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A

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A:

An amount of drug or chemical in units of mass such as milligrams. Special attributes of the amount are indicated by subscripts: A_0 , the amount of drug in the body at “zero-time;” A_B , the amount of drug in the body; A

U , the amount of drug recovered in the urine, etc. The amount of drug in the drug’s volume of distribution is equal to the concentration of the drug times the volume: $A = C \cdot V$

d

.

a :

The earlier segment of a biphasic plot of $\log C$ against t (following intravenous injection of a drug) represents the “distributive phase” of a drug’s sojourn in the body. a is used as a subscript for pharmacokinetic parameters appropriate to the distributive phase, e.g., t

$1/2a$

, V
da
, etc.

Cf. [b](#), [Compartment\(s\)](#), [Volume of Distribution](#), [Half-Life](#)

Absorption Rate Constant:

See [k_a](#)

Accumulation, Accumulation Ratio:

See [C_{ss}](#)

Accuracy:

The use of the word “accurate” – free of error – in referring to a scientific observation or scientific method sometimes obscures the fact that even the best methods and observations are only *relatively* free from error. The use of the single word “accurate” also hides the fact that a number of separate elements contribute to over-all freedom from error. “Accurate” is frequently used to refer indiscriminately to the effect of any of these elements, or to the combined effects of all of them on the freedom from error of a system. Effective use of a method or observation requires that we know the ways and degrees to which the data are free of error, not that we know only that the data are “accurate” or “inaccurate”.

The elements to be taken into account in a complete evaluation of a method or system can be derived from the properties of the quantitative relationship between the “input” and the “output” for the system. The input-output relationship, for all its generality, has specific application—and specific names—in different scientific fields and for different kinds of experimental or observational systems. In physics and engineering, the “stress-strain diagram” is a special representation of the input-output relationship; in pharmacology, the “dose-effect curve” is an example of the input-output relationship. In quantitative chemical analyses, the “calibration curve” is an example of the input-output relationship. Generally, “input” can be

looked on as the measured value of an independent variable or “measurand”; “output” can be viewed as a measurement made under non-standard or test conditions.

“Accuracy”, as formally defined, and the elements that contribute to it can be only briefly outlined here.

Accuracy In engineering, “accuracy” is the ratio of the “error” of a system to the range of values for output that are possible, i.e., the ratio of error to so-called Full-Scale Output. Error is defined as the algebraic difference between an indicated output value and the true measure of the input or measurand. Error, as defined by the engineer, is most like “precision” as defined below.

Validity The degree to which output reflects what it purports to reflect, i.e., input; the degree to which output is a function of known input and it alone. For example, does an essay examination validly measure a student’s knowledge of material, or is it invalid, actually measuring his literary skill or the state of the grader’s digestion?

Reliability The degree to which the input-output relationship is reproducible if the relationship is studied repeatedly under comparable conditions. For example, if a student took the same examination twice, or in two forms, would he get the same grade both times? If the same work were reviewed by two graders, would they both assign the same mark?

Sensitivity The lowest value of input that can be inferred with a given degree of validity and reliability from measurements of output. Analogous to the usage for the word “threshold” is the phrase “threshold dose”. The engineer uses the word “threshold”, however, to mean the smallest *change* in input that will result in change in output.

Amplification The amount of change in measured output per unit change in input. The slope of the input-output, or dose-effect, curve. (Engineers sometimes refer to “amplification” as “sensitivity”.)

Precision The capacity of the system to discriminate between different values of input; the “fineness” with which different values for input can be inferred from measured values of output. The pooled deviation of observed from expected values of output, all divided by the amplification, yields the “index of precision”. The square of the reciprocal of the index of precision is the measure of the amount of *information* that can be delivered by the system.

Specifically, precision is computed in several steps. First, the deviation of each observed value of output from the corresponding predicted value is squared; predicted values are determined from the curve relating input and output for all the data. The squared deviations are summed and divided by $N-2$, the number of “degrees of freedom”; the square root of the quotient is determined and is a number analogous to the standard deviation. This “root mean square deviation” is then divided by the slope of the input-output curve, i.e., the amplification, to yield the “index of precision”; it is assumed that the input-output relationship is linear.

Comparability The ability of a system to deliver data that can be compared in standard units of measurement and by standard statistical techniques with the data delivered by other systems. While not a critical component of accuracy, comparability of data generated by a system is critical to evaluating its accuracy and usefulness.

Economy The ability of a system to deliver

data of high information content at a low overall cost per item of data; economy does not, of course, contribute to "accuracy" but is an important determinant of the practical usefulness of a system or method.

Activity, Intrinsic:

See [Intrinsic Activity](#).

Addiction:

According to DSM-IV (American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Washington, D.C., 1994):

"A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

- * Substance is often taken in larger amounts or over longer period than intended
- * Persistent desire or unsuccessful efforts to cut down or control substance use
- * A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain smoking), or recovering from its effects
- * Important social, occupational or recreational activities given up or reduced because of substance abuse
- * Continued substance use despite knowledge of having a persistent or recurrent psychological, or physical problem that is caused or exacerbated by use of the substance
- * Tolerance, as defined by either: (a) need for increased amounts of the substance in order to achieve intoxication or desired effect; or (b) markedly diminished effect with continued use of the same amount
- * Withdrawal, as manifested by either: (a) characteristic withdrawal syndrome for the substance; or (b) the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms"

Cf. [Dependence](#) , [Drug Dependence](#) , [Habituation](#) , [Tolerance](#) .

Affinity:

The equilibrium constant of the reversible reaction of a drug with a receptor to form a drug-receptor complex; the reciprocal of the dissociation constant of a drug-receptor complex. Under the most general conditions, where there is a 1:1 binding interaction, at equilibrium the number of receptors engaged by a drug at a given drug concentration is directly proportional to their affinity for each other and inversely related to the tendency of the drug-receptor complex to dissociate. Obviously, affinity depends on the chemical natures of both the drug and the receptor. (See: Ariens, E.D. *et al.*, *Pharmacol. Rev.* 9: 218, 1957).

Agonist:

A ligand that binds to a receptor and alters the receptor state resulting in a biological response.

Agonist, Partial:

A partial agonist is an agonist that produces a maximal response that is less than the maximal response produced by another agonist acting at the same receptors on the same tissue, as a result of lower [intrinsic activity](#). See also [Agonist, Full](#).

Agonist, Full:

A full agonist is an agonist that produces the largest maximal response of any known agonist that acts on the same receptor.

Agonist, Inverse:

An inverse agonist is a ligand that by binding to a receptor reduces the fraction of receptors in an active conformation, thereby reducing basal activity. This can occur if some of the receptors are in the active form in the absence of a conventional agonist.

Allergic Response:

Some drugs may act as haptens or allergens in susceptible individuals; re-administration of the hapten to such an individual results in an allergic response that may be sufficiently intense to call itself to the attention of the patient or the physician. The response may be so severe as to endanger the patient's life. The symptomatology of the allergic response is the result of the complex mechanism that is only "triggered" by the hapten. Hence, allergic responses to different haptens are fundamentally alike and qualitatively different from the pharmacologic effects the hapten-drugs manifest in normal subjects, i.e., patients not hypersensitive to the drug. Dose-effect curves obtained after administration of antigen to sensitized subjects usually reflect the dose-effect curves of the products of the allergic reaction even though the severity of the effects measured is proportional to the amount of antigen administered. Positive identification of a response as being allergic in nature depends on the demonstration of an antigen-antibody reaction underlying the response. In the case of specific patients, presumptive diagnoses of an allergic response must sometimes be made since no opportunity exists for formal identification of an antigen-antibody reaction; such diagnoses can be made and justified since the clinical symptomatology of allergic responses is usually characteristic and clear. Obviously, not all untoward effects of drugs are allergic in nature.

Cf. [Side-effects](#) , [Idiosyncratic Response](#) , [Hypersensitivity](#) , [Sensitivity](#)

Amplification:

The amount of change in measured output per unit change in input. The slope of the input-output, or dose-effect, curve. (Engineers sometimes refer to "amplification" as "sensitivity".)

Cf. [Accuracy](#)

Analgesic:

A drug that dulls the sense of pain. It differs from an anesthetic agent in that it relieves pain without loss of consciousness.

Cf. [Anesthetic](#) , [Narcotic](#)

Anesthetic:

Literally: *an* – without + *aisthesis* – perception by the senses (Gr.) A drug that causes loss of sensation.

General anesthetics cause not only loss of sensation, but also loss of consciousness.

Local anesthetics

cause loss of sensation by blocking nerve conduction only in the particular area where they are applied.

Antagonism:

The joint effect of two or more drugs such that the combined effect is less than the sum of the effects produced by each agent separately. The *agonist* is the agent producing the effect that is diminished by the administration of the

antagonist

. Antagonisms may be any of three general types:

Chemical caused by combination of agonist with antagonist, with resulting inactivation of the agonist, e.g., dimercaprol and mercuric ion. Physiological caused by agonist and antagonist acting at two independent sites and inducing independent, but opposite effects.

Pharmacological caused by action of the agonist and antagonist at the same site.

In the case of pharmacological antagonisms, the terms competitive and non-competitive antagonism are used with meanings analogous to competitive and non-competitive enzyme inhibition as used in enzymology. (See Symposium on Drug Antagonism, *Pharm. Rev.* 9: 211, 1952).

Cf. [Synergy](#) , [Potentiation](#) , [Intrinsic Activity](#) , [Affinity](#)

Area Under the Curve:

Abbreviated as [AUC](#) (q.v.)

AUC:

The area under the plot of plasma concentration of drug (not logarithm of the concentration) against time after drug administration. The area is conveniently determined by the “trapezoidal rule”: the data points are connected by straight line segments, perpendiculars are erected from the abscissa to each data point, and the sum of the areas of the triangles and trapezoids so constructed is computed. When the last measured concentration (C_n , at time t_n) is not zero, the AUC from t

t
to infinite time is estimated by C

n
/ k
el
.

The AUC is of particular use in estimating bioavailability of drugs, and in estimating total clearance of drugs (Cl_T). Following single intravenous doses, $AUC = D/Cl_T$, for single compartment systems obeying first-order elimination kinetics; alternatively, $AUC = C$

0
/ k
el

. With routes other than the intravenous, for such systems, $AUC = F \cdot D/Cl$

T
, where F is the bioavailability of the drug. The ratio of the AUC after oral administration of a drug formulation to that after the intravenous injection of the same dose to the same subject is used during drug development to assess a drug's oral bioavailability.

Cf. [Clearance](#) , [Bioavailability](#) , [Compartment\(s\)](#) , [F](#)

Availability:

See [Bioavailability](#)

B

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B:

Body weight. Sometimes, as a subscript, to indicate “of, or in, the body”; thus, A_B is the amount of drug in the body.

b:

The slope of a linear plot of $\log C$ against t , when logarithms to the base 10, common logarithms, are used; the slope of the linear, semi-logarithmic, plot of a first-order reaction when common logarithms are used. $k_{el} = 2.303b$; $t_{1/2} = 0.301/b$.

Cf. [K_{el}](#), [Half-Life](#), [t_{1/2}](#)

b₀:

The slope of a linear plot of C (not the logarithm of C) against t ; the slope of the linear plot of a zero-order reaction, in which, in equal time intervals, equal amounts of chemical undergo reaction.

b_i:

The later segment of a biphasic plot of $\log C$ against t (following intravenous injection of a drug) represents the “elimination phase” of the drug’s sojourn in the body, when eliminative, rather than distributive, processes dominate the rate at which plasma concentrations of drug decrease with the passage of time. b is used as a subscript for pharmacokinetic parameters appropriate to the elimination phase, e.g. $t_{1/2b}$, V_{db} , etc. For systems with more than two phases, the lower case Greek letters following b are used, in order, to designate the third, fourth, etc., phases.

Cf. [a](#) , [Compartment\(s\)](#) , [Volume of Distribution](#) , [Half-Life](#)

Bioassay or Biological Assay:

“The determination of the potency of a physical, chemical or biological agent, by means of a biological indicator . . . The biological indicators in bioassay are the reactions of living organisms or tissues.” Principles characterizing a bioassay include:

1. Potency is a property of the material to be measured, e.g., the drug, not a property of the response. Ordinarily, the relationship between changes in behavior of the indicator and differences in drug dose – (a dose-effect curve) – must be determined as a part of each assay.

2. Potency is relative, not absolute. The potency of one preparation (the “unknown”) can be measured only in relationship to the potency of a second preparation (the “standard” or “reference drug”) that elicits a similar biologic response. When the absolute amounts of standard used in the assay are known, the results of the assay can be used to estimate the amount – in absolute units – of biologically active material contained in the unknown preparation.

3. A bioassay provides only an estimate of the potency of the unknown; the precision of the estimate should always be determined, using the data of the assay.

(See: Bliss, C.I., *American Scientist*, 45: 499, 1957).

