Basic Pharmacokinetics for Pharmaceutical Products

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Quotation

A fool often fails because he thinks what is difficult is easy and a wise man because he thinks what is easy is difficult

John Churlton Collins (1848-1908)

Objectives

This presentation presents a concise understanding of basic concepts of pharmacokinetics, bioavailability, and bioequivalence for individuals who summarize or review information

The presentation does not require comprehension of derivation of mathematical equations

Basic Concepts

This presentation provides sufficient background to enable decisions on:

- **whether use of mathematical equations and compartmental analyses provides anything of value**
- **pertinent questions of pharmacokinetic reports**

Basic Pharmacokinetics for Pharmaceutical Products

Definitions and Brief Discussion of Pharmacokinetic Terms

Pharmacokinetics

Definition

"The study of the kinetics of the absorption, distribution, metabolism, and excretion of drugs in man and animals"

Editors, J Pharmacokin Biopharm 1973; 1 : 3

Pharmacodynamics

Definition

"The study of the kinetics of the pharmacologic, therapeutic, or toxic responses in man and animals"

Editors, J Pharmacokin Biopharm 1973; 1 : 3

Drug Entering Body

Drug Released from Dosage Form

↓ Release

Drug Absorbed

↓ Absorption

Drug Measured in Systemic Circulation

Drug Entering Body

- **Drug Released from Dosage Form**

  Example: from tablet (slow-release)

