance–associated protein (MRP) was first found in some multidrug resistant cell lines, in which no overexpression of either P-glycoprotein or mRNA from the encoding multidrug resistance (MDR1) gene could be detected. MRP is also found in normal cells, and its tissue distribution patterns are similar to those of P-glycoprotein; for instance, MRP can be found, e.g., in liver (canaliculus), erythrocyte membranes, heart, kidneys and intestinal brush border membranes, and lungs. At least two different isoforms of MRP, i.e., MRP1 and MRP2, are present in human and rodent hepatocytes. MRP1 is present in the lateral membrane domains of normal hepatocytes at a very low level, whereas MRP2 is localized exclusively in canalicular membrane of hepatocytes. MRP1 and MRP2 are considered to be the same as the ATP-dependent glutathione (GSH) S-conjugate transporter and the canalicular multispecific organic anion transporter (cMOAT) responsible for active biliary excretion of amphipathic anionic conjugates such as glutathione-, glucuronide-, and sulfate conjugates of various substrates in an ATP-dependent manner, respectively.

Multidrug resistance gene product (see also P-glycoprotein): Multidrug resistance (MDR) gene product (also known as P-glycoprotein or P-gp) functions as an ATP-dependent drug efflux pump in the membrane, which lowers the intracellular concentrations of cytotoxic drugs, and it is one of potential causes of resistance of cancer cells to a wide range of chemotherapeutic agents. MDR gene products are also present in normal cells and their locations are confined to the lumenal domains of cells in specific organs such as the liver, intestine, kidney, and brain. Physiological functions of MDR gene products in normal cells appear to be related to active transport of organic cations. There are two different isoforms in normal human cells, i.e., MDR1 and MDR3, and three *mdr* gene products in rats and mice, i.e., mdr1a, mdr1b, and mdr2. MDR1, mdr1a, and mdr1b confer drug resistance on otherwise drug-sensitive cells, but MDR3 and mdr2 do not. Recent studies have suggested that MDR1 and MDR3 in normal hepatocytes might mediate active biliary excretion of hydrophobic organic (cationic) compounds and phosphatidylcholine across canalicular membrane, respectively (Table G.10).

NADPH (Nicotinamide-adenine-dinucleotide-phosphate): A cofactor required along with oxygen for the oxidation reaction by cytochrome P450 enzymes.

NAT: N-acetyltransferase.

NCE: New chemical entity.

NDA (New drug application, see also Phase III study): After successful phase III clinical trials, the new drug application (NDA) for an investigational new drug (IND) is filed for review by the government regulatory agency.

Neoteny: The retention of formerly juvenile characters by adult descendants produced by retardation of somatic development, i.e., a sort of sustained juvenilization or slow development of animals to adulthood. If related to humans, neoteny is the preservation in adults of shapes and growth rates that characterize juvenile stages of ancestral primates.

N-in-1 dosing (see Cassette dosing).

NOAEL (No adverse effect level): Plasma or blood exposure level of the test compound at which no adverse (toxic) effect is observed during toxicity studies in the test animal species.

Noncompartmental model: A pharmacokinetic approach for estimating pharmacokinetic parameters such as clearance, volume of distribution, mean residence time, and bioavailability from plasma drug concentration *vs.* time profiles without any assumptions of a specific compartmental model for the body. There are various noncompartmental techniques including statistical moment analysis, and a noncompartmental recirculatory model of drug plasma concentration *vs.* time profiles.

Nonlinear condition (see also Nonlinear kinetics): The conditions in which pharmacokinetic processes of a drug during absorption, distribution, metabolism, and excretion cannot be properly described with first-order kinetics. The nonlinearity of the system can be assumed when the dose-normalized plasma drug concentration–timeprofiles at different dose levels are not superimposible and cannot be properly described by the same first-order kinetics.

Nonlinear kinetics (see also Michaelis–Menten equation and Zero-order kinetics): Any pharmacokinetic process that does not follow first-order kinetics. Nonlinear kinetics of a drug in the body can be recognized when there is no superimposibility of plasma drug concentration *vs.* time profiles at different dose levels. Virtually all drug pharmacokinetic processes can be considered to be nonlinear at high dose (or concentration) levels owing to saturation of the various enzymatic or carrier-mediated processes during absorption, distribution, metabolism, or excretion.

NONMEM (Nonlinear mixed effect modeling): A computer program provided as FORTRAN source code, developed by the NONMEM Project Group, University of California at San Francisco, CA. NONMEM performs nonlinear regression analysis of sparse data sets from individual or population pharmacokinetic studies.

NSAID: Nonsteroidal anti-inflammatory drug.

OROS (see Osmotic pump): Oral osmotic pump drug delivery system.

Osmolarity: The osmolar concentration of solution (osmole per liter of water, osm/liter). One osmole is equal to 1 mole of solute, i.e., 6×10^{23} molecules. For instance, osmolarity of a solution containing 1 mole of glucose in 1 liter of water is 1 osmole/liter (osm/liter) of glucose. If a molecule dissociates into more than one ion, osmolarity of a solution is affected by the number of osmotically active molecules or ions in the solution. For instance, a solution that contains 1 mole of sodium chloride has an osmotic concentration of 2 osm/liter, because one molecule of sodium chloride dissociates into two ions, i.e., sodium and chloride.

Osmosis: The net diffusion of water from a solution of low solute concentration to a solution of higher solute concentration across a semipermeable membrane between the two solutions that allows only water molecules to diffuse through.

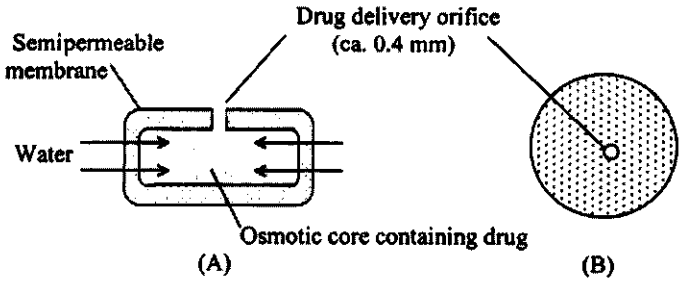

Figure G.11. Cross-sectional (A) and bird's eye view (B) of the oral osmotic pump drug delivery system.