Cf. [Positive Control Drug](#) , [Negative Control Drug](#) , [Dose-Effect Curve](#) , [Time-Concentration Curve](#)

Bioavailability:

The percent of dose entering the systemic circulation after administration of a given dosage form. More explicitly, the ratio of the amount of drug “absorbed” from a test formulation to the amount “absorbed” after administration of a standard formulation. Frequently, the “standard formulation” used in assessing bioavailability is the aqueous solution of the drug, given intravenously.

The amount of drug absorbed is taken as a measure of the ability of the formulation to deliver drug to the sites of drug action; obviously – depending on such factors as disintegration and dissolution properties of the dosage form, and the rate of biotransformation relative to rate of absorption – dosage forms containing identical amounts of active drug may differ markedly in their abilities to make drug available, and therefore, in their abilities to permit the drug to manifest its expected pharmacodynamic and therapeutic properties.

“Amount absorbed” is conventionally measured by one of two criteria, either the area under the *t* *ime-plasma concentration curve (AUC)*

or the

total (cumulative) amount of drug excreted

in the urine following drug administration. A linear relationship exists between “area under the curve” and dose when the fraction of drug absorbed is independent of dose, and elimination rate (half-life) and volume of distribution are independent of dose and dosage form. Alinearity of the relationship between area under the curve and dose may occur if, for example, the absorption process is a saturable one, or if drug fails to reach the systemic circulation because of, e.g., binding of drug in the intestine or biotransformation in the liver during the drug's first transit through the portal system.

Cf. [F](#), [Disintegration Time](#), [Dissolution Time](#), [Generic Drugs](#), [Reference Standard](#), [Equivalence](#),

[First Pass Effect](#),

[AUC](#)

Biopharmaceutics:

The science and study of the ways in which the pharmaceutical formulation of administered agents can influence their pharmacodynamic and pharmacokinetic behavior. Differences in pharmaceutical properties can cause substantial differences in the biologic properties – and therapeutic usefulness – of preparations which are identical with respect to their content of active ingredient. Pharmaceutical properties known to influence the therapeutic efficacy of drugs include: appearance and taste of the dosage form, solubility of the drug form used in the preparation, the nature of “fillers”, binders, or menstrua in the dosage form, particle size, stability of the active ingredient, age of the preparation, thickness and type of coating of a dosage form for oral administration, the presence of impurities, etc.

Cf. [Biotransformation](#) , [Biotranslocation](#) , [Pharmacokinetics](#) , [Bioavailability](#)

Biotransformation:

Chemical alteration of an agent (drug) that occurs by virtue of the sojourn of the agent in a biological system. Spontaneous decay of radium would not be considered a biotransformation even if it occurred within the body; chemical alteration of a chemical by enzymatic attack would be considered a biotransformation even if it occurred in a model system, *in vitro*.

Pharmacodynamics involves the chemical effects of a drug on the body; biotransformation involves the chemical effect of the body on a drug! “Biotransformation” should be used in preference to “drug metabolism”, and the word “metabolism” should probably be reserved to denote the biotransformation of materials essential to an adequate nutritional state.

“Biotransformation” and “detoxication” are not synonyms: the product of a biotransformation may be more, not less, biologically active, or potent, than the starting material.

Cf. [Pharmacokinetics](#) , [Biopharmaceutics](#)

Biotranslocation:

The movement of chemicals (drugs) into, through, and out of biological organisms or their parts. In studying biotranslocation one is concerned with the identification and description of such movement, elucidation of the mechanisms by which they occur, and investigation of the factors which control them. Ultimately, the study of biotranslocation involves consideration of how chemicals cross cellular membranes and other biological barriers.

Cf. [Pharmacokinetics](#) , [Half-Life](#) , [Volume of Distribution](#) , [Biopharmaceutics](#) , k_a , k_{el}

Blind Experiment:

A form of experiment in which the participants are, to some degree, kept ignorant of the nature and doses of materials administered as specific parts of the experiment. The purpose of the

device is, obviously to prevent a prejudiced interpretation of the drug effects observed, and to prevent a presumed knowledge of effects to be expected from influencing the kinds of effects manifested by a subject. Blind experiments are not limited in use to experiments involving only human subjects. Needless to say, both experimenters and subjects may have general knowledge of the purpose, materials and design of the experiment; their ignorance is limited to the nature of individual drug administrations.

In a “single-blind” experiment, one participant – usually the subject – is left uninformed. In a “double-blind” experiment two participants – usually the subject and observer – are uninformed, and in a “triple-blind” experiment the subject, the observer, and the person responsible for the actual administration of the drug are left unaware of the nature of the material administered.

In clinical experimentation, particularly, the use of blind experimentation is frequently associated with the use of dummy or placebo medication as part of the experimental design, and the use of a “cross-over” experimental design.

Cf. [Cross-Over Experiment](#) , [Dummy](#) , [Placebo](#)

C

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C, C_x:

The concentration (in units of mass/volume) of a chemical in a body fluid such as blood, plasma, serum, urine, etc.; the specific fluid may be indicated by a subscript, i.e. C_U, the concentration of drug in the urine; when no subscript is used, C is commonly taken to be the concentration in the plasma.

C₀:

The fictive concentration of a drug or chemical in the plasma at the time (in theory) of an instantaneous intravenous injection of a drug that is instantaneously distributed to its volume of distribution. C₀ is determined by extrapolating, to zero-time, the plot of log C against t (for apparently “first-order” decline of C) or of C against t (for apparently “zero-order” decline of C).

Cf. [Volume of Distribution](#) , [C_{max}](#) , [C_{ss}](#) , [First-Order Kinetics](#) , [Zero-Order Kinetics](#)

C_{max}, C_{min}:

The maximum or “peak” concentration (C_{max}) of a drug observed after its administration; the minimum or “trough” concentration (C

_{min}) of a drug observed after its administration and just prior to the administration of a subsequent dose. For drugs eliminated by first-order kinetics from a single-compartment system, C

_{max}, after n equal doses given at equal intervals is given by C

$$\frac{C_0 (1 - f)^n}{(1 - f)} = C$$

_{max}, and C

$$= C$$

$$- C$$

0

.

The time following drug administration at which the peak concentration of C_{max} occurs, t_p

(for any route of administration but the intravenous), is given by t_p

$$t_p = \frac{\ln k_a - \ln k_{el}}{k_a - k_{el}}$$

$$= \frac{\ln k_a - \ln k_{el}}{k_a - k_{el}}$$

$$= \frac{\ln k_a - \ln k_{el}}{k_a - k_{el}}$$

$$= \frac{\ln k_a - \ln k_{el}}{k_a - k_{el}}$$

(Remember that \ln is the natural logarithm, to the base e , rather than the common logarithm or logarithm to the base 10; $\ln X = 2.303 \log X$.)

Cf. [C_{ss}](#) , [f](#) , [Multiple Dose Regimens](#)

C_{ss}:

The concentration of a drug or chemical in a body fluid – usually plasma – at the time a “steady state” has been achieved, and rates of drug administration and drug elimination are equal. C_{ss} is a value approached as a limit and is achieved, theoretically, following the last of an infinite number of equal doses given at equal intervals. The maximum value under such conditions ($C_{ss,max}$) is given by $C_{ss,max}$

$C_{ss,max}$ is given by $C_{ss,max}$

$$C_{ss,max} = \frac{C_0}{1-f}$$

for a drug eliminated by first-order kinetics from a single compartment system. The ratio $C_{ss,max}/C_0$

$C_{ss,max}$

$/C_0$

0

indicates the extent to which drug accumulates under the conditions of a particular dose regimen of, theoretically, an infinitely long duration; the corresponding ratio $1/(1 - f)$ is sometimes called the Accumulation Ratio, R . C_{ss}

is also the limit achieved, theoretically, at the “end” of an infusion of infinite duration, at a constant rate.

Cf. [Multiple Dose Regimens](#) , [Infusion Kinetics](#) , [First-Order Kinetics](#)

Cl, Cl_x:

Clearance – in volume/unit time – of a drug or chemical from a body fluid, usually plasma or blood, by specified route(s) and mechanism(s) of elimination, as indicated by a subscript, e.g., Cl_R, urinary clearance; Cl_H, hepatic clearance, etc.

Cl_T, total clearance, indicates clearance by all routes and mechanisms of biotransformation and excretion, operating simultaneously. Cl

$Cl_T = k_{el} \cdot V_d$

$Cl_T = k_{el} \cdot V_d$

. Following intravenous administration, Cl

$Cl_T = D/AUC$; following administration of drug by any route other than the intravenous, Cl

$Cl_T = F D/AUC$.

Cf. [Clearance](#) , [AUC](#) , [F](#)

Ceiling:

The maximum biological effect that can be induced in a tissue by a given drug, regardless of how large a dose is administered. The maximum effect produced by a given drug may be less than the maximum response of which the reacting tissue is capable, and less than the maximum response that can be induced by another drug of greater intrinsic activity. "Ceiling" is analogous to the maximum reaction velocity of an enzymatic reaction when the enzyme is saturated with substrate.

Cf. [Intrinsic Activity](#)

Chemotherapy:

Drug treatment of parasitic or neoplastic disease in which the drug has a selective effect on the invading cells or organisms.

Clearance:

The *clearance* of a chemical is the volume of body fluid from which the chemical is, apparently, completely removed by biotransformation and/or excretion, per unit time. In fact, the chemical is only partially removed from each unit volume of the total volume in which it is dissolved. Since the concentration of the chemical in its volume of distribution is most commonly sampled by analysis of blood or plasma, clearances are most commonly described as the "plasma clearance" or "blood clearance" of a substance.

For a single compartment system, total clearance, by all routes (Cl_T), is estimated as the product of the elimination constant and the volume of distribution, in liters:

$$Cl_T = k_{el} \cdot V_d$$

the dimensions of Cl_T

are, of course, volume/time.

Renal Clearance:

Renal plasma (or blood) clearance Cl_R is the volume of plasma (or blood) freed of a substance by only renal mechanisms, per unit time. The amount of drug (A_U)

excreted in the urine during the time interval $t - t'$ is determined; the plasma (or blood) concentration at the mid-point of the interval (C_p)

is found by interpolation on the line relating $\log C$ and t . The urinary excretion rate of the drug,

$A_U/(t - t')$, divided by C_p is the renal clearance.

Renal plasma clearance will vary with such factors as age, weight, and sex of subject, the state of cardiovascular and renal function, the nature of the material being excreted, species, etc. Renal clearance by only glomerular filtration is defined and measured as the clearance of the sugar inulin, which is eliminated from the body by no route other than glomerular filtration. Total renal clearance is defined and measured by clearance of para-amino-hippurate (PAH), a substance that is eliminated by both glomerular filtration and tubular excretion (at the maximum rate of which the tubular mass is capable). Neither inulin nor PAH undergoes reabsorption by the tubules as some materials do. (N.B.: Blood and plasma are completely cleared of PAH by a single "pass" through the kidney; PAH clearance is therefore, the standard measure of renal plasma, or blood, flow).

In normal adult human males, plasma clearance of inulin is about 130 ml plasma/min; of PAH, about 700 ml plasma/min. In normal adult human females, clearance of inulin is about 115 ml plasma/min; of PAH, about 600 ml plasma/min. The relationship between clearance of blood and clearance of plasma is given by the relationship $Cl_R(\text{blood}) = Cl_R(\text{plasma})/(1-\text{Hct})$, where "Hct" is the hematocrit, the proportion, as a fraction – of the blood which consists of cells, not plasma; on the average, normal adult human subjects can be assumed to have a hematocrit of about 0.45.

Like

many other physiological "constants," renal plasma clearance varies regularly and exponentially with body weight, across mammalian species (*Science* 109: 757, 1949). Renal plasma clearances, in normal animals, can be predicted using the following relationships, where Cl_R

Cl_R
is in ml/hr, and body weight (B) is in
grams
:

$$Cl_R(\text{inulin}) = 1.74B^{0.77}$$

$$Cl_R(\text{PAH}) = 5.40B^{0.80}$$

Nonrenal Clearance:

Clearance by the fecal route (Cl_F), respiratory route (Cl_L), salivary route (Cl_S), biliary route (Cl_B),

Cl_B
) , can be computed in a fashion analogous to computation of Cl_R

R
: measuring the amount of substance excreted in the feces, expired air, saliva, etc., over an interval and dividing by the plasma concentration at mid-interval and the length of the interval. Following oral administration of a substance, measurement of fecal clearance may be confounded by the presence, in feces, of unabsorbed substance or of substance absorbed but excreted into the lumen of the gastrointestinal tract in, e.g., bile. Specialized techniques exist for estimating clearance of substances by the liver (Cl

H
) , by biotransformation and/or biliary excretion.