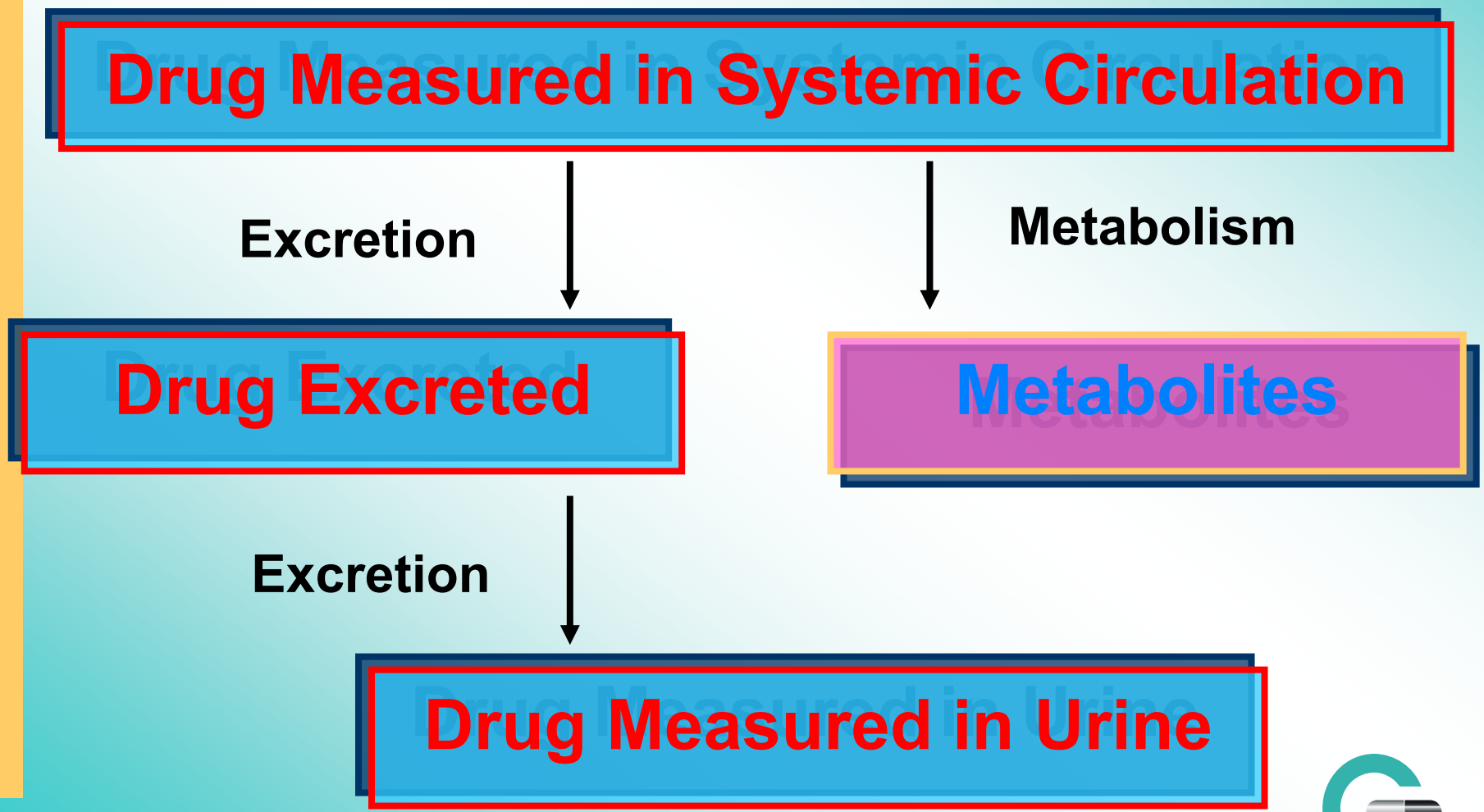
- **Drug Absorbed**

  Example: from stomach and small intestine

- **Drug Measured in Systemic Circulation**

  Example: measured from samples of blood or plasma collected at various times

Drug Exiting Body



Drug Exiting Body

- **Drug Excreted**

  Example: generally through kidneys

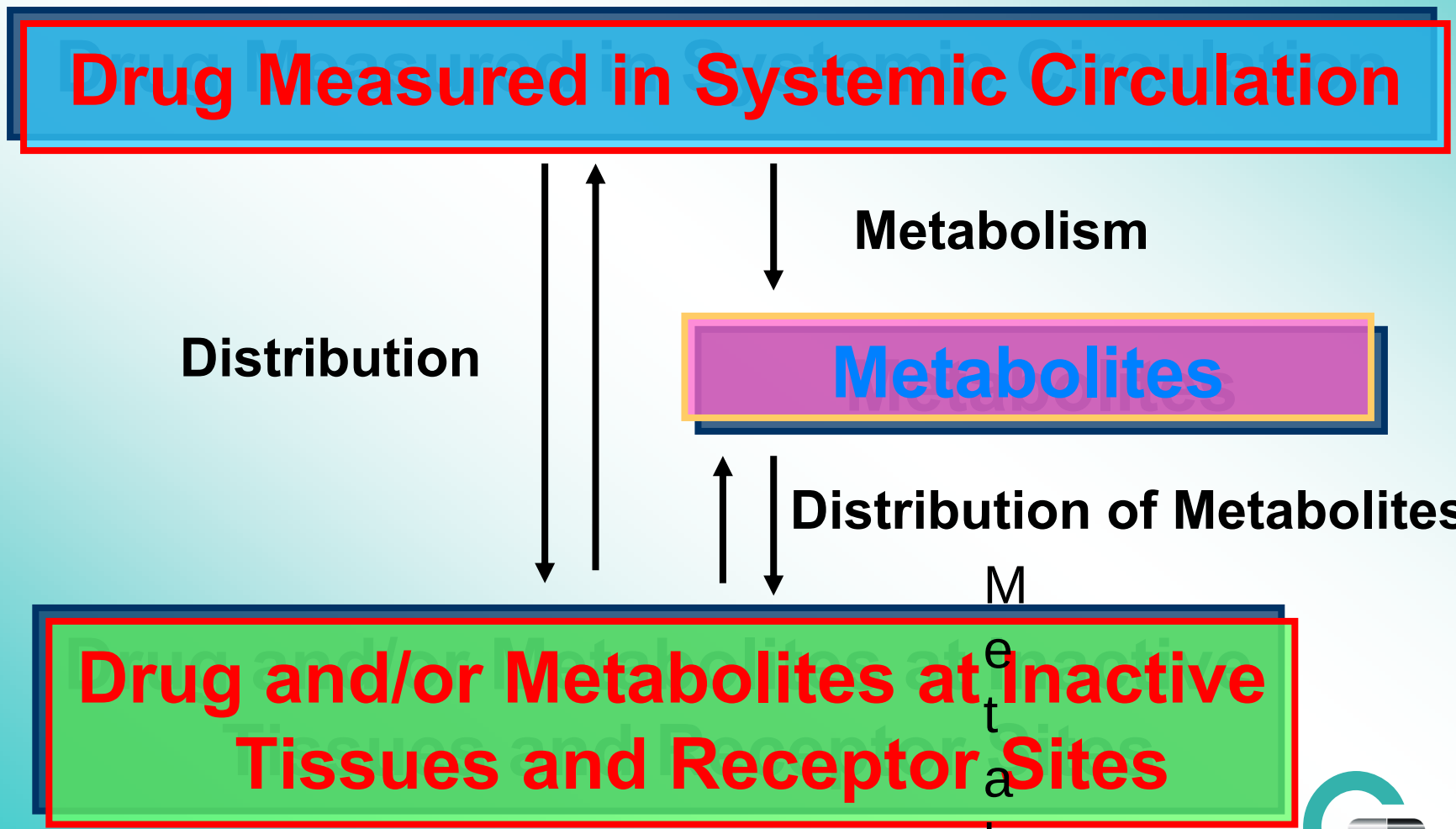
- **Drug Measured in Urine**

  Example: from all urine collected over a time period

- **Metabolites**

  Example: often by liver, then to kidneys
  rarely measured because inactive

Active Drug Substance and/or Metabolites



Active Drug Substance

- **Drug at Receptor Sites**

  Example: anesthetic in nerves

  not measurable directly

  pharmacodynamic response

- **Drug at Inactive Tissues**

  Metabolites at Receptor Sites

  Metabolites at Inactive Tissues

  Example: rarely measured because of inactivity

Active Drug Substance

- **Note that the drug measured in the systemic circulation is always mathematically in balance with the drug at the receptor sites**
- **When one increases (decreases), the other increases (decreases)**

Terms Used for Drug

- **R** Release (from dosage form)
- **A** Absorption
- **D** Distribution
- **M** Metabolism
- **E** Excretion