Osmotic pressure: The exact amount of pressure that has to be applied to a solution to prevent osmosis (the net diffusion of water through a semipermeable membrane). The higher the osmotic pressure of a solution is, the higher its solute concentration.

Osmotic pump (OROS, oral osmotic drug delivery system): A solid oral dosage form developed by Alza Co., Palo Alto, CA. An osmotic pump utilizes osmotic pressure built up by the osmotic drug core and water drawn from the gastrointestinal tract after oral administration, via a semipermeable membrane, and thereby releases a drug solution at a constant rate through single or multiple drug delivery orifices (Fig. G.11).

OTC: Over-the-counter drug.

PAH: Polycyclic aromatic hydrocarbons.

PAPS (Phosphoadenosine-5-phosphosulfate): A cofactor required for sulfation by sulfotransferase.

Parenteral administration: Administration of a drug by injection other than into the gastrointestinal tract, such as intraarterial (artery), intraarticular (joint), intracardiac (heart), intradermal or intracutaneous (skin), subcutaneous (beneath the skin), intramuscular (muscle), intraosseous (bone), intraperitoneal (peritoneal cavity), intraspinal (spine), intravenous (vein), or intrasynovial (joint-fluid region) injection.

Partition coefficient (see also Distribution coefficient): Partition coefficient (P, or log P as generally described) is defined as the ratio of concentrations of the un-ionized compound between organic and aqueous phases at equilibrium. The partition coefficient can be viewed as an indicator for intrinsic lipophilicity of the compound in the absence of ionization or dissociation of the compound.

$$P = \frac{[\text{Un-ionized}]_{\text{organic phase}}}{[\text{Un-ionized}]_{\text{aqueous phase}}}$$

PC-NONLIN: A computer program that performs nonlinear regression analyses of pharmacokinetics and pharmacodynamics data.

PCR: Polymerase chain reaction.

PEG Polyethylene glycol.

Peptidomimetic compounds: Peptidelike compounds in terms of their chemical structures. Compounds with more than one amide moiety bonded in a sequence similar to those of peptides.

Peripheral compartment (see also Deep compartment): The compartment representing organs and tissues in the body into which distribution of a drug in plasma is slower than that into the organs and tissues represented by the central compartment (usually blood and highly perfused organs).

Peroral administration: Administration of drug into the gastrointestinal tract via the mouth.

PD (see Pharmacodynamics).

P-glycoprotein (P-gp, gp170, or *MDR* gene products, see also Multidrug resistance (MDR) gene product): A transmembrane protein with molecular weight of 170 kDa classified as an ATP-dependent primary active transporter belonging to the ATP binding cassette (ABC) transporter superfamily. P-glycoprotein (P-gp) was originally identified as a multi-drug resistance (MDR) gene product, which pumps out numerous anticancer agents such as, e.g., vinblastine and daunomycin from tumor cells causing a decrease in their intracellular concentrations and thus resistance to those drugs. Its wide range of substrate specificity has been recognized as one of mechanisms for multidrug resistance of cancer cells with enhanced expression of P-gp. Its substrates other than anticancer agents include several peptides such as cyclosporin, calcium channel blockers such as verapamil, and various cations. P-gp has been also found in lumenal membranes of normal tissues including liver (canalicular membrane of hepatocytes), intestine (brush border membrane of enterocytes), kidneys, adrenals, and brain. One of physiological functions of P-gp has been identified as phosphatidylcholine transporter in canalicular membrane of hepatocytes based on findings from mdr2 knockout mice experiments.

pH: The negative logarithm of the hydrogen ion concentration of a chemical substance in water as a measure of the acidity or the alkalinity of the compound expressed as a number from 0 to 14: $pH = -\log[H^+]$.

Phagocytosis: The process of intake ("engulfment") of solid particles by a cell.

Pharmacodynamics: The study that examines relationships between drug concentrations at the effect site(s) where target enzymes or receptors are located and the magnitude of the pharmacological efficacy of the drug.

Pharmacogenetics: The study of the hereditary (genetic) basis of the differences in responses to or metabolism of various pharmaceutical agents.

Pharmacokinetics: The study of the behavior of drug molecules in the body after administration in terms of absorption, distribution, metabolism, and excretion (ADME) processes through examination of the concentration profiles of drug in readily accessible body fluids, such as blood or plasma as a function of time.

Phase I study: First-in-man (FIM) trials of an investigational new drug (IND). The trials consist of short-term studies in a small number of healthy male subjects or patients suffering from the target disease to be treated. The primary objectives of phase I clinical trials are to establish a dose–tolerance relationship and evaluate pharmacological properties and efficacy of the drug, if possible. The number of subjects usually ranges from 20 to 80.

Phase II study: Pilot therapeutic studies in patients following a phase I study. The main objectives of phase II trials are to assess the effectiveness and determine the common short-term side effects of an investigational new drug (IND). The studies provide information on clinical pharmacokinetic and pharmacodynamic relationships, often with short-term response parameters, the so-called surrogate endpoints. In general, phase IIa is exploratory (controlled or not) in nature and phase IIb is controlled. The number of patients with the target disease to be treated ranges from 100 to 200, and the controlled studies are usually conducted under double-blind and placebo-treated conditions.

Phase III study: Upon obtaining preliminary evidence of the effectiveness of an investigational new drug (IND) from phase II studies, expanded controlled and uncontrolled clinical trials are initiated. The main purposes of phase III studies are to gather additional information about the effectiveness and side effects (safety) for the overall benefit and risk relationship of the IND and to verify its dosage range. The number of patients with the target disease or more than one disease condition usually ranges from 600 to 800. After successful phase III trials, the new drug application (NDA) for the IND is filed for review by the government regulatory agency.

Phase IV study (postmarketing surveillance): Postmarketing surveillance and/or clinical trials of a drug already on the market. During this stage, new indications, pharmaceutical formulations, methods of administration, dosage regimen, and target population of the drug on the market are continuously surveyed and studied. If required, clinical trials can be performed as trials of new medicinal products with similar objectives as premarketing trials in some countries.