Unlike half-lives, clearances are directly additive and for any substance:

$$Cl_T = Cl_R + Cl_L + Cl_H + Cl_S + Cl_F + \dots \text{ etc.}$$

Clinical Therapeutic Index:

Some indices of relative safety or relative effectiveness cannot be defined explicitly and uniquely, although it is presumed that the same quantifiable and precise criteria of efficacy and safety will be used in comparing drugs of similar kinds. The Food and Drug Administration has considered the following definition of an *improved* Clinical Therapeutic Index to be used in comparing different drug combinations or formulations; the assumption is retained that an improved or "better" drug has a *higher* Clinical Therapeutic Index " (1) increased safety (or patient acceptance) at an accepted level of efficacy within the recommended dosage range, or (2) increased efficacy at equivalent levels of safety (or patient acceptance) within the recommended dosage range."

Cf. [Food and Drug Administration](#) , [Therapeutic Index](#) , [Standardized Safety Margin](#) , [Effective](#)

Compartment(s):

The space or spaces in the body, which a drug appears to occupy after it has been absorbed. Pharmacokinetic compartments are mathematical constructs and need not correspond to the fluid volumes of the body which are defined physiologically and anatomically, i.e., the intravascular, extracellular and intracellular volumes.

Some drugs make the body “behave” as if it consisted of only a single pharmacokinetic compartment. Tissue and plasma concentrations of the drug rapidly and simultaneously reach equilibrium in all the tissues to which the drug is distributed. A plot of plasma concentration against time after intravenous administration can be rectified into only a single straight line of negative slope, which can intersect the ordinate at only one point; only one volume of distribution can be calculated. Hence, the existence of only one compartment or volume of distribution can be inferred.

Some drugs make the body appear to consist of two or more pharmacokinetic compartments, since tissue/plasma equilibrium is achieved at different times in different tissues or groups of tissues. A plot of plasma concentration against time after intravenous administration can, at best, be resolved into a series of connected straight-line segments with progressively decreasing slopes. *Each* of these segments may be extrapolated to intersect the ordinate, and one may infer the existence of as many pharmacokinetic compartments, or volumes of distribution, for the drug as there are intersections or segments.

Compartments in which equilibrium is achieved relatively late are referred to as “deep” compartments; compartments in which equilibrium is achieved early – and from which drug is redistributed to other sites – are referred to as “shallow” or “superficial” compartments.

Cf. [a](#), [b](#), [Volume of Distribution](#), [V_d](#)

Compliance:

The extent to which a patient agrees to and follows a prescribed treatment regimen.

Cross-Over Experiment:

A form of experiment in which each subject receives the test preparation at least once, and every test preparation is administered to every subject. At successive experimental sessions each preparation is “crossed-over” from one subject to another. The purpose of the cross-over experiment is to permit the effects of every preparation to be studied in every subject, and to permit the data for each preparation to be similarly and equally affected by the peculiarities of each subject. In a well-designed cross-over experiment, if it is at all possible, the sequence in which the test preparations are administered is not the same for all subjects, in order to avoid bias in the experiment as a result of changes in the behavior of the subjects that are a function of time rather than of drug administration, or a function of drug interactions. At least, the cross-over design permits detecting such biases when they occur. The preparations under test in a cross-over experiment may – ideally, should – include one or more doses, of an experimental or “unknown” drug, one or more doses of a dummy or placebo medication (“negative control drugs”), and one or more doses of a standard drug, the actions of which are expected to be similar to those of the “unknown” (“positive control drug”). Even for the investigator with the best knowledge and intentions, the economics and logistics of experimentation may prevent carrying out a complete and perfect cross-over experiment.

Cf. [Bioassay](#) , [Positive Control Drug](#) , [Blind Experiment](#)

Cross-Tolerance:

[Tolerance](#) to a drug that generalizes to drugs that are chemically related of that produce similar affects. For example, a patient who is tolerant to heroin will also exhibit cross-tolerance to morphine.

CT Index:

A measure of drug “potency” calculated from data appropriate to the construction of a Time-Concentration curve; the product of the concentration (C) of an agent applied to a biological system to produce a specific effect and the duration (T) of application required to produce the effect. The index is calculated on the assumption that the time-concentration curve is precisely and symmetrically hyperbolic and convex to the origin, and that the products of the coordinates for all points on the line are constant. The time-concentration curve of an agent with high potentiality for producing a specified effect lies closer to the axis than the curve for an agent of lesser potential; the CT index for the agent of greater potential is smaller than the index for the agent of lesser potential, i.e., the smaller the CT index, the more “potent” the compound. CT indices have found their greatest application in toxicology, in assessing the potential for effect of noxious vapors, etc.

Cf. [Time-Concentration Curve](#) , [Potency](#) , [Dose-Effect Curve](#) , [Latency](#)

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D*:

[Loading Dose](#) (q.v.)

D:

Dose (q.v.); also the “maintenance doses” administered after a loading dose (q.v.)

Dependence:

A somatic state which develops after chronic administration of certain drugs; this state is characterized by the necessity to continue administration of the drug in order to avoid the appearance of uncomfortable or dangerous (withdrawal) symptoms. Withdrawal symptoms, when they occur, may be relieved by the administration of the drug upon which the body was “dependent.”

Cf. [Addiction](#) , [Habituation](#)

Desensitization:

A decline in the response to repeated or sustained application of an agonist that is a consequence of changes at the level of the receptor.

Cf. [Tachyphylaxis](#) , [Tolerance](#)

Disintegration Time:

The time required for a tablet to break up into granules of specified size (or smaller), under carefully specified test conditions. The conditions of the laboratory test, *in vitro*, are set to simulate those that occur *in vivo*. Factors such as the kind and amount of tablet binders and the degree of compression used in compacting the tablet ingredients help determine disintegration time. The active ingredients in a disintegrated tablet are not necessarily found to be in solution and available for absorption. A long disintegration time is incompatible with rapid drug absorption; a short disintegration time, by itself, does not ensure rapid absorption.

Cf. [Dissolution Time](#) , [Generic Drugs](#) , [Biopharmaceutics](#)

Dissolution Time:

The time required for a given amount (or fraction) of drug to be released into solution from a solid dosage form. Dissolution time is measured *in vitro*, under conditions that simulate those that occur *in vivo*

, in experiments in which the amount of drug in solution is determined as a function of time. Needless to say, the availability of a drug in solution – rather than as part of insoluble particulate matter – is a necessary preliminary to the drug's absorption.

Cf. [Disintegration Time](#) , [Bioavailability](#) , [Generic Drugs](#) , [Biopharmaceutics](#)

Distribution:

See [Volume of Distribution](#) , [Pharmacokinetics](#)

Dosage Form:

The physical state in which a drug is dispensed for use. For example: a frequent dosage form of procaine is a sterile solution of procaine. The most frequent dosage form of aspirin is a tablet.

Dose:

The quantity of drug, or dosage form, administered to a subject at a given time; for example, the usual dose of aspirin for relief of pain in an adult is 300-600 milligrams. Dose may be expressed in terms appropriate to a specific dosage form, i.e., one teaspoonful of a liquid medication, rather than the weight of drug in the teaspoonful. Dose may be described as an *absolute dose* (the total amount administered to a subject) or as a *relative dose* (relative to some property of the subject as body weight or surface area, mg/kg, or mg/m²).

Cf. [Dosage Form](#) , [Multiple Dose Regimens](#)

Dose-Duration Curve:

The curve describing the relationship between dose (as the independent variable) and duration of drug effect (as the dependent variable, T). The slope of the curve is always positive, in contrast to the slope of the time-concentration curve (q.v.). There has been increased interest in the dose-duration curve as a useful measure of drug action since Levy's demonstration that the constants describing the straight *log dose-duration* curve of a drug can be used to infer pharmacokinetic and pharmacodynamic properties of the drug, such as the elimination half-life and the threshold dose. (

Clin. Pharmacol. & Therap. 7:

362, 1966).

Cf. [Dose-Effect Curve](#) , [Time-Concentration Curve](#) , [Pharmacokinetics](#)

Dose-Effect Curve:

A characteristic, even the *sine qua non*, of a true drug effect is that a larger dose produces a greater effect than does a smaller dose, up to the limit to which the cells affected can respond. While characteristic of a drug effect, this relationship is not unique to active drugs, since increasing doses of placebos (q.v.) can, under certain conditions, result in increasing effects. Distinguishing between "true" and "inactive" drugs requires more than demonstration of a relationship between "dose" and effect.

The curve relating effect (as the dependent variable) to dose (as the independent variable) for a drug-cell system is the "dose-effect curve" for the system. For a unique system, i.e., one involving a single drug and a single effect, such curves have three characteristics, regardless of whether effects are measured as

continuous (measurement) or discontinuous (quantal, all-or-none) variates:

1. The curves are continuous, i.e. there are no gaps in the curve, and effect is a continuous function of dose. Some effect corresponds to every dose above the threshold dose (q.v.), and every dose has a corresponding effect; there is no inherent invalidity in interpolating doses or effects from a dose-effect curve.

2. The curves are “monotonic”. The curve may have a positive slope, or a negative slope, but not both if the system under study is unique. The slope of the curve may show varying degrees of positivity (negativity), but the sign of the slope stays the same throughout the range of testable doses. When monotonicity of a dose-effect curve does not obtain, one may infer that the system under study is not unique or singular: either more than one active agent or more than one effect is under study.

3. The curves approach some maximum value as an asymptote, and the asymptote is a measure of the intrinsic activity (q.v.) of the drug in the system.

Cf. [Bioassay](#) , [Median Effective Dose](#) , [Time-Concentration Curve](#) , [Dose-Duration Curve](#) , [Metameter](#) ,

Drug:

A chemical used in the diagnosis, treatment, or prevention of disease. More generally, a chemical, which, in a solution of sufficient concentration, will modify the behavior of cells exposed to the solution. Drugs produce only quantitative changes in the behavior of cells; i.e., drugs increase or decrease the magnitude, frequency, or duration of the normal activities of cells. Drugs used in therapy never produce qualitative changes in cell behavior short of producing death of the cell, e.g., a nerve cell cannot be made to contract or a muscle cell cannot be made to secrete saliva by use of a drug. The degree to which this point of view will be modified by the discovery and development of agents which act on cells

at a genetic level remains to be seen.

Drug Abuse:

Use or misuse of a drug under conditions, or to an extent, considered “more destructive than constructive for society and the individual.” More specifically, the use of drugs for their effects chiefly on the central nervous system, to an extent and/or at a frequency and/or for a duration of time that is inimical to the welfare of the user and/or the total of social groups in which she/he lives. The abuse potential of a drug depends on its capacity to induce compulsive drug-seeking behavior in the user, its capacity to induce acute and chronic toxic effects (and to permit occurrence of associated diseases), and upon social attitudes toward the drug, its use, and its effects.

Cf. [Drug Dependence](#) , [Addiction](#) , [Habituation](#) , [Harrison Act](#)

Drug Dependence:

“Drug Dependence” has been recommended as a term to be substituted for such words as “addiction” and “habituation” since it is frequently difficult to classify specific agents as being only addictive, habituating, or non-addicting or non-habituating. It has been suggested that the general term be used and modified, appropriately, in specific instances, e.g., drug dependence of the barbiturate type.

Cf. [Addiction](#) , [Habituation](#) , [Drug Abuse](#) , [Harrison Act](#)

Dummy:

“A counterfeit object;” a form of treatment – as in an experimental investigation of drug effects – which is intended to have no effects, to be biologically inert. The dummy treatment should mimic in every way (dosage form, route of administration, etc.) the purportedly active ingredient upon which the effectiveness of the active treatment is expected to depend. In contrast to a dummy, a placebo is *expected* to have an effect through the agency of “suggestion” or other psychological mechanisms, even though the effects of placebos may be psychological or physical. Dummies may, of course, have the effects of placebos, but it is useful to be aware of the difference expected to exist between the two.

According to Gaddum, dummies have two functions: 1) to distinguish between drug effects in a subject and other effects, such as those of suggestion: obviously, an experiment might properly incorporate both a dummy and a placebo. 2) to obtain an unbiased assessment of the result of a pharmacologic experiment. (See Gaddum, J.H., *Proc. Roy. Soc. Med.* 47: 195, 1954).

Cf. [Placebo](#) , [Negative Control Drug](#) , [Cross-Over Experiment](#)

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EC₅₀:

The concentration of an agonist that produces 50% of the maximal possible effect

of that agonist. Other percentage values (EC_{10} , EC_{20} , etc.) may be specified. Concentration is preferably expressed in molar units, but the mass concentration (g/l) may be used if the molecular weight of the substance is unknown.

ED₅₀:

1. In a quantal assay, the [median effective dose](#).
2. In a graded (non-quantal) assay, the dose of a drug that produces 50% of the maximal response to that drug. It is preferable, where possible, to express potency in terms of EC_{50} but ED_{50} is appropriate for *in vivo* measurements and for those *in vitro* experiments where the absolute concentration is uncertain. If the maximum response is unknown, it is acceptable to express the effectiveness of a drug in terms of the dose that produces a particular level of response, for example a certain change in blood pressure or heart rate. In such a case, the appropriate units must be included (e.g. ED_{50} mmHg) to avoid confusion.