> Elimination

Distribution + Elimination = Disposition

Pharmacokinetic Definition Restated

After drugs are released for absorption, the study of the kinetics of the absorption and disposition of drugs in man and animals

or

Kinetics of drugs entering and exiting the body

Linear Pharmacokinetics

For most drugs within the therapeutic range, the pharmacokinetic properties are independent of:

amount of dose administered

number of doses administered

This is linear pharmacokinetics

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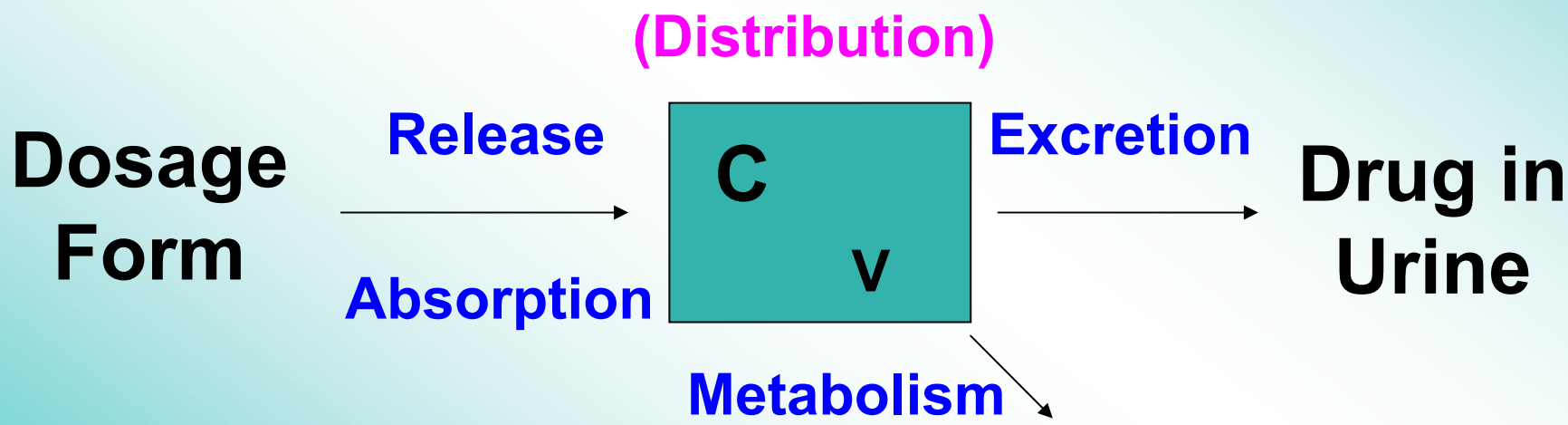
Brief Discussion of Mathematical Equations

Compartmental Analyses

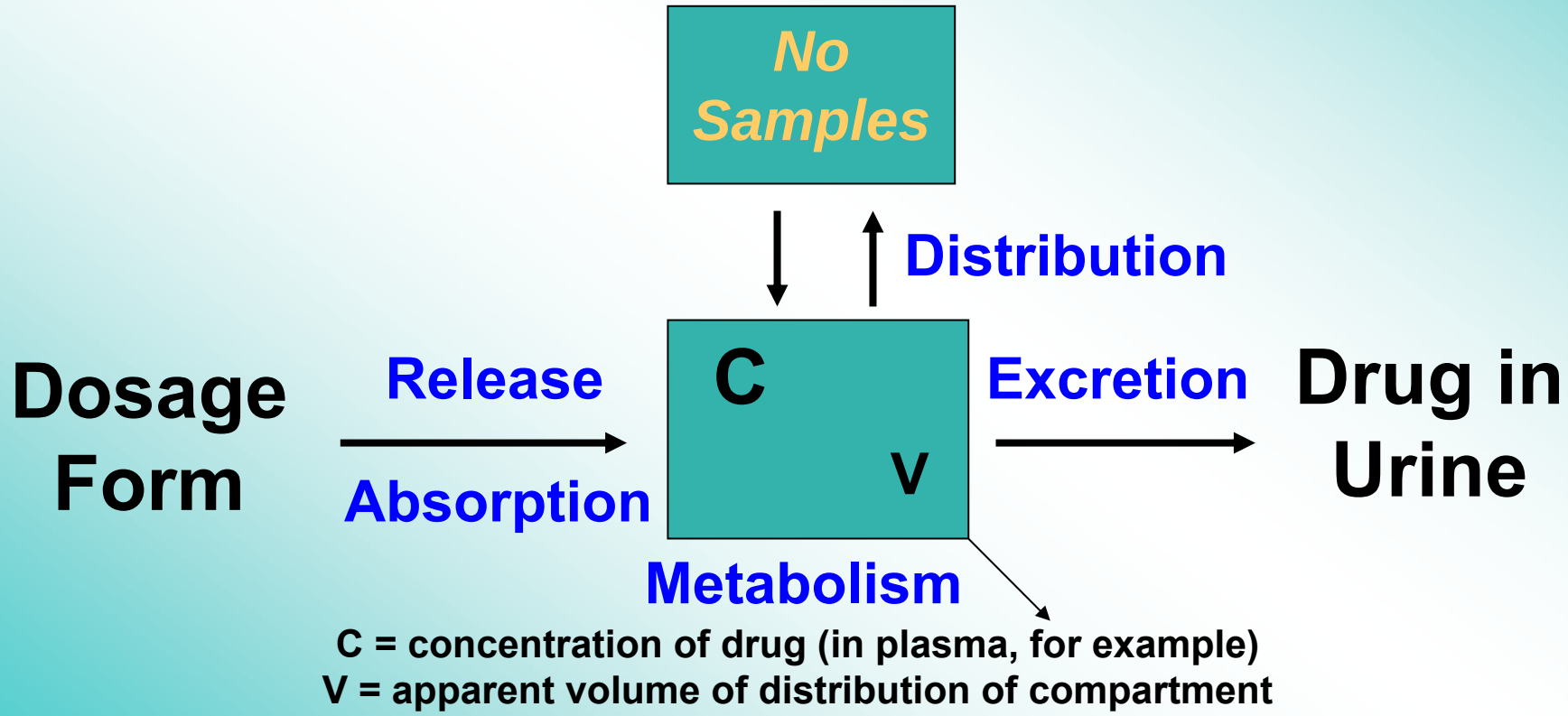
One Compartment Disposition Model



C = concentration of drug (in plasma, for example)
V = apparent volume of distribution of compartment