Phenotype: The observable structural and functional properties of an organism produced by the interaction between an organism's genetic potential (genotype) and the environment surrounding it.

Physiologically based pharmacokinetic (PBPK) model (or Physiological pharmacokinetic model): A pharmacokinetic model based on actual animal physiology and anatomy. Unlike conventional compartment models, e.g., one- or two-compartment models for drug disposition in the entire body without a detailed understanding of animal physiology, the physiologically based pharmacokinetic model describes the body or the organs with compartments relevant to their anatomical location and physiological function. In other words, compartments in these physiologically more realistic models represent actual organs or tissues in the body with actual volumes and are connected according to their anatomical locations in the body with appropriate organ blood flows. Drug concentrations in different organs or tissues are experimentally measured at the same time, so that an exact description of the time course of drug concentrations in organs or tissues of interest becomes available. In addition, the parameters estimated in these models correspond to actual physiological and physicochemical measures such as organ blood flow rates and volumes and partition coefficients of drugs between blood and tissues. Thus, any changes in the disposition kinetics of a drug as a result of physiological or pathological alterations in the functions of particular organs or tissues can

be estimated and/or predicted. Since the parameters of these models reflect actual physiological and anatomical measurements, animal scale-up based on physiological pharmacokinetics provide a rational basis for parameter extrapolation between different species.

p*I* (see Isoelectric point).

Pinocytosis: The active intake process of fluid by the cell.

Pittsburgh cocktail: Five probe drugs, i.e., caffeine (a probe for CYPlA2), mephenytoin (CYP2C19), debrisoquin (CYP2D6), chlorzoxazone (CYP2E1), and dapsone (CYP3A and N-acetylation), simultaneously administered as a metabolic cocktail to estimate phenotypic activities of cytochrome P450 and N-acetyltransferase enzymes in humans *in vivo* (Frye R. F. *et al.,* Validation of the five-drug "Pittsburgh cocktail" approach for assessment of selective regulation of drug-metabolizing enzymes, *Clin. Pharmacol. Ther.* **62:** 365–376,1997).

PK (see Pharmacokinetics).

pK_a (see also Henderson–Hasselbalch equation): The negative logarithm of K_a, the equilibrium dissociation constant of acids or bases. The pK_a of an ionizable compound is the same as the pH at which the concentration of an ionized compound is the same as that of un-ionized compound. The smaller the pK_a value, the stronger the acid, whereas the larger the pK_a, the stronger the base.

Placebo effect: Apparent (usually beneficial) therapeutic effect observed in patients, which arises from psychological factors following administration of an inert substance (placebo).

Plasma (see also Serum): The clear supernatant after centrifuging blood. Plasma still contains the coagulating factors.

Plasma protein binding: Plasma protein binding indicates how much of the total amount of drug in plasma is bound to plasma proteins such as albumin or α_1-acid glycoprotein.

Poor metabolizer [PM, see also Extensive metabolizer (EM)]: An individual with deficient metabolic ability of a particular drug in a certain metabolizing enzyme(s) owing to a genetic defect.

P.O. administration: Oral administration.

Polymorphism: (1) A Mendelian or monogenic trait that exists in the population in at least two phenotypes (and presumably at least two genotypes), neither of which shows a frequency of less than 1–2% of the population. If the frequency is lower than 1–2%, it is called a rare trait. **(2)** More than one crystalline form of the same chemical substance. Some chemicals can exist in several different types of crystalline forms, depending on the conditions for inducing crystallization including, e.g., temperature, solvent, time, and pressure. There is only one form of a pure chemical substance most stable at a given temperature and pressure as compared with other less stable forms. These are called metastable forms and convert in time to the more stable crystalline form. The various polymorphic forms of the same chemical can differ in many physical properties including, e.g., aqueous solubility and melting point. In general, the metastable forms exhibit higher kinetic aqueous solubility and thus higher dissolution rates than the stable crystal form of the same drug. However, the most stable crystalline form in a

given storage condition is frequently preferred in a pharmaceutical dosage formulation because of its greater resistance to chemical degradation.

Postmarketing surveillance (see Phase IV study).

Precision of assay (see also Accuracy of assay): Reproducibility of replicate determination within a run (intrarun method precision) and reproducibility between determinations from separate runs (interrun precision).

Presystemic elimination (see First-pass effect).

Primary cell culture: A cell culture started from cells, tissues, or organs taken directly from an organism.

Primary metabolite (see also Secondary metabolite): A metabolite originally produced from the parent compound that has not been further metabolized.

Principles of superposition (see Superposition).

Prodrug: Any compound that undergoes biotransformation and/or chemical degradation *in vivo* to produce the active parent drug. Prodrugs can be divided into two classes, i.e., the carrier-linked prodrug (commonly known as prodrug) and the bioprecursors. The carrier-linked prodrug contains a specific nontoxic moiety (carrier), which is mostly of a lipophilic nature, linked with the active parent drug, in order to alter undesirable physicochemical properties of the parent drug usually related to poor aqueous solubility and/or membrane permeability. A simple chemical or enzymatic hydrolysis can cleave this carrier linkage and release the active drug *in vivo* at the right moment. The carrier is usually linked via an ester or amide bond. The bioprecursor is a compound for which a metabolite *in vivo* is expected to be active. It is different than the carrier-linked prodrug in that it does not imply a simple temporary linkage between the active drug and a carrier moiety, but involves a chemical modification of the active molecule, which becomes subject to *in vivo* metabolism. Typical criteria for designing a carrier-linked prodrug are: (1) the linkage of the carrier-linked prodrug is usually a covalent bond; (2) the linkage is cleaved mainly *in vivo;* (3) the production of the active parent drug must occur with the right kinetics to ensure effective drug levels at the site of action and to minimize metabolism of prodrug itself; and (4) the prodrug and the carrier released *in vivo* are nontoxic.

Product inhibition: Inhibition of metabolism of a parent compound by its own metabolite(s).