Effective:

Under the Kefauver-Harris Drug Amendments of 1962 (amending the Food, Drug, and Cosmetic Act of 1938), a drug is considered to be effective that has been designated as such by the Food and Drug Administration on the basis of "substantial evidence." Such evidence was defined by Congress as "... adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."

Cf. [Food and Drug Administration](#), [U.S.P.](#)

Efficacy:

Broadly, efficacy refers to the capacity of a drug to produce an alteration in a target cell/organ after binding to its receptor. A competitive antagonist, that occupies a binding site without producing any alteration in the receptor, is considered to have an efficacy of zero.

Efficacy is generally independent of potency/affinity, and is related to the maximum effect that a particular drug is capable of producing.

As originally formulated by Stephenson (1956), binding of an agonist A to its receptor R is considered to result in a "stimulus" $S = \tau_A \times P_{AR}$ where τ_A is the efficacy of A and

P_{AR}

is the proportion of the receptors occupied. The effect of the drug on the cell or tissue is given by Effect =

f

(S), where

f

is an unspecified monotonic function that is dependent upon the nature of the receptor and its interaction with the cell or tissue. Efficacy is both agonist and tissue-dependent.

Efficacy is related to [Intrinsic Activity](#), which was originally defined by Furchgott (1966) as $e = \tau / R_T$, i.e. as the efficacy *per receptor*

. In practice, the two terms are sometimes loosely used synonymously. See [Effective](#).

Elimination Rate Constant:

See [k_{el}](#)

Equipotent:

Equally potent, or equally capable of producing a pharmacologic effect of a specified intensity. The masses of the drugs required to produce this degree of effect may be compared, quantitatively, to yield estimates of "potency" of the drugs. Obviously, if two drugs are not both capable of producing an effect of a given intensity, they cannot be compared with respect to potency; i.e., drugs with different intrinsic activities or ceiling effects cannot be compared with respect to potency in doses close to those producing the ceiling effect of the drug with the greater intrinsic activity.

Cf. [Potency](#) , [Intrinsic Activity](#)

Equivalence:

In 1969, a federal Task Force on Prescription Drugs recommended that the words "generic equivalents" no longer be used in describing and comparing drug preparations. The Task Force recommended that an appropriate nomenclature should take into account three kinds of equivalence of drug preparations:

Chemical Equivalents: Those multiple-source drug products which contain essentially identical amounts of the identical active ingredients, in identical dosage forms, and which meet existing physicochemical standards in the official compendia. **Biological Equivalents:** Those chemical equivalents which, when

administered in the same amounts, will provide essentially the same biological or physiological availability, as measured by blood levels, etc. Clinical Equivalents: Those chemical equivalents which, when administered in the same amounts, will provide essentially the same therapeutic effect as measured by the control of a symptom or a disease.

Cf. [Bioavailability](#) , [Generic Drugs](#)

Experiment:

See [Bioassay](#) , [Cross-Over Experiment](#) , [Blind Experiment](#)

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f:

The fraction of C_0 remaining at some specified time after drug administration; more generally, the fraction of C , or A_B , remaining after some specified time interval. For first-order, single compartment systems (i.e. those yielding a single straight line when $\log C$ is plotted against t), f can be determined from the relationship: $\log C = \log C_0 - \frac{t}{t_{1/2}}$

When t is the time after drug administration, or the interval between two administrations, and $t_{1/2}$

is the elimination half-life of the drug, f is 0.5 raised to a power that is the ratio of the time interval to the elimination half-life, i.e.

, 0.5
t/t?

Cf. [Half-Life](#) , [C_{max}](#) , [C_{ss}](#) , [Multiple Dose Regimens](#) , [Infusion Kinetics](#) , [Compartment\(s\)](#)

,
[First-Order Kinetics](#)

F:

The fraction of a dose which is absorbed and enters the systemic circulation following administration of a drug by any route other than the intravenous route; the availability of drug to tissues of the body, generally. When the total clearance and the dose of drug administered are known, F can be determined from the relationship: $(AUC \times Cl_T)/D = F$. When identical doses of a drug have been given by the intravenous and by some other route (x), and the AUCs have been determined, the bioavailability of the drug after administration by route X can be determined: $F = \frac{AUC_x}{AUC_{iv}}$. The amount of *free* drug recovered in the urine (A

U
) after administration of identical doses given intravenously and by route X can also be used to determine bioavailability: $F = \frac{A_{U,x}}{A_{U,iv}}$

U,x
/A
U,iv

Cf. [Bioavailability](#) , [First Pass Effect](#) , [AUC](#)

First-Order Kinetics:

According to the law of mass action, the velocity of a chemical reaction is proportional to the product of the active masses (concentrations) of the reactants. In a monomolecular reaction, i.e., one in which only a single molecular species reacts, the velocity of the reaction is proportional to the concentration of the unreacted substance (C). The change in concentration (dC) over a time interval (dt) is the velocity of the reaction (dC/dt) and is proportional to C . For infinitely small changes of concentration over infinitely small periods of time, the reaction velocity can be written in the form of a differential equation: $-dC/dt = kC$. Here, dC/dt is the reaction velocity, C is concentration, and k is the constant of proportionality, or monomolecular velocity constant, which uniquely characterizes the reaction. The minus sign indicates that the velocity decreases with the passage of time, as the concentration of unreacted substance decreases; a plot of C against time would yield a curve of progressively decreasing slope.

The mechanisms, the kinetics, described by the differential equation are termed *first order kinetics*

because – although the exponent is not written – concentration (C) is raised to only the first power (C

¹
).

The differential equation above may be integrated and rearranged to yield: $\ln(C/C_0)$

⁰
)= kt , where \ln indicates use of the natural logarithm, to the base e ; C_0

⁰
is the concentration of unreacted substance at the beginning of an observation period; t is the duration of the observation period; and k is the familiar proportionality or velocity constant. The units of k are independent of the units in which C is expressed; indeed, since a logarithm is dimensionless, and t has the dimension of time, the integrated equation balances, dimensionally, because k has the dimension of reciprocal time, t

⁻¹

. Notice that for observation periods of equal length, the ratio C/C_0

0

is always the same; after equal intervals, the final concentration is a constant fraction of the starting concentration, or, in equal time intervals, constant fractions of the starting concentration are lost, even though absolute decreases in concentration become progressively less as time passes and C becomes smaller and smaller.

Let $t_{1/2}$ represent the length of time required for C_0 to be halved, so that $C=0.5 C_0$. Then, substituting in the integrated equation above, $\ln 0.5 = -kt$

$1/2$

, or, since -0.693 is the natural logarithm of 0.5: $-0.693 = kt$

$1/2$

. Multiplying both sides of the equation by -1 yields $0.693 = kt$

$1/2$

or $0.693/k = t$

$1/2$

: the natural logarithm of 2 (0.693) divided by the monomolecular velocity constant yields the time required for the concentration to be halved, the "half-life" or "half-time" of the reaction.

Since $\ln (C/C_0)$ may be rewritten $(\ln C - \ln C_0)$, the integrated equation may be rewritten and given the form of a linear equation: $\ln C = \ln C_0 - kt$

0

$- kt$. The existence of a monomolecular reaction can be established by plotting $\ln C$, for unreacted material, against t and finding the relationship to be linear; the slope of the line is the original proportionality or velocity constant, and the intercept of the line with the ordinate is the natural logarithm of the original concentration of unreacted material. Since natural logarithms have a fixed relationship to common logarithms, i.e., logarithms to the base 10 ($\ln X = 2.303 \log X$), one may write: $2.303 \log C = 2.303 \log C_0 - kt$. When common logarithms of C are plotted against t , a first order reaction yields a straight line with a slope of $k/2.303$, and an intercept that is the common logarithm of C_0 .

0

.

When two molecular species react with each other (a bimolecular reaction), but one of the substances is present in a concentration greatly in excess of the concentration of the other and/or does not change in concentration during the reaction, the velocity of the reaction at any time is really determined only by the concentration of the other substance. Such a pseudo-monomolecular reaction, because the velocity is determined by the concentration of only one of the two reactants, still follows *first order kinetics*.

Following administration of a drug, it may be eliminated from the body only after “reacting” with tissue components which are present in high concentrations and which are not used up to any degree during the drug’s stay in the body. Such eliminative processes mimic pseudo-monomolecular reactions, and the drug is eliminated from the body according to first order kinetics,. The apparent velocity constant determined for such a process is called the elimination rate constant, k_{el} , and the elimination half-life can be computed as $0.693/k$

el

.

Cf., [Half-Life](#), $t_{1/2}$, [Zero-Order Kinetics](#)

First Pass Effect:

The biotransformation and/or excretion of a drug by intestinal and hepatic, including biliary, mechanisms following absorption of the drug from the gastrointestinal tract, before drug gains access to the systemic circulation.

Cf. [Bioavailability](#), F

Food and Drug Administration (F.D.A.):

An agency of the Department of Health, and Human Services which is responsible for ensuring compliance with the amended federal Food, Drug and Cosmetic Act. This agency must pass judgment on the safety of drugs, the labels affixed to drug packages, and all printed material accompanying a packaged drug before that drug may be introduced to interstate commerce. The law empowers the F.D.A. to pass on the efficacy of a new drug or pharmaceutical preparation and gives the agency ultimate jurisdiction over the clinical testing of a drug before it is approved for general sale and use. Prosecution of violation of the F.D. and C. Act is carried out by the Attorney General's Office on recommendation of the F.D.A.

Cf. [U.S.P.](#) , [Harrison Act](#) , [Effective](#)

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Generic Drugs:

Drug formulations of identical composition with respect to the active ingredient, i.e., drugs that meet current official standards of identity, purity, and quality of active ingredient. Drug dosage forms considered as "generically equivalent" are more properly considered as "chemically equivalent" in that they contain a designated quantity of drug chemical in specified stable condition and meet pharmacopoeial requirements for chemical and physical properties.

Each of a number of preparations of a given drug entity may carry a different “proprietary name” or “trademark”; such a name is registered with the U.S. Patent Office and identifies the special brand of the drug with the firm owning the name. All such preparations – identical with respect to content and specification of active ingredient – may be looked upon as comprising a “genus”; they are generically equivalent and are generic drugs. FDA regulations require manufacturers of generic drugs to establish biological equivalence of their product to the original patented drug product.

It is well recognized that a number of factors other than quantity of drug present in a dose can determine the ultimate therapeutic usefulness of the drug preparation, and even the availability of drug to the site of action once the preparation has been given. Drugs may be generically equivalent but not therapeutically equivalent. Factors which affect therapeutic usefulness or efficacy of drug preparations include appearance, taste, disintegration and dissolution properties of the preparation, interaction of active materials with other ingredients including binders and solvents, pH, particle size, age of preparation, conditions of manufacture such as degree of tablet compression, and the nature and amount of coating of enteric-coated tablets.

When the patent of a proprietary drug expires, a manufacturer must establish the biological equivalence of its generic formulation in order to market the product. To do so, the bioavailability of the generic formulation is compared to the proprietary product in a cross-over experiment.

Cf. [Biopharmaceutics](#) , [U.S.P.](#) , [Bioavailability](#) , [Equivalence](#)

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Habituation:

A condition characterized by a psychological craving for the effects produced by the administration of a drug.

The Expert Committee on Addiction-Producing Drugs of the World Health Organization defines habituation (1957) as: "...a condition resulting from the repeated consumption of a drug. Its characteristics include: (1) a desire (but not compulsion) to continue taking the drug for the sense of improved well-being which it engenders; (2) little or no tendency to increase the dose; (3) some degree of psychic dependence on the effect of drug; but absence of physical dependence and hence of the abstinency syndrome; (4) detrimental effects, if any, primarily on the individual." (See Seevers, M.H., *J.A.M.A.* 181 :92, 1962.)

Cf. [Addiction](#) , [Narcotic](#) , [Dependence](#) , [Tolerance](#) , [Drug Dependence](#)

Half-Life:

The period of time required for the concentration or amount of drug in the body to be reduced to exactly one-half of a given concentration or amount. The given concentration or amount need not be the maximum observed during the course of the experiment, or the concentration or amount present at the beginning of an experiment, since the half-life is completely independent of the concentration or amount chosen as the "starting point". Half-lives can be computed and interpreted legitimately only when concentration or amount varies with time according to the law appropriate to the kinetics of a first order reaction: the common logarithm of the concentration or amount is related linearly to time, e.g.:

$$\log C = a + bt$$

where C is concentration at time t , a (in logarithmic units) is the intercept of the line with the ordinate, and b (which has a negative sign) is the slope of the line. The parameters of the equation can be estimated from the plot of experimental values of $\log C$ and t . The half-life can be computed simply by dividing the slope of the curve into 0.301, the difference between the logarithm of a number (C) and the logarithm of number half as large ($C/2$); the symbol for half-life is $t_{1/2}$.