Compartmental Analyses

Two Compartment Disposition Model
(most representative of three possibilities)



C = concentration of drug (in plasma, for example)
V = apparent volume of distribution of compartment

First-Order Processes

Most processes resulting in movement of drug from one area to another are:

shown to be

or

approximated at low concentrations by

first-order processes and equations

First-Order Equations

The rate of change is proportional to the amount to be changed at that time

Mathematically:

$$\frac{dX}{dt} = kX$$

where k is the proportionality constant (units of reciprocal time)

First-Order Equations

The rate of loss of drug is proportional to the amount of drug still to be lost at that time

Mathematically:

$$-\frac{dX}{dt} = \beta X$$

where β is the first-order rate constant

First-Order Rate Constants

- The first-order rate constant (β) is the algebraic sum of pharmacokinetic rate constants for one or more processes
- β may be an excretion rate constant only
  - or an elimination rate constant
  - or a disposition rate constant
- As nothing is certain, β is normally referred to as the terminal rate constant

Terminal Half-Life ($t_{1/2}$)

Definition

"Time required for the concentration of drug in the systemic circulation to be halved in the terminal phase"

Mathematically:

$$t_{1/2} = \ln(2)/\beta = 0.693/\beta$$

Model Independent Analyses

"The principal purpose of pharmacokinetic analysis is to gain information regarding

- (systemic) clearance, renal clearance
- volume of distribution
- metabolic disposition
- accumulation characteristics on multiple dosing
- absorption of a drug

Model independent methods are now available to attain these ends"

Gibaldi and Perrier, Pharmacokinetics, 1982, p475

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Graphical plots of data used in pharmacokinetics

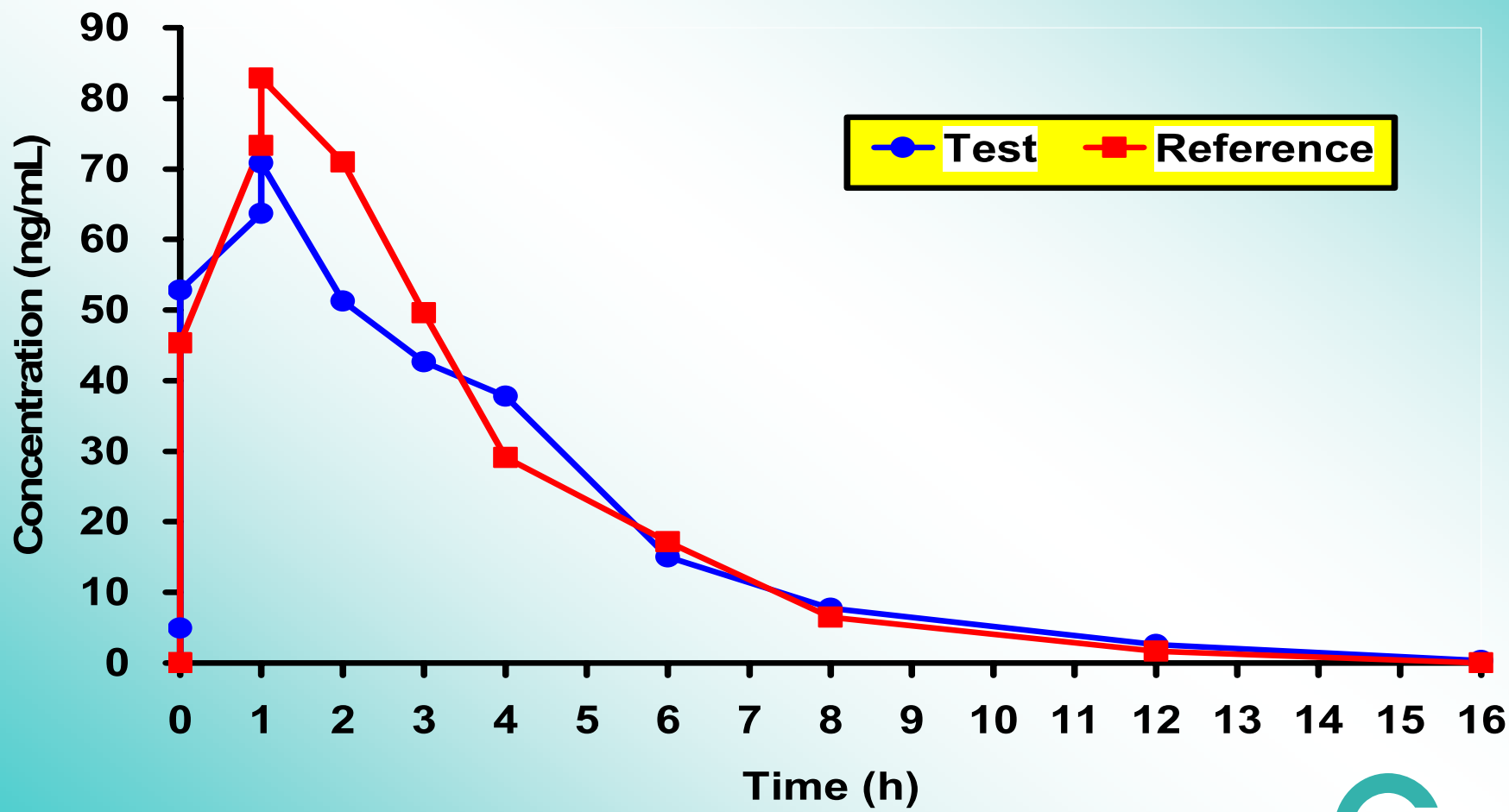
Graphical Plots

An example illustrating data from two tablets with uncomplicated characteristics is shown in two different ways