Prosthetic group: A nonpeptide portion of certain protein molecules that may be intimately concerned with the specific biological activities of the protein. For instance, *heme* is the prosthetic group of hemoglobin.

Proteresis (see Hysteresis).

Pseudodistribution equilibrium phase [see also Beta (β) phase]: When a semilogarithmic plot of plasma drug concentration *vs.* time [log $C_p(t)$ *vs.* t] after intravenous bolus drug administration exhibits a biexponential decline, the straight terminal segment of the plot is called the pseudodistribution equilibrium phase. This phase is also called a β-, postdistribution, elimination, or terminal phase. During this phase, the ratio of amounts of the drug between the plasma pool and all the tissues in the body becomes constant.

Quantitative structure–activity relationship (QSAR): The relationship between various physicochemical parameters of a series of congeneric compounds and the quantitative potency of a particular biological or pharmacological activity. If the studies on the quantitative structure–activity relationship (QSAR) demonstrate that certain physicochemical properties are important for a particular pharmacological activity, a series of structural modifications that will enhance such properties can lead to compounds with greater potency. One of most widely used QSAR methods in drug design is the Hansch approach (Hansch C. and Leo A., *Substituent Constants for Correlation Analysis in Chemistry and Biology,* John Wiley & Sons, New York, 1979).

Racemate (Racemic mixture, see also Enantiomers): A mixture of equimolar parts of enantiomers. A racemic mixture does not rotate the plane of polarized light. Often, the prefix (±) is used to specify the racemic nature of the particular sample. For instance, 1:1 mixture of (+) lactic acid and (–) lactic acid is a racemic mixture of lactic acid and can be indicated as (±) -lactic acid.

Rate constant: Proportionality constant relating the rate of change in the amount of drug (dA/dt) to the amount of drug (A), e.g., $dA/dt = k \cdot A$ for the simplest situation, where k is a first-order rate constant.

Rate-limiting step: The process with the slowest rate constant in sequential kinetic processes, which governs the overall rate of the processes to the final outcome.

Regiospecific reaction: Characteristics of the particular reaction, which yields exclusively or nearly exclusively one of several possible isomeric products.

Relative bioavailability (see also Absolute bioavailability): The proportion of a drug reaching the systemic circulation upon extravascular administration as compared to that of a standard dose of the drug administered via the same route. The relative bioavailability can be assessed for several dosage forms of the same drug without knowing its exposure levels after intravenous administration. For instance, the relative bioavailability of a drug in a dosage form A compared to a dosage form B after oral administration can be obtained as follows:

$$F = \frac{AUC_{0-\infty,A} \cdot D_B}{AUC_{0-\infty,B} \cdot D_A}$$

where $AUC_{0-\infty, A}$ and $AUC_{0-\infty, B}$ are AUC from time zero to infinity after oral administration of a drug in the dosage forms A or B, respectively; D_A and D_B are oral doses of a drug in the dosage forms A or B, respectively; F is the bioavailability (in this case, relative bioavailability).

Renal clearance: Clearance of a drug via the kidneys, which is composed of glomerular filtration, active secretion, and passive reabsorption. Renal clearance can be estimated by the following equation:

$$\text{Renal clearance} = \frac{\text{Amount of unchanged drug excreted in the urine}}{\text{AUC of drug}}$$

Reversible metabolism: Interchangeability between a substrate and its metabolite(s) by a single metabolizing enzyme.

Rule of 5: A general guideline proposed by Lipinski (Lipinski C. A. *et al.,* Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, *Adv. Drug Del. Rev.* **23:** 3–25, 1997) to spot potential oral absorption problems of a compound in humans during drug discovery processes, based on its physicochemical properties. According to this hypothesis, poor absorption of a compound *in vivo* owing to its limited aqueous solubility and/or membrane permeability is more likely when any combination of two or more of the following conditions are observed: (1) the molecular weight of the compound is greater than 500; (2) there are more than 5 H-bond donors in the molecule; (3) there are more than 10 H-bond acceptors (the sums of N's and O's) in the molecule; and (4) the calculated log P (ClogP) of the compound is greater than 5 (or M log P > 4.15). These guidelines are not appropriate for peptidomimetic compounds or compounds subject to active transport mechanisms in the intestinal membranes.

Safety margin (see also Therapeutic index): The ratio between the no adverse effect (toxic) exposure level (NOAEL) in animals and the exposure level required to produce a satisfactory pharmacological response in humans.

SAR: Structure-activity relationship (see also Quantitative structure–activity relationship).

S.C. injection: Subcutaneous injection.

Secondary metabolite (see also Primary metabolite): A metabolite produced from the metabolite originally generated from the parent compound.

Selectivity: The intrinsic ability of an assay method to differentiate and quantify the analyte of interest in the presence of other constituents in a sample.

Serum (see also Plasma): The clear supernatant after centrifuging blood without an anticoagulant, allowing the red blood cells to clot. Serum does not contain coagulating factors.

SHAM analysis: Data analysis to obtain information on slope, height, area, and moment (SHAM) from plasma drug concentration *vs.* time profiles after drug administration.

Sham operation: Surgical operation usually done on control animals to measure its effects on pharmacokinetic or pharmacological properties of compounds tested on study animals that have undergone the same type of the operation.

SIM (Selected ion monitoring): A mass spectrometry operating mode in which a single ion specific for the target compound is monitored.

Soft drug: A pharmacologically efficacious compound that undergoes a predictable and controllable metabolic deactivation *in vivo* to nontoxic moieties after playing its therapeutic role.

Solution: A liquid dosage formulation that contains one or more soluble chemical substances usually dissolved in water.

SRM (Selected reaction monitoring): A sequential sample monitoring process for an analyte of interest used in tandem-mass spectrometry (MS/MS). It consists of three sequential steps: (1) isolation of the precursor ion (parent ion) of the analyte in the first quadrupole of the

instrument, (2) fragmentation of this ion in a collision chamber with argon atoms, and (3) isolation of an intense and/or characteristic product ion (daughter ion) of the precursor in the third quadrupole of the instrument.