The half-life of a drug in plasma or serum is frequently taken as indicating the persistence of the drug in its volume of distribution; this interpretation may be incorrect unless the material can move freely and rapidly from one fluid compartment of the body to another, and is not bound or stored in one or another tissue. The term "biological half-life" should not be used instead of the specific terms "plasma half-life" or "serum half-life". The tissue for which the half-life of a drug is determined should always be specified, e.g., "serum half-life"; the half-life of a drug in muscle, kidney, etc., or in the whole organism can be determined. Drug half-lives are frequently based on the results of chemical analyses, i.e., the results of the reaction of a reagent with a specific chemical group of a drug molecule; it should be remembered that detection of the group *per se* does not necessarily imply its continuous existence as part of a biologically active drug molecule.

A drug molecule that leaves the plasma may have any of several fates: it can be destroyed in the blood; it can be eliminated from the body; or it can be translocated to a body fluid compartment other than the intravascular to be stored, biotransformed, or to exert its pharmacodynamic effects.

When the plot of log plasma or serum concentration (during the period of its

decline) against time is composed of two straight line segments, the inference may be made that two first order processes are involved in the distribution and biotransformation and elimination of the drug. The earlier phase – represented by the line segment of greater slope – is termed the distributive phase, and corresponds to the period during which translocation of the drug to its ultimate volume of distribution occurs and is the dominant process; the later phase – represented by the line of lesser slope – is termed the eliminative phase, and corresponds to the period when biotransformation and elimination of drug are dominant processes. For two-phase systems, three phase systems, etc., half-lives of the drugs in the various phases can be determined only after more sophisticated analysis of the data than that described above.

Cf. [First Order Kinetics](#) , [Compartment\(s\)](#) , [Volume of Distribution](#) , [Pharmacokinetics](#) , [Biotransformation](#)

,
[Biotranslocation](#)

,
[a](#)

,
[b](#)

Harrison Act:

A federal law passed in 1916 that regulated the manufacture, importation, transportation, and distribution (wholesale, retail, dispensing) of all “narcotics” defined by the act. Coca leaves and derivatives, opium and derivatives, and various synthetic agents were subject to the act and are officially designated as “narcotics”. The effect of the law was to regulate possession and use of the materials designated as narcotics. Since regulation was achieved through taxation, the law was enforced by the Treasury Department, Bureau of Internal Revenue. Traffic in marihuana was first controlled by the Marijuana Tax Act of 1937.

More recently, additional materials, e.g., barbiturates, amphetamines, etc., were recognized by Congress as requiring legal control, and were included with narcotics and marihuana in the Controlled Substances Act of 1970. The law is implemented by placing a nominal tax on certain materials under the law, and by requiring that physicians, dentists, etc., be specially licensed, annually, to legally prescribe materials covered by the law. The Act of 1970 is enforced by the Drug Enforcement Administration of the U.S. Department of Justice.

Cf. [Narcotic](#) , [Addiction](#)

Hazard:

The potential for causing harm; that which is a potential cause of harm. With respect to chemicals which are capable of causing harm, “hazard” is about equivalent in meaning to “toxicity”; measuring the hazard or toxicity of a chemical is to measure its potency in producing harm: the lower the dose required to produce harm, the greater the hazard or toxicity, the more hazardous or toxic is the substance.

Since the time of Paracelsus, in the early 16th century, it has been recognized that all chemicals, given in sufficient doses, are capable of producing harm. Therefore, it is not very meaningful simply to call a chemical a hazard, or to speak of a chemical as hazardous, without qualification or definition. Three categories of information are needed to define a hazard: specific descriptions of the harms it can produce, specific identification of the species or kinds of subjects that can be harmed, and specification of the kinds of exposure to the chemical (including dose) which can result in the respective harms.

Observe that hazard is the *potential* for causing harm. However hazardous a chemical might be, it may present no *risk* if potential victims are not exposed to it!

Risk management

is the effort to limit the likelihood that the hazard of a chemical will be realized or manifested.

For chemicals, such as drugs, it is frequently more informative to consider their hazards relative to their potential for producing benefit, rather than relative to the hazards of other chemicals. An extremely potent therapeutic agent may also be potent in producing harm, but it may be a useful drug because of its large therapeutic index or standardized safety margin.

Cf. [Risk](#) , [Potency](#) , [Therapeutic Index](#) , [Standardized Safety Margin](#) , [CT Index](#) , [Toxic Effects](#)

Hypersensitivity:

The physiological state necessary for a subject's manifesting an allergic response or reaction; the state is dependent on the administration of a hapten or allergen to a susceptible individual, and the development of antibodies and immune mechanisms capable of being activated by a subsequent administration of the haptene. Hypersensitivity may exist but not be manifested until a second administration of hapten occurs. The dose of hapten (or drug) required to produce the allergic response may be smaller, larger, or the same size as the dose required for the drug to produce its characteristic *pharmacologic effects*; hence hypersensitivity is not the same as sensitivity and the two words should not be used as synonyms. The nature of the response to haptene in a hypersensitive subject is determined by the immune mechanisms and effector organs and is not, in general, related to the nature of the hapten; the allergic response in the hypersensitive subject is generally qualitatively different from the expected pharmacodynamic response to the hapten or drug, being determined

by the immune system, rather than by the receptor(s) that mediate that drug's pharmacodynamic effect.

Cf. [Sensitivity](#) , [Allergic Response](#) , [Idiosyncratic Response](#)

Hypnotic:

A drug that produces a state clinically identical to sleep by means of action in the central nervous system.

Cf. [Anesthetic](#)

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Idiosyncratic Response:

A qualitatively abnormal or unusual response to a drug which is unique, or virtually so, to the individual who manifests the response. "Idiosyncratic Response" usually applies to a response that is not allergic in nature and cannot be produced with regularity in a substantial number of subjects in the population, and which is ordinarily not produced in a greater intensity in an individual, or in a greater fraction of the population, by the expedient of increase in the dose. In other words, were frequency or intensity of idiosyncratic response used as a measure of effect in constructing a dose-effect curve, a curve might indeed be

constructed, but its slope would be found to be 0 (zero), indicating that effect was not significantly a function of dose. In practice, the mechanism of production of an idiosyncratic response is unknown; once the mechanism is known, the response can usually be classified in some other way.

Cf. [Toxic Effects](#) , [Side Effects](#) , [Allergic Response](#)

Infusion Kinetics:

Infusion, as a means of drug administration, involves an effectively continuous flow of a drug solution into the blood stream over a relatively long period of time. (Intravascular *injections* are separate administrations of drug solutions, each over a short period of time.) A major purpose of an infusion is to maintain a steady blood or plasma concentration of drug over a long period of time, i.e. to achieve and maintain C_{ss} .

The C_{ss} achieved during infusion of a drug is directly proportional to the rate of drug administration (D/T , or k_d), and inversely proportional to both the rate of elimination (k_{el}), and to the volume of body throughout which the drug is distributed: C

$$C_{ss} = (D/T)/k_{el}$$

V_d

. Since, $k_{el} = Cl/V_d$

V_d

Cl equals total clearance: C

$$C_{ss} = (D/T)/Cl$$

T
, or C

ss
 $= k$

0
 $/Cl$

T
. The concentration finally achieved varies directly with the infusion rate and indirectly with the total clearance of the drug (always assuming first-order elimination and a single compartment system).

For a drug given by infusion, and eliminated by first-order kinetics from a one-compartment system, the rate at which C_{ss} is achieved depends only on the half-life of the drug. In the absence of other doses (such as a [loading dose](#)

[q.v.]) the plasma concentration at any time after beginning the infusion (C

T
) , expressed as a fraction of the C

ss
to be achieved, is given by $(1 - f)$:

$$C_T/C_{ss} = 1 - 0.5^{T/t}$$

After duration of infusion of one half-life, 50% of the final concentration will have been achieved; after a duration of infusion of 4 half-lives, about 95% of the final concentration will have been achieved.

Cf. [C_{ss}](#) , [F](#) , [Multiple Dose Regimens](#) , [First-Order Kinetics](#) , [Compartment\(s\)](#)

Intrinsic Efficacy (or Intrinsic Activity):

The property of a drug that determines the amount of biological effect produced per unit of drug-receptor complex formed. Two agents combining with equivalent sets of receptors may not produce equal degrees of effect even if both agents are given in maximally effective doses; the agents differ in their intrinsic activities and the one producing the greater maximum effect has the greater intrinsic activity. Intrinsic activity is not the same as “potency” and may be completely independent of it. Meperidine and morphine presumably combine with the same receptors to produce analgesia, but regardless of dose, the maximum degree of analgesia produced by morphine is greater than that produced by meperidine; morphine has the greater intrinsic activity. Intrinsic activity – like affinity – depends on the chemical natures of both the drug and the receptor, but intrinsic activity and affinity apparently can vary independently with changes in the drug molecule.

Cf. [Affinity](#) , [Receptors](#) , [Ceiling](#) . [Antagonism](#) , [Dose-Effect Curve](#)

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k_a :

The “absorption rate constant” for a drug administered by a route other than the intravenous. The rate of absorption of a drug absorbed from its site of application according to first-order kinetics. k_a is determined directly, or indirectly, as the slope of the linear relationship between the logarithm of the amount

un

absorbed and t , when natural logarithms, i.e. logarithms to the base e , are

used. The half-time for absorption is computed as $0.693/k_a$

, i.e. $\ln 2/k_a$

a
.

Cf. [k_{el}](#), [k₀](#), [t_{1/2}](#), [Half-Life](#), [First-Order Kinetics](#), [C_{max}](#)

k_{el}:

The “elimination rate constant” for a drug eliminated according to the laws of first-order reaction kinetics; the slope of the plot of the logarithm of concentration against time, when natural logarithms, i.e. logarithms to the base e, are used.

$$t_{1/2} = 0.693/k_{el}. \quad k_{el} = 2.303b. \quad Cl_T = k_{el} V_d. \quad AUC \text{ from } T_n \text{ to infinity} = C_n/K_{el}.$$

Cf. [b](#), [t_{1/2}](#), [Half-Life](#), [k_a](#), [First-Order Kinetics](#)

k₀:

The “absorption rate constant” when rate of absorption (D/T) does not vary. k_0 describes the rate at which drug enters the body during constant-rate intravenous infusions, or during use of “sustained” release preparations for oral or transdermal drug administration.

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Latent Period or Latency:

The period of time that must elapse between the time at which a dose of drug is applied to a biologic system and the time at which a specified pharmacologic effect is produced. In general, the latent period varies inversely with dose; the relationship between dose and latent period for a given agent is described by a *ti* *me-dose*

or

time-concentration

curve.

Cf. [Time-Concentration Curve](#) , [CT Index](#)

LD₅₀:

See [Median Effective Dose](#)

Loading Dose:

A larger than normal dose (D^*) administered as the first in a series of doses, the others of which are smaller than D^* but equal to each other. The loading dose is administered in order to achieve a therapeutic amount in the body more rapidly than would occur only by accumulation of the repeated smaller doses. The smaller doses (D) which are given after D^* are called “maintenance doses”. The effect of D^* on C becomes relatively less with each succeeding maintenance dose; finally $C_{ss,max}$ and $C_{ss,min}$ are determined by D , and are uninfluenced by D^* .

The relative sizes of D and D^* can be adjusted so that peak plasma concentrations (C_{\max}) are the same following every dose, including the first with D^* , and all are equal to $C_{ss,\max}$. These conditions are met when $D/D^* = 1-f$.

Cf. [Dose](#), [C_{max}](#), [C_{ss}](#), [F](#), [Multiple Dose Regimens](#)

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Maintenance Dose:

See [Loading Dose](#)

Median Effective Dose:

The dose of a drug predicted (by statistical techniques) to produce a characteristic effect in 50 percent of the subjects to whom the dose is given. The median effective dose (usually abbreviated ED_{50}) is found by interpolation from a dose-effect curve. The ED_{50} is the most frequently used standardized dose by means of which the potencies of drugs are compared. Although one can determine the dose of drug predicted to be effective in one percent (ED

ED_1) or 99 percent (ED

99

) of a population, the ED

50

can be determined more precisely than other similar values. An ED

50

can be determined only from data involving all or none (quantal) response; for quantal response data, values for ED

0

and ED

100

cannot be determined. In analogy to the median effective dose, the pharmacologist speaks of a median lethal dose (LD

50

), a median anesthetic dose(AD

50

), a median convulsive dose (CD

50

), etc.

Cf. [Dose-Effect Curve](#) , [Therapeutic Index](#) , [Standardized Safety Margin](#) , [Bioassay](#) , [Metameter](#) , [M](#)

Metameter:

A term used to designate “the measurement or transformation of the measurement used in evaluating biological tests.” Examples of metameters of dose include “milligrams,” “moles,” “log milligrams,” “log milligrams per kilogram of body weight,” etc. Metameters of response include “increase in blood pressure, in mmHg,” “Maximum blood pressure achieved, in mmHg,” and “percent increase in blood pressure.” Metameters are frequently and erroneously chosen only to facilitate statistical summary and analysis of data; the metameter used may also obscure or influence the biological interpretation of the data in a manner not intended or expected by the investigator. For example, implicit in the

calculation of “percent change in blood pressure ” is the statement that the final state of the system is a function of the initial state that may or may not be true.