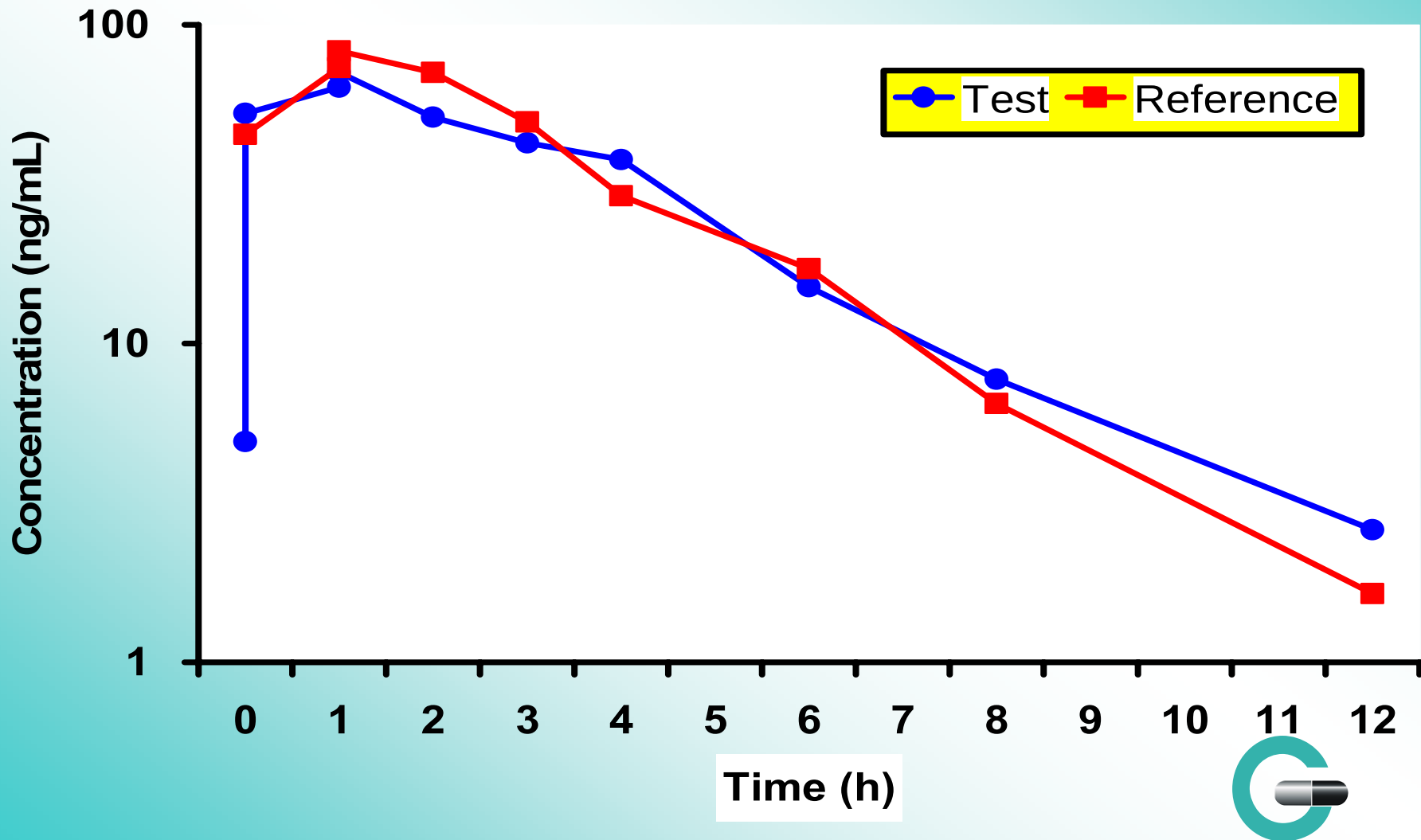
Tablets are designated as “test” and “reference” dosage forms

Dosage forms will be compared later for bioequivalence

Arithmetic Plot



Logarithmic Plot



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Bioavailability

Definition

This is taken directly from:

Guidance for Industry

“Conduct and Analysis of Bioavailability and Bioequivalence Studies -

Part A : Oral Dosage Formulations Used for Systemic Effects”

Section 9 (Glossary of Terms)

Published by Health Products and Food Branch

Guidance Document 1992

Bioavailability

Definition

“The rate and extent of absorption of a drug into the systemic circulation”

Measurement of Rate of Absorption

Despite what may be said about the importance of the rate of absorption, it is often considered (maybe unfortunately) to be a secondary characteristic to extent of absorption

Measurement of Rate of Absorption

Graphical examples of the measurement of rate of absorption will be shown later in the bioequivalence section

Measurement of Rate of Absorption

- **Definition**

  The maximum concentration (C_{max}) and time when C_{max} occurs (t_{max})

- **Mathematically**

  Linear pharmacokinetic equations (may be complex)