Steady state condition: The condition at which the rate of input (rate of administration) of a drug into the system (e.g., body) equals the rate of output (rate of elimination) of that drug from the system. For instance, the steady state of a drug in the body can be achieved after constant-rate intravenous infusion. When a drug is infused into the systemic circulation (blood) at a constant rate, the plasma drug concentration starts to increase until the rate of infusion of the drug (rate of input) is equal to the rate of elimination (rate of output). At steady state, the rate of change in the net amount of the drug in the body becomes zero.

Stereoisomers (see also Diastereomers and Enantiomers): The particular kind of structural isomers that differ from each other only in the spatial orientation of their atoms. There are two different types of stereoisomers, i.e., diastereomers and enantiomers.

Stereoselective reaction (see also Diastereomers and Enantiomers): Characteristics of the particular reaction that produces one diastereomer preferentially (or a pair of enantiomers) over all other possible diastereomers.

Stereospecific reaction (see also Diastereomers and Enantiomers): Characteristics of the particular reaction in which stereoisomeric starting materials (substrates) yield stereoisomerically different products.

Stoichiometry: The relative quantities of the substances participating in any chemical reaction measured according to their molar proportions in the reaction.

Structure–activity relationship (SAR, see also Quantitative structure–activity relationship): Quantitative or qualitative relationship between various molecular structures and their pharmacological and/or biochemical activity.

Subcutaneous injection: Injection beneath the skin.

Sublingual administration: Administration of a drug under the tongue.

Suicide inhibitor (see Mechanism-based inhibitor).

Superposition (dose-proportionality, see also First-order kinetics): The phenomenon that plasma concentration *vs.* time profiles of a drug at different dose levels are superimposed when normalized to the dose. Superposition of exposure profiles of a drug can be observed when its pharmacokinetic processes follow first-order (linear) kinetics. Superposition can be indicative of the linear pharmacokinetic behavior of a drug in the body.

Suspension: Fine solid particles of a drug suspended in a suitable vehicle. Oral suspensions are usually formulated in an aqueous vehicle, whereas suspensions for other purposes, e.g., intramuscular injection, can be prepared in nonaqueous vehicles such as oil. Suspensions are useful for administering large amounts of a drug, where conventional solid dosage forms such as tablets or capsules are not convenient.

Sustained-release dosage form (see also Controlled-release dosage form): A solid dosage form designed to release a drug substance over an extended period of time at a considerably slower rate *in vivo* compared to a conventional dosage form containing an equivalent dose. The conventional solid dosage forms such as tablets or capsules are designed to release their medication rapidly and completely *in vivo.* The advantage of sustained-release dosage forms is that they require less frequent administration than ordinary dosage forms to maintain therapeutic drug concentrations, and thereby improve patient compliance.

Synergism: An apparent total effect of two different drugs after their coadministration that is greater than the addition of their individual effects (the additive effect) after separate administration.

Tablet: A solid dosage form prepared by compression or molding of solid drug particles with or without other pharmaceutical adjuncts such as diluents, disintegrants, coatings, or colorants.

Tachyphylaxis (see also Tolerance): The loss of response to a drug following its rapid and repeated administration.

TDR (see Therapeutic drug monitoring).

Terminal half-life (see also Half-life): The half-life of a compound during the terminal phase of its plasma concentration *vs.* time profile:

$$t_{1/2} = \frac{-0.693}{\lambda_z}$$

where $t_{1/2}$ is the terminal half-life; and λ_z is the negative slope during the terminal phase of the log–linearplot of the plasma drug concentration *vs.* time. Note that λ_z is the same as k or β in the case of one- or two-compartment models, respectively.

Therapeutic drug monitoring: Monitoring the concentration(s) of a particular drug(s) of interest followed by proper adjustment of the dosage regimen to achieve optimal therapy in the individual patient. The rationale for therapeutic drug monitoring (TDM), sometimes called drug concentration monitoring (DCM), is that there is a significant interindividual variability in pharmacokinetics, which results in a wide range of steady state drug concentrations at any given dose rate. Adequate TDM becomes especially important in connection with drugs with a relatively narrow therapeutic index, i.e., a relatively small ratio of toxic to therapeutic concentrations.

Therapeutic equivalence: Comparable clinical efficacy and safety of a drug in different products or formulations.

Therapeutic index (see also Safety margin): The ratio between the maximum drug concentration in blood or plasma that can be tolerated and the minimum drug concentration to show a satisfactory pharmacological response in humans.

Tissue compartment (see Peripheral compartment).

Tolerance: A decrease in the magnitude of drug response after one or more doses. The damped response can be due to changes in drug concentration at the effect site and/or desensitization of the drug receptors.

Toxicokinetics: Pharmacokinetic principles and techniques applied to concentration *vs.* time data generated at the (high) dose levels that are customary in toxicity studies, in order to determine the rate, extent, and duration of exposure of the test compound in the test animal species.

Tween SO: Polyoxyethylene sorbitan monooleate, an emulsifying agent.

UDPGA (uridine disphosphoglucuronic acid): A cofactor for uridine diphosphate glucuronosyl transferase.

UDPGT: Uridine diphosphate glucuronosyl transferase.

Unstirred water layer (UWL): A stagnant water layer adjacent to the luminal surface of the intestinal membrane, which behaves as a barrier against absorption of drug molecules from the intestinal lumen.

Uremic middle molecules (see Middle molecules).

Volume of distribution: A proportionality constant relating the amount of drug present in the body to drug concentration measured in a reference body fluid such as blood or plasma. The volume of distribution does not necessarily represent identifiable physiological organs/tissues or volumes, but rather a hypothetical volume accounting for the total amount of a drug in the body referred to the body fluid in which the drug concentration is measured. The extent of the volume of distribution is dependent on various physicochemical properties of a compound, such as lipophilicity, as well as physiological factors, including protein binding in plasma and tissue and actual volumes of blood and tissue. Three important quantities in regard to the drug are the volume of distribution of the central compartment (V_c), at steady state (V_{ss}), and at pseudodistribution equilibrium (V_β).

WBA: Whole body autoradiography.

Zero-order kinetics (see also First-order kinetics): A kinetic process in which the rate of change in concentration or the amount of drug with time is constant and independent of both drug concentration and time, i.e.,

$$\text{Rate of change of drug concentration} = k_0$$

where k_0 is the zero-order rate constant.