Cf. [Parameter](#) , [Bioassay](#) , [Dose-Effect Curve](#)

Multiple Dose Regimens:

The pharmacokinetic aspects of treatment schedules that involve more than one dose of a drug are discussed below. The relationships described involve assumptions of instantaneous intravenous administration and distribution of a drug that is eliminated by first-order kinetics from a single-compartment system, and is given in equal doses at equal time intervals. The relationships become less accurate in describing real situations to the extent that the real systems depart from the ideal model, i.e. to the extent that k_a is not much greater than k_{el} , and to the extent that V

da

is not much smaller than V

db

.

When equal doses are administered at equal intervals, the peak plasma concentration after the n th dose, $C_{max,n}$ is given by the relationship:

$$C_{max,n} = C_0 (1 - f^n)/(1 - f)$$

The “trough” concentrations (C_{min}) for the two conditions are:

$$C_{\min,n} = C_{\max,n} - C_0, \text{ and}$$

$$C_{ss,\min} = C_{ss,\max} - C_0, \text{ respectively.}$$

Knowing the half-life of a drug and the $C_{ss,\max}$ and $C_{ss,\min}$ desired to produce optimum therapy, the dose interval, τ (tau), necessary to achieve and maintain these maximum and minimum concentrations can be determined from the relationship:

$$\tau = 1.443 (t_{1/2}) \ln(C_{ss,\max}/C_{ss,\min}).$$

(Remember that $\ln X = 2.303 \log X$, that $t_{1/2} = 0.693/k_{el}$, and that $1/0.693 = 1.443$.)

The doses to be administered at intervals, τ , to produce the desired $C_{ss,\max}$ and $C_{ss,\min}$ are inferred from experimental data relating the size of single doses to the peak plasma concentrations (C_{\max})

each produces, or are estimated from the relationship $F \cdot D/V$

$= C_{\max}$, when the V_d

and F of the drug are known. (The relationship among $C_{ss,\max}$

, $C_{ss,\min}$

and expected therapeutic outcome, including occurrence of side effects, are inferred from dose-effect relationships established in clinical pharmacologic experiments.)

With repeated doses, at equal intervals, peak plasma concentrations (C_{\max}) approach but, in theory, never reach $C_{\text{ss,max}}$

$C_{\text{ss,max}}$

. In practice, it is useful to know how long it takes for $C_{\text{ss,max}}$

$C_{\text{ss,max}}$

to reach some specified level with respect to $C_{\text{ss,max}}$

$C_{\text{ss,max}}$

, i.e., how long it takes for $C_{\text{ss,max}}$

$C_{\text{ss,max}}$

$C_{\text{ss,max}}$

$C_{\text{ss,max}}$

to reach, say, 0.95. Knowing the expected value of $C_{\text{ss,max}}$

$C_{\text{ss,max}}$

and the fractional achievement desired, e.g. 0.95, it is easy to compute the desired $C_{\text{ss,max}}$

$C_{\text{ss,max}}$

. Then, knowing the dose interval, τ , and the half-life of the drug, the time required to reach the desired $C_{\text{ss,max}}$

$C_{\text{ss,max}}$

is given by the relationship:

$$n\tau = 1.443 (t_{1/2}) \ln [(C_{\text{ss,max}} - C_{\text{max}})/C_{\text{ss,max}}]$$

where the time required ($n\tau$) is expressed as the product of the number of doses and the duration of the dose interval (τ). The number of doses required to achieve the desired ratio of C_{max} to $C_{\text{ss,max}}$ may be determined by dividing the right hand member of the equation by the length of the dose interval.

When τ is long, relative to $t_{1/2}$, many doses may have to be given, and much time may have to pass if a reasonable fraction of $C_{\text{ss,max}}$ is to be achieved by administering identical doses at equal interval. Under such

circumstances, prompt achievement of therapeutically effective blood levels may require beginning the treatment regimen with a “loading dose” (q.v.).

Cf. [C_{max}](#), [C_{ss}](#), [Infusion Kinetics](#), [First-Order Kinetics](#), [Compartment\(s\)](#)

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N:

The number of doses in a series; as a subscript, the last dose in a series or the number of the last dose.

Cf. [C_{max}](#), [C_{ss}](#), [Multiple Dose Regimens](#)

Narcotic:

Formerly, an agent capable of producing coma or stupor (from Greek *narke*: torpor, numbness). Now, usually, any drug which produces analgesia and is capable of producing stupor: pain is relieved by a dose of narcotic before the occurrence of sleep or unconsciousness. Legally, the term “narcotic” is applied only to those drugs the sale and use of which is regulated by the Harrison Narcotic Act.

Cf. [Addiction](#) , [Anesthetic](#) , [Analgesic](#)

National Formulary (N.F.):

A reference volume published formerly by the American Pharmaceutical Association containing standards of purity and methods of assay for some drugs, and formulae and methods of manufacture for a variety of pharmaceutical preparations. Drugs were included on the basis of demand as well as therapeutic value. The N.F. and the U.S.P. are recognized by the F.D.A. as official standards, and the two are now published as a single volume.

Cf. [U.S.P.](#) , [Food and Drug Administration](#)

Negative Control Drug or Negative Control Procedure:

A treatment incorporated into an experiment with the intention that it have no effects on the experimental system like those expected of the independent variable. In a pharmacologic experiment, the negative control drug mimics in every way the drug preparation under investigation (including identity of dosage form, vehicle, mode of application, etc.) except that the negative control drug lacks the ingredient that is expected to be responsible for the biological effect of the test preparation. The negative control drug has two functions in an experiment: 1.) To permit ascribing a causal relationship between treatment with the independent variable and changes in the experimental system which follow treatment. If the experimental system responds to both the negative control drug and the drug preparation under test, one cannot – in the absence of other information – legitimately infer that the effects of the test preparation are caused by the supposedly pharmacodynamically active test preparation. 2.) To serve as a basis for quantitative estimation of the effects of the independent variable in excess of those effects produced by non-specific changes in the environment or the experimental system. A test drug preparation may have non-specific effects

like those of the negative control drug, but may also have specific effects that can be attributed to the ingredient that is unique to the test preparation.

Careful use of a negative control drug in an experiment prevents erroneous conclusions about the apparent activity of a test preparation; use of a positive control drug prevents making erroneous conclusions about apparent inactivity of a test preparation.

Cf. [Positive Control Drug](#) , [Dummy](#) , [Placebo](#) , [Bioassay](#) , [Cross-Over Experiment](#)

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Parameter:

1. One of the elements of an experiment which can be varied, but which the experimenter tries to control or maintain constant during the course of a specific experiment, while intentionally altering the *independent variable* and observing changes in the *dependent variable*.

Parameters in one experiment (stimulus strength, for example) might well be independent variables in another.

2. Terms of an equation that do not vary within the context of an experiment, but may be different under different circumstances. Parameter should be

distinguished from the independent and dependent variables. For example, in the equation of a straight line, $y = mx + b$, x is normally the independent variable (the variable under experimental control),

y is the dependent (measured) variable, and the slope m and intercept b are parameters, which are the same for a given line, but may be different for a different line.

Cf. [Metameter](#) , [Bioassay](#)

Pharmacodynamics:

The science and study of the biological effects produced by chemical agents; more specifically, the science and study of how chemical agents produce their biological effects. In medical pharmacology, the science and study of how drugs produce their effects.

Cf. [Pharmacology](#) , [Pharmacokinetics](#) , [Therapeutics](#) , [Pharmacogenetics](#)

Pharmacogenetics:

The science and study of the inheritance of characteristic patterns of interaction between chemicals (drugs) and organisms. Pharmacogenetics involves identification and description of such patterns, discriminating them from non-heritable patterns, and elucidation of the mechanism of inheritance. Pharmacogenetic studies illuminate many intraspecific and interspecific similarities, and differences in pharmacodynamic and pharmacokinetic mechanisms.

Cf. [Pharmacodynamics](#) , [Pharmacology](#)

Pharmacokinetics:

The science and study of the factors which determine the amount of chemical agents at their sites of biological effect at various times after the application of an agent or drug to biological systems. Pharmacokinetics includes study of drug absorption and distribution (“biotranslocation”), study of the chemical alterations a drug may undergo in the body, (“biotransformation”), and study of the means by which drugs are stored in the body and eliminated from it.

Cf. [Pharmacodynamics](#) , [Pharmacology](#) , [Biotransformation](#) , [Biotranslocation](#) ,
[Half-Life](#)
,
[Volume of Distribution](#)
,
[Bioavailability](#)

Pharmacology:

(Gr. *Pharmakon* – drug, and *Logos* – word) is the study of drugs in all their aspects. Pharmacy, although often confused with pharmacology, is, in fact, an independent discipline concerned with the art and science of the preparation, compounding, and dispensing of drugs. Pharmacognosy is a branch of pharmacy that deals with the identification and analysis of the plant and animal tissues from which drugs may be extracted. Pharmacodynamics, which in common usage is usually termed “pharmacology”, is concerned with the study of drug effects and how they are produced. The pharmacodynamicist, or pharmacologist, identifies the effects produced by drugs, and determines the

sites and mechanisms of their action in the body. The pharmacologist studies the physiological or biochemical mechanisms by which drug actions are produced. The pharmacologist also investigates those factors that modify the effects of drugs, i.e. the routes of administration, influence of rates of absorption, differential distribution, and the body's mechanisms of excretion and detoxification, on the total effect of a drug. Pharmacotherapeutics is the study of the use of drugs in the diagnosis, prevention, and treatment of disease states. Toxicology is the study of drug effects that are inimical to health. The toxicologist may investigate such diverse problems as the effects of overdoses of pharmacotherapeutic agents; the diagnosis, treatment, and prevention of lead poisoning in the paint manufacturing industry; the possibility that criminal poisoning was the cause of an otherwise inexplicable death, etc.

“Experimental pharmacology, in the broadest sense, deals with the reactions of living organisms to chemical agents, or, to put the matter in another way, the behavior of organisms to changes in the chemical environment in which they live. Pharmacology is a part of biology... Of all the vast number of pharmacologic reactions, those that the physician attempts to use for curative purposes are of the greatest interest and most deserved of study. This part of pharmacology, the scientific knowledge of remedial agents, forms the theoretical foundation for therapeutics...” H.H.Meter and R. Gottlieb, *Experimental Pharmacology as a Basis for Therapeutics: A Textbook for Students and Physicians*, 1910 (trans. by V. E. Henderson).

Cf. [Therapeutics](#), [Pharmacodynamics](#), [Pharmacokinetics](#), [Pharmacogenetics](#), [Toxicology](#)

Placebo:

(Latin: I will satisfy). “A medicine or preparation with no inherent pertinent pharmacologic activity that is effective only by virtue of the factor of suggestion attendant upon its administration.” A placebo is frequently used as a negative

control in a [blind experiment](#) to prevent results from being confounded by the effect of suggestion.

Cf. [Dummy](#) , [Negative Control Drug](#) , [Positive Control Drug](#)

Positive Control Drug:

A drug preparation incorporated into an experiment with the intention that it have effects on the experimental system qualitatively similar to those expected of the independent variable. The positive control drug has two functions in an experiment: 1) to verify that the experimental system is indeed capable of undergoing the changes expected to follow manipulation of the independent variable. If the system fails to respond to the positive control drug, its failure to respond to the independent variable is uninterpretable; 2) to serve as a basis for quantitative estimation of the relative efficacy of the independent variable. In these terms, the positive control drug is a “standard”, and the independent variable may be considered the “unknown” in a bioassay.

Cf. [Negative Control Drug](#) , [Bioassay](#) , [Cross-Over Experiment](#) , [Reference Standard](#)

Potency:

An expression of the activity of a drug, in terms of the concentration or amount needed to produce a defined effect; an imprecise term that should always be further defined (see [EC₅₀](#) , [ED₅₀](#)).

Cf. [Sensitivity](#) , [Dose-Effect Curve](#) , [Intrinsic Activity](#) , [Bioassay](#) , [Equipotent](#)

Potentialiation:

A special case of synergy (q.v.) in which the effect of one drug is increased by another drug that by itself has no effect. For example, although physostigmine has no acetylcholine-like activity of its own, it potentiates the actions of acetylcholine by inhibiting the enzymes responsible for the destruction of acetylcholine. Intensity of effect may be *potentiated*, duration of effect may be prolonged: potentiation and prolongation are independent phenomena, but frequently occur together.

Cf. [Synergy](#) , [Antagonism](#)

Priming Dose:

See [Loading Dose](#)

Prodrug:

A chemical with little or no pharmacologic activity that undergoes change in the body into a more active material. The change may be a result of biotransformation, or may occur spontaneously, in the presence of, e.g., water, an appropriate pH, etc.