Measurement of Rate of Absorption

- **Technically**

  C_{max} and t_{max} are generally measured by direct observation of values as close to the maximum as possible

Measurement of Rate of Absorption

Measurement of C_{max} and t_{max} is always an estimate of true values

How close the measured estimate is to the true values depends on:

number of observed data points

accuracy of observed data

Control by appropriate study design

Measurement of Extent of Absorption

- **Definition**

  The area under the blood (or plasma, or serum) concentration against time curve is known as AUC_I

- **Mathematically**

  AUC_I is the integral of the concentration between time zero and infinity

  (for a single-dose of a drug product)

Measurement of Extent of Absorption

- **Technically**

  AUC_I is calculated from observed data at available time points by

  "Linear trapezoidal rule" calculated between available time points to the last quantifiable concentration (C_T)

  plus

  calculated area (C_T/ß) from C_T to infinity,

  where ß is the terminal rate constant constant

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Bioequivalence

Definitions

These are taken directly from:

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Part A : Oral Dosage Formulations Used for Systemic Effects”

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Bioequivalence

Definition

"A high degree of similarity in the bioavailabilities of two pharmaceutical products (of the same galenic form) from the same molar dose that are unlikely to produce clinically relevant differences in therapeutic effects, or adverse effects, or both"

Bioequivalent Products

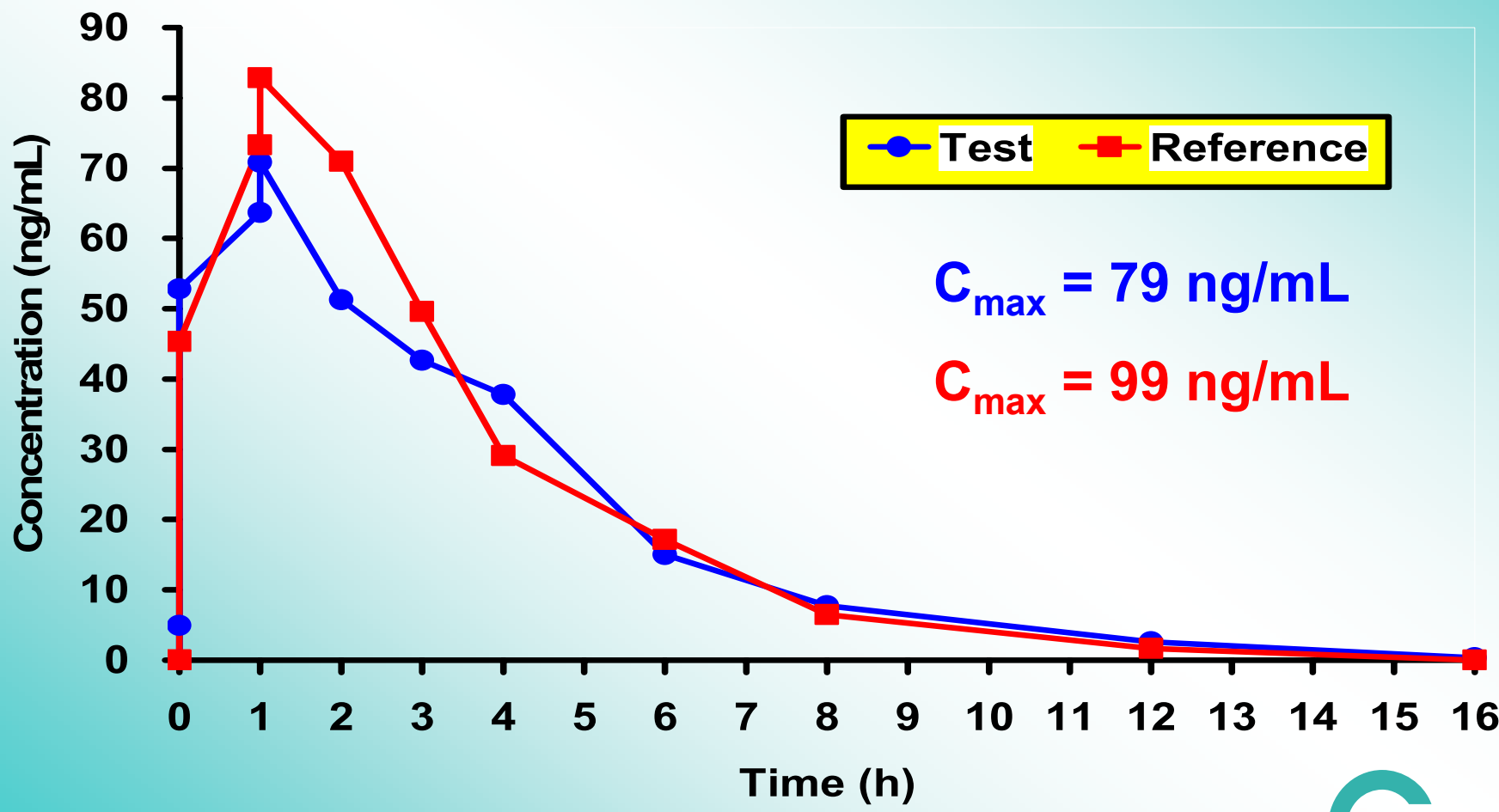
Definition

"Test and reference products containing an identical drug or drugs, after comparison in an appropriate bioavailability study, are found to meet the standards for rate and extent of absorption specified in the guidelines"