Appendix

A. Important Pharmacokinetic Equations

1. Plasma Drug Concentration at Time t in a One-Compartment Model under Linear Kinetics

AFTER INTRAVENOUS ADMINISTRATION:

$$C_p(t) = C_0 \cdot e^{-t}$$

C_0: Estimated plasma concentration at time zero (intravenous dose/volume of distribution in the central compartment).
$C_p(t)$: Plasma drug concentration at time t after intravenous bolus injection.

AFTER ORAL ADMINISTRATION

$$C_p(t) = \frac{k_a \cdot F \cdot D_{po}}{V \cdot (k_a - k)} \cdot (e^{-k \cdot t} - e^{-k_a \cdot t})$$

$C_p(t)$: Plasma drug concentration at time t after oral administration.
D_{po}: Oral dose.
F: Oral bioavailability.
k_a, k: Absorption and elimination rate constants, respectively.
V: Apparent volume of drug distribution.

2. Systemic Plasma Clearance

$$Cl_s = \frac{D_{iv}}{AUC_{iv,0-\infty}}$$

Cl_s: Systemic (plasma) clearance.
$AUC_{iv,0-\infty}$: Area under the plasma drug concentration *vs.* time curve from time zero to infinity after intravenous bolus injection.

D_{iv}: Intravenous dose.

3. Systemic Blood Clearance vs. Systemic Plasma Clearance

$$Cl_b \cdot AUC_b = Cl_p \cdot AUC_p$$
$$Cl_b \cdot C_b = Cl_p \cdot C_p$$

AUC_b, AUC_p: Area under the blod or plasma drug concentration *vs.* time curves after intravenous bolus injection, respectively.
C_b, C_p: Blood or plasma drug concentrations, respectively.
Cl_b: Systemic blood clearance.
Cl_p: Systemic plasma clearance.

4. Hepatic Blood Clearance

WELL -STIRRED MODEL:

$$Cl_h = \frac{Q_h \cdot f_{u,b} \cdot Cl_{i,h}}{Q_h + f_{u,b} \cdot Cl_{i,h}}$$

PARALLEL -TUBE MODEL:

$$Cl_h = Q_h \cdot (1 - \exp(-f_{u,b} \cdot Cl_{i,h}/Q_h))$$

Cl_h: Hepatic clearance.
$Cl_{i,h}$: Intrinsic hepatic clearance.
$f_{u,b}$: Ratio between unbound and total drug concentrations in blood.
Q_h: Hepatic blood flow rate.

5. Renal Plasma Clearance

$$Cl_r = \frac{A_{e,0-\infty}}{AUC_{0-\infty}}$$

$A_{e,0-\infty}$: Cumulative amount of drug excreted unchanged in urine from time zero to infinity.
$AUC_{0-\infty}$: Area under the plasma drug concentration–time curve from time zero to infinity regardless of the route of administration.
Cl_r: Renal clearance.

6. Volume of Distribution at Steady State

$$V_{ss} = \underbrace{\frac{D_{iv}}{AUC_{iv,0-\infty}}}_{Cl_s} \cdot \underbrace{\frac{AUMC_{iv,0-\infty}}{AUC_{iv,0-\infty}}}_{MRT}$$

$AUC_{iv,0-\infty}$: Area under the plasma drug concentration *vs.* time curve from time zero to infinity after intravenous bolus injection.

$AUMC_{iv,0-\infty}$: Area under the first-moment curve of plasma drug concentration *vs.* time curve from time zero to infinity after intravenous bolus injection.

Cl_s: Systemic plasma clearance.

MRT: Mean residence time.

V_{ss}: Volume of distribution at steady state.

or

$$V_{ss} = V_P + \frac{f_u}{f_{u,t}} \cdot V_t$$

V_p: Actual physiological volume of plasma.

V_t: Actual physiological volume of extravascular space (interstitial fluid and tissue) outside plasma, which drug molecules distribute into.

f_u: Ratio between unbound and total drug concentrations in plasma.

$f_{u,t}$: Averaged ratio between unbound and total drug concentrations in extravascular space.

7. Terminal Half-Life

$$t_{1/2} = \frac{-0.693}{\lambda_z}$$

λ_z: The negative slope during the terminal phase of the log–linear plot of plasma drug concentration *vs.* time. λ_z is the same as k or β, exponential coefficients of mono- or biexponential differential equations describing for plasma concentration–time profiles of drug, respectively.

$t_{1/2}$: Terminal half-life.

or

$$t_{1/2} = \frac{-0.693 \cdot V_{ss}}{Cl_s}$$

which is true only when the plasma drug concentration *vs.* time curve after intravenous injection can be properly described by a one-compartment model. Otherwise, $t_{1/2}$ is a function of V_β, the volume of distribution at the terminal phase, not V_{ss}, the volume of distribution at steady state ($V_\beta > V_{ss}$).

8. Oral Bioavailability

$$F = \frac{AUC_{po,0-\infty} \cdot D_{iv}}{AUC_{iv,0-\infty} \cdot D_{po}}$$

$AUC_{iv,0-\infty}$: AUC from time zero to infinity after intravenous bolus injection.
$AUC_{po,0-\infty}$: AUC from time zero to infinity after oral administration.
D_{iv}: Intravenous dose.
D_{po}: Oral dose.
F: Oral bioavailability.

9. Mean Residence Time

$$MRT = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}}$$

$AUC_{0-\infty}$: AUC from time zero to infinity regardless of the route of administration.
$AUMC_{0-\infty}$: AUMC from time zero to infinity regardless of the route of administration.
MRT: Mean residence time.

10. Mean Absorption Time

$$MAT = MRT_{po} - MRT_{iv}$$

MAT: Mean absorption time.
MRT_{iv}, MRT_{po}: MRT after intravenous bolus injection or oral administration, respectively.

11. Plasma Drug Concentration at Steady State after Continuous Intravenous Infusion

$$C_{p,ss} = \frac{k_0}{Cl_s}$$

$C_{p,ss}$: Plasma drug concentration at steady state after continuous intravenous infusion.
Cl_s: Systemic plasma clearance.
k_0: Infusion rate.