Precision:

The capacity of the system to discriminate between different values of input; the “fineness” with which different values for input can be inferred from measured values of output. The pooled deviation of observed from expected values of output, all divided by the amplification, yields the “index of precision”. The square of the reciprocal of the index of precision is the measure of the amount of *information* that can be delivered by the system.

Specifically, precision is computed in several steps. First, the deviation of each observed value of output from the corresponding predicted value is squared; predicted values are determined from the curve relating input and output for all the data. The squared deviations are summed and divided by $N-2$, the number of “degrees of freedom”; the square root of the quotient is determined and is a number analogous to the standard deviation. This “root mean square deviation” is then divided by the slope of the input-output curve, i.e., the amplification, to yield the “index of precision”; it is assumed that the input-output relationship is linear.

See [Accuracy](#)

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R:

Accumulation Ratio, see [C_{ss}](#).

Receptors:

Actual or hypothetical "...small, chemically defined areas (of a cell) which give (initiate) a biological response upon uniting with chemically complementary areas of natural or foreign molecules (drugs)". The receptor hypothesis is indispensable to pharmacologists in analyzing and interpreting the actions of some drugs; however, reasonable care should be exercised that "receptor" does not become a catch-all phrase used to explain all drug actions or the actions of all drugs.

Cf. [Intrinsic Activity](#) , [Affinity](#) , [Antagonism](#)

Reference Standard:

A drug, chemical, or dosage form, etc., of specified properties used as the basis for quantitative comparison with other materials of qualitatively similar properties. The purpose of such a comparison is to express the amount or degree of the designated property in the "other" material as a fraction or multiple of the amount or degree of the property contained in the standard. The reference standard serves as a unit of measurement for the properties of the other, or "unknown," material.

Even physical systems of measurement are based on reference standards. The use of reference standards is of particularly great importance to the design and interpretation of biological experiments. In biological experiments, particularly, variability and instability of the biological test system can markedly influence the apparent effects and effectiveness of substances being tested.

Reliability:

The degree to which the input-output relationship is reproducible if the relationship is studied repeatedly under comparable conditions. For example, if a student took the same examination twice, or in two forms, would he get the same grade both times? If the same work were reviewed by two graders, would they both assign the same mark?

See [Accuracy](#).

Risk:

The likelihood that harm will result from exposure to a hazard. More generally, the probability that an event has occurred, or will occur, in members of a population under specified conditions, e.g., of exposure to a hazardous chemical; the “population at risk” consists of the subjects who could experience the event, e.g., who were exposed to the chemical. Risk is calculated by dividing the number of subjects who experience an event by the number of subjects in the population at risk. The risk, so calculated, is one of the bases used to estimate the likelihood that the event will occur in the future, the predicted risk. Risk, calculated as described, also indicates the probability that any individual subject in the population at risk experienced the event. (Formally, the idea of “risk” is applicable to the study of both desirable and undesirable events.)

For a meaningful estimate of risk (following exposure of subjects to some hazard), it is necessary to have carefully defined the harm that was done, to have characterized the population at risk, and to have specified the conditions of exposure. Interpreting an estimate of risk requires comparing the data with those from a “control” population, ideally one never exposed to the hazard. The statistical techniques used to estimate risks and to compare them are, generally, the techniques used in epidemiology.

Perceived risk is the *subjective* assessment of the importance of a hazard to individuals or to groups of individuals. For example, hazards that affect children generally have higher perceived risks than those that tend to affect adults. Hazards viewed as under a person's control (e.g., driving a car) generally have lower perceived risks than those viewed as not under such control (e.g., riding in a aircraft piloted by someone else). Hazards that produce fatalities grouped in time and space (e.g., airplane crashes) generally have higher perceived risks than those which produce fatalities scattered in time and space (e.g., automobile accidents), etc. Perceived risks are not necessarily correlated with the risks, for the same hazards, measures by epidemiologic techniques.

Risk management is the effort to reduce the likelihood that a hazard will produce harm. Risk management may involve decreasing the size of the population at risk (e.g., by prohibiting the use of a chemical as a food additive), altering the conditions of exposure (e.g., requiring adequate ventilation in an industrial environment), developing and using therapeutic regimens to minimize the consequences of exposure, etc.

Cf. [Hazard](#) , [Toxicology](#)

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Selectivity:

The capacity or propensity of a drug to affect one cell population in preference to

others, i.e., the ability of a drug to affect one kind of cell, and produce effects, in doses lower than those required to affect other cells. Selectivity can be measured or described by means of such numbers as the Therapeutic Index, or the Standardized Safety Margin: not infrequently one wishes to express selectivity of drug action with respect to two potentially beneficial effects, or two potentially toxic doses, or two toxic doses, instead of one each.

“Selectivity” is not to be confused with “potency”; a potent drug may be non-selective or a selective drug may be impotent. “Selectivity” is however, a measure of the relative potency of a drug in producing different effects.

Selectivity is generally a desirable property in a drug, e.g., it is desirable that an antibacterial agent affect parasites in doses too small to affect host cells. Sometimes, selectivity of action is virtually precluded by the nature of the drug, e.g., in the case of analogs of hormones that have many target cells or tissues. Sometimes selectivity of action for cells within an organism is not necessarily desirable, as in the case of certain economic poisons, i.e., pesticides, herbicides, rodenticides; even in this case, however, it is desirable to have a drug selective for cells of a particular species, and this criterion can most easily be met by drugs selective for certain cell types in the organisms of the target species.

“Selectivity” and “specificity” are, unfortunately, frequently used as synonyms for each other. They describe separate phenomena, each of which deserves an unambiguous name.

Cf. [Specificity](#) , [Therapeutic Index](#)

Sensitivity:

The ability of a population, an individual or a tissue, relative to the abilities of others, to respond in a qualitatively normal fashion to a particular drug dose. The smaller the dose required to produce an effect, the more sensitive is the responding system. A patient would be considered abnormally *sensitive* to aspirin if a small fraction of the normal analgesic dose gave adequate pain relief; or, were an abnormally large dose of aspirin required to afford pain relief, the subject would be said to be “insensitive” to aspirin. Conversely, the drug would appear to be extraordinarily

potent

or

impotent

in such a patient. If a patient manifested an allergic response after taking aspirin, he would be considered hypersensitive to aspirin, regardless of whether the aspirin afforded him relief from pain, and regardless of the size of the dose required to elicit the allergic response. Such a patient might be simultaneously

hypersensitive

to aspirin, and insensitive to aspirin, acting as an analgesic agent.

Every subject is sensitive to a drug; the question of importance is “how sensitive?” In any event sensitivity is a property ascribed to the organism; potency is a property ascribed to the drug. Hypersensitivity is a property ascribed to a subject in a particular immunologic state.

Sensitivity may be measured or described quantitatively in terms of the point of intersection of a dose-effect curve with the axis of abscissal values or a line parallel to it; such a point corresponds to the dose just required to produce a given degree of effect (see *Threshold*). In analogy to this, the “sensitivity” of a measuring system is defined as the lowest input (smallest dose) required to produce a given degree of output (effect).

Cf. [Supersensitivity](#) , [Hypersensitivity](#) , [Allergic Response](#) , [Potency](#) , [Accuracy](#)

Side Effects:

Drug effects which are not desirable or are not part of a therapeutic effect; effects other than those intended. For instance, in the treatment of peptic ulcer with atropine, dryness of the mouth is a side effect and decreased gastric secretion is the desired drug effect. If the same drug were being used to inhibit salivation, dryness of the mouth would be the therapeutic effect and decreased gastric secretion would be a side effect.

Pharmacological side effects are true drug effects. With increasing doses of a drug, the intensity of pharmacological side effects in individuals, and/or the frequency with which a pharmacological side effect is observed in a population is increased.

Cf. [Idiosyncratic Response](#) , [Toxic Effects](#) , [Allergic Response](#)

Spare Receptors:

A pharmacological system has spare receptors (a receptor reserve), if an agonist can induce a maximum response when occupying less than 100% of the available receptors. The existence of spare receptors reflects a circumstance in which the maximum effect produced by an agonist is limited by some factor other than the number of activated receptors. Whether or not a system has spare receptors depends upon the nature of the receptor and its coupling to the measured response, the number of receptors, and the [intrinsic activity](#) of the agonist.

Specificity:

The capacity of a drug to manifest only one kind of action. A drug of perfect specificity of action might increase, or decrease, a specific function of a given cell type, but it would not do both. Nicotine is not specific in its actions in autonomic ganglia; it both stimulates and depresses ganglionic function by a number of means. Atropine is quite specific in only blocking the actions of acetylcholine at certain receptors; in general atropine does not stimulate cellular activity when it combines with receptors, nor does it block interaction with receptors of agonists other than acetylcholine. In affecting exocrine glands, acetylcholine itself is very specific, in that it causes only stimulation or secretion; acetylcholine, at the same time, is *non-selective* in its action, in that stimulation of all exocrine glands is produced by about the same dose of acetylcholine.

Selectivity is concerned with *site of action*; *specificity*, with the kinds of action at a site.

Cf. [Selectivity](#)

Standard Drug:

See [Bioassay](#) , [Positive Control Drug](#) .

Standardized Safety Margin:

A number, $LD_{1}-ED_{99}/ED_{99} \times 100\%$, which is a measure of the selectivity of action or relative “safety” of a drug. The standardized safety margin indicates by what percentage of itself a dose effective in virtually all (99%) of a population must be exceeded in order to produce a lethal effect in a minimum number (1%) in the population. The *therapeutic index* (q.v.) measures by what factor an effective dose must be increased to produce a standard lethal

effect in a population. Clinically, the standardized safety margin probably has greater practical meaning than does the therapeutic index, and, unlike the therapeutic index, the meaningfulness of the standardized safety margin does not depend on the parallelism of the dose effect curves from which the LD

¹
and ED

⁹⁹
are inferred. The standardized safety margin (more frequently than the therapeutic index) can sometimes be computed from clinical data not involving lethal effects, e.g., the ED

⁹⁹
for control of epileptic seizures and the ED

¹
for the production of drowsiness or ataxia, in a population of patients with epilepsy. See: Foster, R.H.K.,
J. Pharmacol
. 65: 1, 1939.

Cf. [Therapeutic Index](#) , [Median Effective Dose](#) , [Selectivity](#) , [Clinical Therapeutic Index](#)

Supersensitivity:

An extreme and high degree of sensitivity to a drug or chemical. Usually a high degree of sensitivity induced by some specific procedure such as denervation, administration of another drug, etc. Sensitivity to a drug, of some degree, is inherent in every organism; supersensitivity is a state that has had to be produced in the organism. In the supersensitive subject, the actions of the drug are qualitatively like those observed in a subject of normal sensitivity, and unlike those produced in a subject who is hypersensitive to the drug.

Cf. [Hypersensitivity](#) , [Sensitivity](#)

Synergy:

A mutually reinforcing drug interaction such that the joint effect of two drugs administered simultaneously is greater than the sum of their individual effects. Synergism is distinguished from *additivity*, in which the joint effect of two drugs is equal to the sum of their individual effects. If the joint effect is less than the sum of the two drugs' independent effects, the interaction is said to be antagonistic.

Cf. [Antagonism](#) , [Potentiation](#)

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T or ?:

A point in time or a time interval; frequently a time interval following administration of a drug or the time interval between doses of a drug. The definition of a specific T or ? may be explicit or may be inferred from the context in which it is found. Specific times of interest may be indicated by subscripts, e.g., T_0 is the time of drug administration; T_n is the time of administration of the nth dose in a series.

$t_?$:

The “half-life” of a drug; the amount of time required for the concentration of a drug in, e.g., a body fluid such as plasma, serum, or blood, to be halved. The idea of half-life is legitimately applied only to the case of a drug eliminated from body fluid according to the laws of first-order reaction kinetics. $t_{1/2} = 0.301/b = 0.693/k_{el}$, where 0.301 and 0.693 are the logarithms of 2 to the bases 10 and e, respectively.

Cf. [Half-Life](#), [b](#), [k_{el}](#), [First-Order Kinetics](#)

Tachyphylaxis:

A decline in the response to repeated applications of agonist, typically occurring over a relatively short time scale (seconds to hours). See also [Desensitization](#), [Tolerance](#)

Therapeutic Index:

A number, LD_{50}/ED_{50} , which is a measure of the approximate “safety factor” for a drug; a drug with a high index can presumably be administered with greater safety than one with a low index. The therapeutic index is ordinarily calculated from data obtained from experiments with animals. As in comparing ED

LD_{50}
s from two different drugs, the comparison of the LD

ED_{50}
and ED

ED_{50}
(therapeutic index) is most meaningful when the dose-effect curves from which the ED

LD_{50}
and LD

50

are inferred are parallel.

The therapeutic index is a measure of drug selectivity, and analogous index numbers are frequently computed to measure selectivity that does not involve lethal effects. For example, to measure the selectivity of a drug potentially useful in the treatment of epilepsy, the ED_{50} for producing ataxia in mice might be compared to the ED_{50} for abolishing electrically-induced convulsions in mice.