Discussions on Bioequivalence

- Discussions on bioequivalence can be complex (for example, statistically)
- Complexities are vital and welcomed
- Also important to remind individuals of basic concepts
- Probably most drug products have uncomplicated characteristics

Maximum Concentration (C_{max})



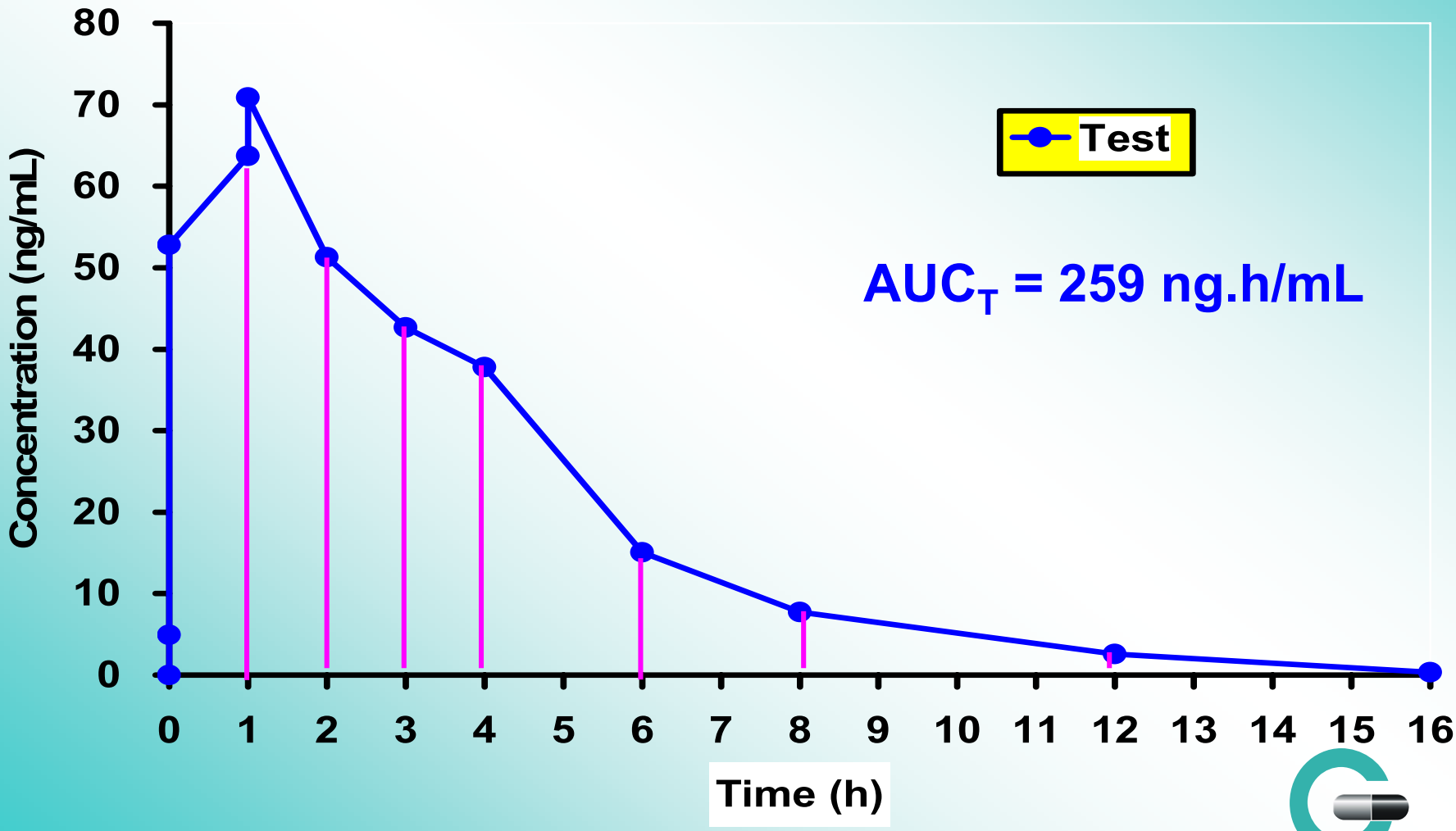
Ratio of C_{max}

C_{max} /C_{max} = 79/99 = 0.80

C_{max} ratio is 80%

This C_{max} ratio complies with standards for bioequivalence

Linear Trapezoidal Rule



Ratio of AUC_T

AUC_T/AUC_T = 259/281 = 0.922

AUC_T ratio is 92.2%

This AUC_T ratio complies with standards for bioequivalence

Ratio of AUC_I

Standards for bioequivalence do not require the comparison of areas under the curve to infinity (AUC_I) to calculate ratio of AUC_I