12. Metabolite Kinetics

$$AUC_{0-\infty} \cdot f_m \cdot Cl_s = AUC_{0-\infty,m} \cdot Cl_m$$

$AUC_{0-\infty}$, $AUC_{0-\infty,m}$: AUC from time zero to infinity of the drug and its metabolite, respectively regardless of the route of administration.
Cl_s, Cl_m: Systemic plasma clearance of the drug and its metabolite, respectively.
f_m: Fraction of the dose of the drug transformed to the metabolite.

13. Relationship between Blood and Plasma Concentrations

$$C_b = Hct \cdot C_{rbc} + (1 - Hct) \cdot C_p$$

C_b: Drug concentration in blood.
C_{rbc}: Drug concentration in red blood cells.
C_p: Drug concentration in plasma.
Hct: Hematocrit.

14. Amount of a Drug Absorbed into the Portal Vein after Oral Administration

MASS BALANCE METHOD:

$$A_a = Q_{pv} \cdot (AUC_{po,pv} - AUC_{po,sys})$$

A_a: Amount of the drug absorbed into the portal vein after oral administration.
$AUC_{po,pv}$ $AUC_{po,sys}$: AUC of the drug from time zero to infinity in the portal vein and systemic blood (or plasma when blood concentrations are the same to plasma concentrations) after oral administration, respectively.
Q_{pv}: Portal vein blood flow rate.

CLEARANCE METHOD

$$A_a = Cl_b \cdot AUC_{po,pv}$$

Cl_b: Systemic blood (or plasma when blood concentrations are the same as plasma concentrations) clearance.
$AUC_{po,pv}$: AUC of drug in portal vein blood (or plasma when blood concentrations are the same as plasma concentrations) after oral administration.

B. Typical Pharmacokinetic Issues and Their Potential Causes

Route of administration	Issues	Potential causes
Oral administration	Low bioavailability	Limited absorption Poor aqueous solubility (dissolution rate-limited) Poor membrane permeability (permeation rate-limited) Efflux by P-glycoprotein or multidrug resistance-associated protein in the intestine Microfloral metabolism in the intestine, e.g., reduction of azo compounds Extensive first-pass effect Presystemic intestinal metabolism (CYP3A4, CYP2C9, UDPGT, etc) Presystemic hepatic clearance (metabolism and/or biliary excretion)
	Multiple peaks in exposure profile	Enterohepatic circulation Enterohepatic circulation of parent drug Biliary excretion of metabolites followed by subsequent conversion to the parent drug in intestinal lumen (e.g., biliary excretion of glucuronide conjugates of drug and subsequent deconjugation in gut lumen) Variability in pH in the stomach Delayed gastric emptying
	Flip-flop kinetics (a longer terminal half-life after P.O. than I.V. dosing)	Slow absorption of drug The rate of absorption of drug from the intestine is slower than the rate of elimination from body
	Less than dose-proportional increase in exposure as dose increases	Nonlinear absorption and/or clearance Limited aqueous solubility Saturation of active transporters in enterocytes during absorption Saturation of protein binding
	More than dose-proportional increase in exposure as dose increases	Nonlinear absorption and/or clearance Saturation of efflux mechanism(s) in enterocytes during absorption Saturation of clearance mechanisms
	Decreasing exposure after multiple doses	Induction Autoinduced metabolism Induction of P-glycoprotein for biliary and/or intestinal excretion
Intravenous administration	Biexponential declining of exposure profile	Multicompartmental distribution Nonlinear protein binding Saturated protein binding at high concentrations during the initial phase Nonlinear metabolism Product inhibition on metabolism of parent drug during the later phase

Route of administration	Issues	Potential causes
	Sustained or elevated exposure at the beginning and then declining	Nonlinear clearance Substrate inhibition of metabolism during the initial phase Precipitation of drug at the injection site and subsequent dissolution
	Short half-life	Rapid clearance Extensive metabolism, biliary and/or renal elimination Low protein binding Small volume of distribution Confinement of drug in plasma More extensive protein binding in plasma than in tissues
	Longer half-lives at higher dose levels	Nonlinear clearance Limitation of assay sensitivity at low concentrations (no dose dependent half-life changes with better assay sensitivity) Product inhibition

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D. Abbreviations

α: exponential coefficient of a biexponential differential equation
A_a: total amount of a drug absorbed into the portal vein after oral administration
$A_c(t)$: amount of the drug in the central compartment at time t
A_e: amount of the drug excreted unchanged in the urine
$A_{e,0}$-∞: cumulative amount of a drug excreted unchanged in the urine from time zero to infinity
$A_m(t)$: amount of the metabolite produced from the drug in the body at time t after intravenous administration
A(t): amount of a drug in the body at time t
ADME: absorption, distribution, metabolism, and excretion
AUC: area under the plasma drug concentration *vs.* time curve
AUC_m: area under the plasma metabolite concentration *vs* time curve
AUC_{ia}: area under the plasma drug concentration *vs* time curve after intraarterial injection
AUC_{ip}: area under the plasma drug concentration *vs* time curve after intraportal vein (or intraperitoneal) injection
AUC_{iv}: area under the plasma drug concentration *vs* time curve after intravenous injection
AUC_{po}: area under the plasma drug concentration *vs* time curve after oral administration
$AUC_{po,pv}$: AUC of a drug in portal vein blood (or plasma) after oral administration
$AUC_{po,ve}$: AUC of a drug in vena cava blood (or plasma) after oral administration
AUMC: area under the first-moment curve of plasma drug concentration *vs* time curve
β: exponential coefficient of a biexponential differential equation

C: concentration

$C_{avg,ss}$: average drug concentration in plasma during a dosing interval at steady state after multiple dosing of a fixed drug dose at the same dosing interval

$C_b(t)$: drug concentration in blood at time t

$C_e(t)$: drug concentration at the effect site at time t

$C_{in,ss}$: drug concentration in blood entering the eliminating organ at steady state