Cf. [Median Effective Dose](#) , [Selectivity](#) , [Standardized Safety Margin](#) , [Clinical Therapeutic Index](#)

Therapeutics:

The science and techniques of restoring patients to health. Properly, therapeutics has many branches, any or all of which may be needed in the treatment of a specific patient. In addition to pharmacotherapeutics or drug therapy, there exist coordinate fields of therapeutics such as *surgical therapy*, *psychotherapy*, *physical therapy*, *occupational therapy*, *dietotherapy*, etc. Drugs are commonly considered capable of participating in one or more of the following general kinds of therapy:

Curative or specific therapy: treatment directed toward eradication of one or more of the agencies etiologic to the patient's condition. Antimicrobial drugs such as penicillin have specific or curative effects. Palliative or symptomatic therapy treatment directed only toward relief of the patient's symptoms, toward making the patient feel better without necessarily altering the natural course of the disease. Analgesic agents such as aspirin or morphine have obvious palliative effects. Supportive therapy treatment directed toward maintaining the patient's physiological or functional integrity until more definitive treatment can be carried out, or until the patient's recuperative powers function to obviate the need for

further treatment. Many drugs can provide supportive therapy; even in a single patient supportive therapy can be provided from agents of such different classes as sedatives, diuretics, antihypertensives, etc. Substitutive or replacement therapy treatment directed toward supplying a material normally present in the body, but absent in a specific patient because of disease, injury, congenital deficiencies, etc. Adrenocortical hormones used in the treatment of a patient with Addison's Disease are used as substitutive therapy. Restorative therapy therapy directed at rapid restoration of health, usually regardless of the nature of the original disease; restorative therapy is most frequently given during convalescence. Vitamin supplements or sex hormones used for their anabolic effects might be considered as providing restorative therapy.

A single drug may have two or more therapeutic effects in the same patient at the same or different times, or in different patients. A patient may require more than one kind of therapy at a given time, or in the course of his/her disease.

Drugs may be used prophylactically to prevent disease or to diminish the severity of a disease should it occur subsequent to or during treatment; with a fine disregard for precision of definition, such a use of drugs is commonly called "prophylactic therapy". Drugs are sometimes used to measure bodily function and contribute toward the diagnosis of disease; such *diagnostic agents* have not yet been accused of participating in "*diagnostic therapy*"

“

Threshold Dose:

A dose of drug just sufficient to produce a pre-selected effect. Frequently, and improperly, restricted to the dose just sufficient to produce a minimal detectable effect. In fact, an LD₅₀ is a threshold dose if the pre-selected effect is "death in 50% of a population".

Cf. [Median Effective Dose](#) , [Sensitivity](#) , [Potency](#)

Time-Concentration Curve:

The graphical representation of the relationship – for a given drug and a given biological system – between concentration (or dose) and *latency* or latent period: the period of time elapsing between the time the dose is administered and the time a given effect is produced. Time-concentration curves tend to be hyperbolic in form: as dose increases latency decreases and vice versa. Latency is an inverse function of concentration. But the hyperbolic relationship never approaches the axes as asymptotes; there is always a concentration below which the drug is ineffective, regardless of the duration of exposure of the tissue to the drug, and there is always a finite interval between the time of exposure to the drug and the time the response occurs. The

time-concentration curve

is analogous to the

strength-duration curve

that the physiologist uses to determine rheobase and chronaxie. It is characteristic of true drug effects that a generally hyperbolic relationship exists between dose and latency. If, with increasing doses of material, a time-concentration curve and a dose-effect curve cannot be demonstrated, one *cannot*

conclude that the material is responsible for the effects observed.

Cf. [Dose-Effect Curve](#) , [CT Index](#) , [Latent Period](#)

Tolerance:

A condition characterized by a reduced effect of a drug upon repeated administration. In some cases, it may be necessary to increase the dose of the drug to attain the same effect, or the original level of effect may be unattainable.

Tolerance typically develops over days to weeks, and is distinguished from [tachyphylaxis](#), a more rapid decline in the effect of a drug. Tolerance can result from multiple mechanisms, including changes in drug metabolism and alteration in the number or responsiveness of receptors (see [desensitization](#)). “Tolerance” should not be used to mean “lack of sensitivity” manifested toward a single dose of a drug. A non-habitual drinker who is unaffected by several drinks of whisky downed in rapid succession is probably insensitive to alcohol rather than tolerant to its effects.

Cf. [Addiction](#), [Sensitivity](#), [Habituation](#), [Dependence](#)

Toxic Effects:

Responses to drug that are harmful to the health or life of the individual. Almost by definition, toxic effects are “side effects” when diagnosis, prevention, or treatment of disease is the goal of drug administration. Toxic effects are not side-effects in the case of pesticides and chemical warfare agents. Toxic effects may be idiosyncratic or allergic in nature, may be pharmacologic side effects, or may be an extension of therapeutic effect produced by overdose. An example of the last of these is the apnea produced by an anesthetic agent.

Cf. [Idiosyncratic Response](#), [Side Effects](#), [Allergic Response](#), [Therapeutic Index](#), [Standardized Safety Margin](#), [Clinical Therapeutic Index](#)

Toxicology:

The scientific discipline concerned with understanding the mechanisms by which chemicals produce noxious effects on living tissues or organisms; the study of the conditions (including dose) under which exposure of living systems to chemicals is hazardous.

Cf. [Hazard](#) , [Pharmacology](#) , [Toxic Effects](#)

Two-state Model:

A simplified model of receptor activation by agonists. The receptor is hypothesized to be in conformational equilibrium between an inactive conformation R and an active conformation R*, with the equilibrium in the absence of agonist normally favoring the inactive state. [Agonists](#) bind preferentially (i.e. with greater affinity) to the active state, and by mass action shift the conformational equilibrium such that a greater proportion of receptors are in the active R* conformation. Inverse agonists shift the conformational equilibrium such that a greater proportion of receptors are in the inactive R conformation.

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United States Pharmacopoeia (U.S.P.):

The *United States Pharmacopoeia* is a reference volume, published every five

years by the U.S. Pharmacopoeial Convention, which describes and defines approved therapeutic agents, as well as sets standards for purity, assay, etc. Agents are included on the basis of their therapeutic value. The U.S.P. is recognized by the F.D.A. as the official standard for the agents described therein.

The purposes of the *Pharmacopoeia*, as described in the Preface to the first edition in 1820 by Dr. Jacob Bigelow, are to :

1. Select the best, established drugs (those “the utility of which is most fully established and best understood”).
2. Set standards of pharmaceutical quality for them (“form from them preparations and compositions in which their powers may be exerted to the greatest advantage”).
3. Name them (“distinguish those articles by convenient and definite names, such as may prevent trouble or uncertainty in the intercourse of physicians and apothecaries”).
4. Encourage their use (“the value of a Pharmacopoeia depends upon the fidelity with which it conforms to the best state of medical knowledge of the day. Its usefulness depends upon the sanction it receives from the medical community and the public; and the extent to which it governs the language and practice of those for whose use it is intended:”).

V

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V_d :

The volume of distribution of a drug; the size of the “compartment” into which a

drug apparently has been distributed following absorption. Computed as D/C_0 for a one-compartment system, i.e. one yielding a single straight line when $\log C$, or C , is plotted against time after drug administration. Using absolute dose to compute V

^d
yields V

^d
in units of volume, i.e. liters. Using relative dose (D/B) to compute V

^d
yields V

^d
in relative units, e.g. liters per kilogram, the volume of distribution as a fraction of body weight. When the plot of $\log C$ against t yields a biphasic relationship (a two compartment system), V

^d
is computed by a different method, such as one based on the area under the C vs. t curve.

Cf. [Volume of Distribution](#) , [Compartment\(s\)](#)

Validity:

The degree to which output reflects what it purports to reflect, i.e., input; the degree to which output is a function of known input and it alone. For example, does an essay examination validly measure a student's knowledge of material, or is it invalid, actually measuring his literary skill or the state of the grader's digestion?

See [Accuracy](#)

Volume of Distribution:

The volume, in an organism, throughout which a drug appears to have been distributed; the volume into which a drug appears to have been dissolved after administration to an organism. Symbolized by V_d .

Suppose a drug has been completely absorbed from its site of application, has reached an equilibrium in its distribution among the several tissues of the body, and that no biotransformation or excretion of the drug has occurred. If one knew the mass (dose) of drug administered and the average concentration of the drug in the body, the apparent volume into which the drug had been dissolved could be determined from the relationship or definition: concentration = mass/volume. Since these idealized conditions are unobtainable in practice, the volume of distribution of a drug can only be approximated using experimental data.

With the assumption that the concentration of the drug in the plasma (or serum) reflects the average drug concentration in its whole volume of distribution, plasma concentration can be plotted against time after drug administration, and the resulting line can be extrapolated to yield a fictive concentration (C_0) “predicted” to have existed at the instant the drug was administered – further assuming instantaneous and complete administration, absorption, and distribution of the drug. Obviously, C_0

, is the value expected to have occurred at a time when mechanisms of biotransformation and excretion had no significant effect on the amount of drug in the body. Needless to say, it is assumed for proper interpretation of C_0

, that the drug as measured in the plasma is identical to the agent that was administered, and that the drug underwent no chemical alteration in the course of administration, absorption, or distribution.

When C_0 is divided into the mass of the total dose administered, the quotient

indicated the volume into which the drug appears to be dissolved. When C_0 is divided into dose expressed in terms of body weight (e.g., mg/kg), the quotient is dimensionless – since kilograms and liters are considered equivalent – and indicates the fraction of body weight into which the drug appears to be dissolved. The volumes, or fractions, can be readily compared with parts of body weight occupied by the various fluid compartments (e.g., intravascular, extracellular, intracellular, etc.), and the approximate locus of drug distribution may be inferable. A volume of distribution corresponding to more than about the volume of total body water is presumptive evidence that the drug is distributed nonuniformly throughout the body, and is concentrated at one or more sites, usually sites of drug storage, biotransformation or elimination, or at a site of drug application when a route of administration other than the intravenous one has been used. Obviously, legitimate and valid interpretation of calculated volume of distribution depends on the degree to which experimental facts are in concordance with the assumption given above. The idealized state is most closely approximated when the drug is given rapidly intravenously, and blood samples for chemical analysis of their drug content are taken at short intervals, beginning very soon after the time of drug administration.

Two more qualifications – first, special account must be taken mathematically, to yield validly interpretable volumes of distribution when binding of drug to plasma protein significantly restricts the mobility of drug molecules. Second, when the plot of plasma concentration against time gives evidence of a system involving two (or more) phases – i.e., two volumes into which drug tends to be distributed to different degrees at different times – special mathematical treatment of the data (more complicated than the treatment described above) is needed to permit calculation of the volumes of the several phases.

Cf. [Compartment\(s\)](#) , [Pharmacokinetics](#) , [Half-Life](#) , [V_d](#) .

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Zero-Order Kinetics:

Mechanisms of chemical reaction in which the reaction velocity is apparently independent of the concentration of all the reactants. Typically, in biological systems, one reactant (X) is present in a concentration greatly exceeding that of the other (Y), but is capable of undergoing change, while the concentration of Y, in contrast, does not undergo substantial change during the course of the reaction.

For example, consider the inactivation of a drug (X), present in the body in an overwhelming quantity, by an enzyme (Y) present in a limited concentration in cells and having a specific maximum capacity to inactivate X. A sufficiently high concentration of X would “saturate” Y and make the system operate at, effectively, its maximum velocity; the *amount* of X inactivated per unit time would be constant and would depend on the maximum velocity per mass of Y and the total amount of Y present in the body; modest changes in concentration of X would not detectably change the velocity of the system operating at virtually its maximum rate. (Recollect the shape of the velocity – substrate concentration curve.) The reaction velocity would be independent of the concentrations of both X and Y. Eventually, the concentration of X would decrease to the point that it did not saturate Y, and the inactivation would proceed according to first-order kinetics.

For a zero-order reaction, the plot of C (not \ln or \log C) against t yields a straight line: $C = C_0 - b_0 t$, in which the slope (b_0) is in units of concentration per unit time. The *amount* of change in concentration per unit time is constant; in the case of first-order kinetics, the *fractional* change in concentration per unit time is constant.

Following administration of a drug eliminated by zero-order kinetics, the linear plot of C against t can be used to infer C_0 and C and (if the dose is known) V_d , but no half-life ($t_{1/2}$) can be determined. The elegant properties of [multiple dose regimens](#) (q.v.) for drugs eliminated according to first-order kinetics do not obtain for drugs eliminated by zero-order kinetics: C_{max} for “zero-order drugs” does not approach $C_{ss,max}$ as an asymptote; for zero-order drugs, C_{max} increases progressively without limit with each dose, when equal doses are administered at equal intervals. Drugs that obey first-order kinetics with low doses may obey zero-order kinetics with large doses.

$t_{1/2}$
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Cf. [First-Order Kinetics](#) , [Half-Life](#)

Source: [Boston University](#)