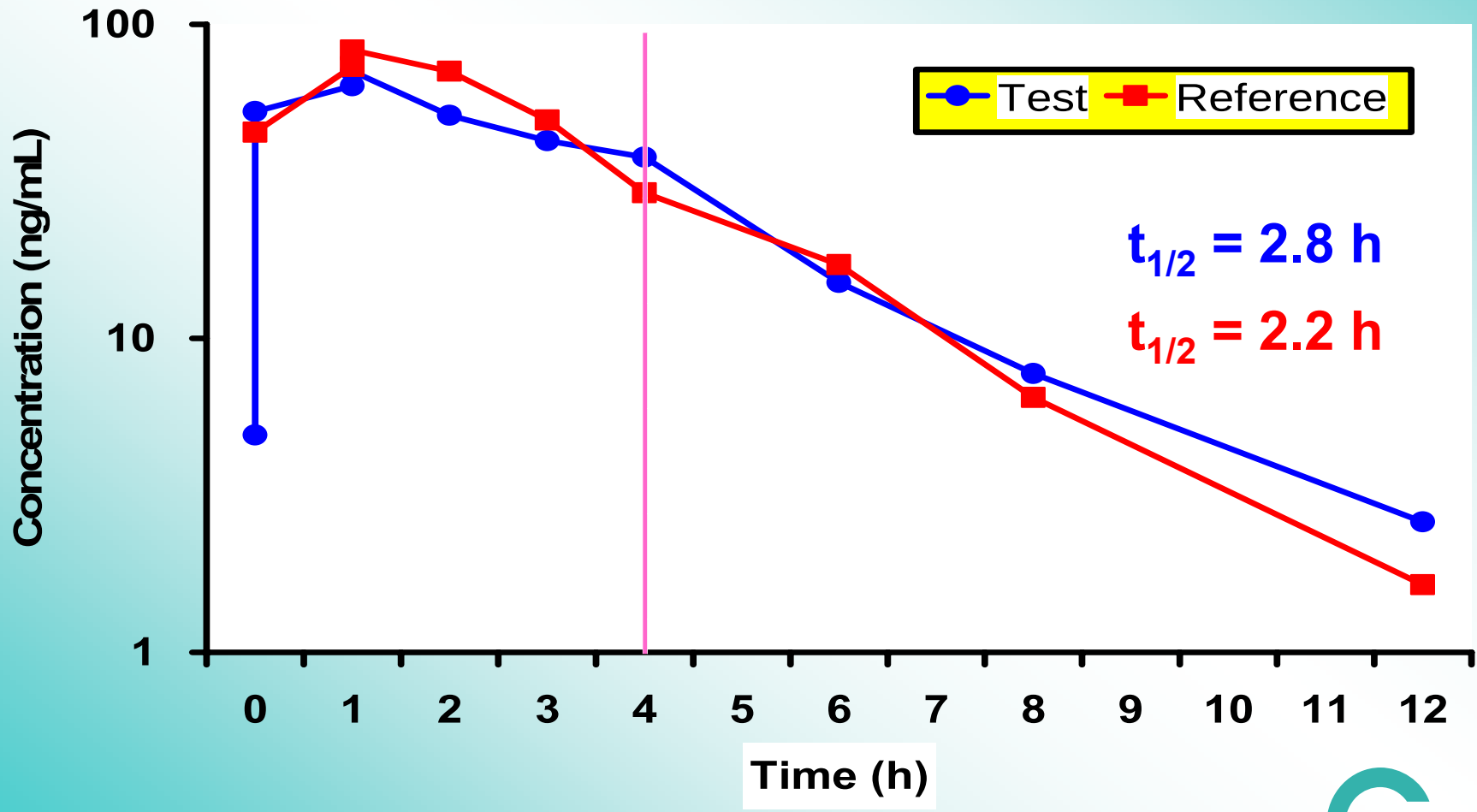
AUC_I may be calculated using the AUC to the last quantifiable concentration (AUC_T) plus a calculation involving the last quantifiable concentration (C_T) and terminal half-life ($t_{1/2}$)

Determination of $t_{1/2}$

Terminal half-life ($t_{1/2}$) may be determined from logarithmic plots of the data

Usually, at least three points on a linear line are required

Terminal Half-Life ($t_{1/2}$)



Measurement of Extent of Absorption

Measurement of AUC_I is always an estimate of true AUC_I

How close the measured estimate is to the true value depends on

- **number of observed data points**
- **accuracy of observed data**

Control by appropriate study design

Study Subjects

Drug products "with uncomplicated characteristics can usually be tested in normal, healthy volunteers"

"The minimum number of subjects is 12, but a larger number is often required"

Part B, Section 6.3 (Number of Subjects), 2003

Assumptions of Bioequivalence

- **Intensity of a pharmacologic response is somehow related to concentration of drug in blood**
- **The alternative is to measure the clinical intensity of the response (known as pharmacodynamics)**

Assumptions of Bioequivalence

- Intensity of a pharmacologic response is **not** directly related to concentration in blood

Therefore

- A doubling of intensity does **not** occur with a doubling of concentration

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Assumptions and challenges of bioavailability and bioequivalence measurements

Assumption One

- **Intensity of pharmacologic response is roughly related to log of concentration in blood**

  (between 20-80% of maximum response)

Therefore

- **A rough doubling of intensity requires approximately a ten-fold increase in concentration**

Assumption Two

- **Concentration in blood is directly related to concentration at site of action (possibly at receptors)**

Therefore

- **Bioavailability and bioequivalence relate to therapeutic effect**

Challenges

While it will always be important to remind individuals of basic concepts of pharmacokinetics, the practical outcomes of discussions on "surrounding" issues should never be discounted

Challenges

Some “surrounding” issues

- oral modified-release dosage forms (MRDF)
- drugs with narrow therapeutic range
- drugs exhibiting non-linear pharmacokinetics
- highly variable drugs and drug products
- requirements for studies with food effects
- drugs whose therapeutic effect is not mediated through systemic absorption
- correlation between absorption (*in vivo*) and dissolution (*in vitro*)

Quotation

Crafty men condemn studies,
simple men admire them,
and wise men use them

Francis Bacon (1561-1626)
English Philosopher, Politician,
and Essayist

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Any questions?