3. Bioavailability and Absorption

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ABSORPTION

Although this term is widely used and seemingly unambiguous, there is a risk of misunderstanding, mainly due to the lack of a clear definition by regulatory authorities in Brazil (ANVISA) and abroad (Food and Drug Administration/USA; EEC; Canada), even when they use the term in resolutions addressing bioavailability studies (see below). Curiously, most pharmacology textbooks also fail to define the absorption process clearly. Therefore, it seems useful to present here a consensual definition based on the sources consulted (e.g., *Principles of Pharmacology: Basic Concepts & Clinical Applications*, eds. Munson, P.L., Mueller, R.A., & Breese, G.R., Chapman & Hall):
"*Absorption involves the passage of drug molecules across barrier(s) between the site of administration and the vascular compartment*". It is essential to emphasize that the vascular compartment to be considered (which is not always clear and is a matter of controversy) is that of the **local circulation** (e.g., the mesenteric veins for intestinal absorption), not the systemic circulation. This precision is crucial to avoid confusion between the concepts of absorption and bioavailability (see the propranolol example below). It should be noted that there is controversy in the literature, as several authors consider the term "absorption" to reflect the arrival of the drug into the systemic circulation ("systemic absorption").

BIOAVAILABILITY

Although this concept is extremely important in drug quality control, among other purposes, to ensure bioequivalence between generic and similar medicines relative to reference products (ANVISA Resolution RDC No. 60, 10/10/2014), there is a large number of erroneous or at least ambiguous definitions in the specialized literature, both in textbooks and in regulatory agency resolutions.

Before drawing attention to some conceptual errors found in the literature, we present a definition that we regard as one of the best because it is simple, objective, comprehensive, and up to date: "Bioavailability measures the rate and extent to which a drug reaches the systemic circulation" (Canada - *Guidance for Industry: Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part B: Oral Modified Release Formulations*). A similar definition is found in several specialized textbooks (e.g., *Introduction to Pharmacokinetics and Pharmacodynamics*, Tozer & Rowland; *Applied Biopharmaceutics and Pharmacokinetics*, Shargel & Yu; *Textbook of Clinical Pharmacology and Therapeutics*, Grahame-Smith & Aronson).

Most common conceptual errors

1. Definitions presented by the American (FDA) and European (EMEA) regulatory agencies refer to drug availability at the **site of action**, which is impossible to measure in practice and renders the definition sterile and incoherent with respect to

the parameters actually used to quantify bioavailability (AUC, C_{max}, and T_{max}). Due to the influence of the FDA and historical reasons, this admittedly confusing definition is repeated in several textbooks.

2. Although less common, another conceptual error is found in Brazilian legislation, which uses the term **"absorption"** (see definition above) instead of **"absorption and systemic availability".** Indeed, ANVISA Resolution RDC No. 60 (10/10/2014) states that bioavailability "indicates the rate and extent of absorption of an active ingredient from a pharmaceutical dosage form, based on its concentration-time curve in the systemic circulation or its urinary excretion, measured on the basis of peak exposure and the magnitude or partial exposure." This terminological "error" (possibly due to the use of the term "absorption" in the sense of "systemic absorption") can generate significant confusion. For example, a drug that undergoes an extensive hepatic first-pass effect (such as propranolol) has a low bioavailability factor (a parameter that measures the **extent** of bioavailability) despite being well absorbed. In fact, propranolol readily crosses the intestinal mucosal barrier and reaches the local circulation but is extensively metabolized in the liver before reaching the systemic circulation, resulting in low systemic availability of the unchanged (non-metabolized) drug.

3. A third serious, and unfortunately very common, conceptual error is the confusion between **bioavailability** and the **bioavailability factor (F)**, a parameter that measures only the **extent** of bioavailability (and not its **rate**). Unfortunately, this error appears in three pharmacology textbooks widely used by our undergraduate students, beginning with the "pharmacologist's bible": *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (Brunton et al., 12th ed.), *Basic and Clinical Pharmacology* (Katzung et al., 12th ed.), and *Rang & Dale's Pharmacology* (Rang et al., 7th ed.).