C_{int}: drug concentration in the gastrointestinal fluid

$C_{i,u}$: unbound drug concentration within hepatocytes or available for metabolizing enzyme(s) and/or biliary excretion

$C_m(t)$: metabolite concentration in plasma at time t

C_{max}: the highest drug concentration in plasma after extravascular administration

$C_{out,ss}$: drug concentration in blood leaving the eliminating organ at steady state

$C_p(O)$: imaginary drug concentration in plasma at time zero after intravenous injection of a drug, estimated by extrapolation of the plasma drug concentration–timecurve to time zero

$C_p(t)$: drug concentration in plasma at time t

$C_{p,ss}$: plasma drug concentration at steady state after intravenous infusion

C_{rbc}: drug concentration in red blood cells

C_{ss}: drug concentration at steady state

$C_t(t)$: average drug concentration in the extravascular space, into which the drug distributes at time t

$C_T(t)$: average drug concentration in the peripheral (tissue) compartment at time t

$C_u(t)$: concentration of drug not bound to blood components at time t

Cl_b: systemic blood clearance

Cl_{bl}: biliary clearance

Cl_d: distributional clearance

Cl_g: intestinal clearance

Cl_h: hepatic (blood) clearance

$C_{li,h}$: intrinsic hepatic clearance

Cl_m: metabolic drug clearance to produce a particular metabolite

$Cl_{(m)}$: systemic metabolite clearance

Cl_{nr}: nonrenal clearance

Cl_{other} clearance other than via the metabolic pathway of a drug to a particular metabolite

Cl_p: plasma clearance

Cl_r: renal clearance

Cl_s: systemic (plasma) clearance

Cl_u: drug clearance based on unbound drug concentration

CYP: cytochrome P450

D_{ia}: intraarterial dose

D_{ip}: intraportal vein (or intraperitoneal) dose

D_{iv}: intravenous dose

D_n: dispersion number

D_{po}: oral dose

E: extraction ratio or drug effect

E_g: intestinal extraction ratio
E_h: hepatic extraction ratio
E(t): pharmacological effect of drug at time t
EC_{50}: concentration of drug showing 50% of its maximum effect
E_{max}: maximum effect of drug
F: (oral) bioavailability
F_a: fraction of the dose absorbed into gastrointestinal epithelial cells (enterocytes) from the intestinal lumen after oral administration of a drug
f_e: fraction of the dose excreted unchanged in the urine
F_g: fraction of the amount of a drug absorbed into enterocytes after oral administration of a drug that escapes the presystemic intestinal elimination
F_h: fraction of the amount of a drug entering the liver that escapes elimination by the liver on a single pass through the organ, or the fraction of a drug entering the liver that escapes the presystemic hepatic elimination after oral administration
F_l: fraction of the amount of a drug entering the lung that escapes elimination by the lung on a single pass through the organ, or the fraction of a drug entering the lung that escapes the presystemic pulmonary elimination after oral administration
f_m: fraction of the dose metabolized
F_r: fraction of the amount of a drug reabsorbed from the renal distal tubule after being filtered and secreted in the glomerulus and the proximal tubule
F_s: fraction of a dose reaching the systemic circulation as unchanged drug after oral administration (considering first-pass effect by the lung as well)
f_u: ratio between the unbound and total drug concentrations in plasma
$f_{u,b}$: ratio between the unbound and total drug concentrations in blood
$f_{u,t}$: average ratio between unbound and total drug concentrations in tissues (extravascular space)
GFR: glomerular filtration rate
Hct: hematocrit
IC_{50}: concentration of drug showing 50% of its maximum inhibitory effect
k: first-order rate constant
k_{10}: first-order elimination rate constant from the central compartment
k_{12},k_{21}: first-order distribution rate constants from the central to the peripheral compartments or from the peripheral to the central compartments, respectively
k_a: first-order absorption rate constant
K_m: Michaelis–Menten constant or the apparent Michaelis–Menten constant for metabolizing enzyme(s) and/or biliary excretion
k_m: first-order rate constant associated with the formation of metabolites from the parent drug
$k_{(m)}$: first-order rate constant associated with the elimination of metabolites
k_0: drug infusion rate or zero-order rate constant
MAT: mean absorption time of a drug after oral administration
MIT: mean input time of a drug

MRT: mean residence time of a drug
MRT_{abs}: MRT for the absorption of drug molecules dosed in solution into the systemic circulation
MRT_{disint}: MRT for the disintegration of the orally dosed solid dosage form of a drug to a suspension
MRT_{diss}: MRT for the dissolution of the orally dosed solid drug particles to solution
MRT_{iv}: MRT after intravenous injection
MRT_{po}: MRT after oral administration
P450: cytochrome P450
P_{app}: apparent membrane permeability
P_{int}: intestinal membrane permeability
Q: blood flow rate
Q_h: hepatic blood flow rate
Q_{pv}: portal vein blood flow rate
Q_r: renal blood flow rate
R: accumulation factor
S_{int}: effective surface area of intestinal membranes available for drug absorption
$t_{1/2}$ half-life of a drug during the terminal phase of plasma drug concentration–time profile
t_{last}: the last time point when a quantifiable drug concentration can be measured
t_{max}: time at which C_{max} is observed following extravascular administration of drug
V: apparent volume of distribution of a drug
V_β : apparent volume of distribution at the β phase (or terminal phase) based on drug concentration in plasma
V_c: apparent volume of the central compartment based on the drug concentration in plasma
$V_{extrapolated}$: initial dilution volume of a drug

V_m: apparent volume of distribution of metabolite
V_{max}: maximum rate of enzymatic reaction or the apparent maximum rate of metabolizing enzyme(s) and/or biliary excretion
V_p: actual physiological volume of plasma
V_{ss}: apparent volume of distribution at steady state based on the drug concentration in plasma
V(t): apparent volume of distribution of a drug at time t
V_t: actual physiological volume of extravascular space (blood cells, interstitial fluids, and tissues) outside the plasma into which the drug distributes
V_T: apparent volume of the peripheral (tissue) compartment of drug
λ: the negative slope of the terminal phase of a plasma drug concentration–time profile on a semilogarithmic scale.

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