1. INTRODUCTION

- The U.S. Food and Drug Administration (FDA) define bioavailability as "the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action". Because in practice it is rare that drug concentrations can be determined at the site of action (e.g., at a receptor site), bioavailability is more commonly defined as "the rate and extent that the active drug is absorbed from a dosage form and becomes available in the systemic circulation."

- Usually bioavailability refers to the absorption of a drug from the gastrointestinal tract following oral administration of a dosage form. The dosage form may be any type of product, including a solution, suspension, tablet, capsule, powder, or elixir. Bioavailability can also refer to other types of dosage form, such as intramuscular injections, ointments and other topical preparations, transdermal patches, and implants, which also require an absorption step prior to reaching the systemic circulation. The only route of drug administration that should always result in a bioavailability of 100% is an intravenous injection, in which the amount of drug reaching the systemic circulation is equal to the total administered dose.

- Each drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.’ In some instance, two pharmaceutical alternatives exhibit markedly different bioavailability, for example, a rapidly absorbed elixir vs. a more slowly absorbed capsule. In other cases, two different dosage forms (e.g., a tablet and a capsule) may or may not exhibit very similar bioavailability. While the mechanisms by which a formulation affects bioavailability and bioequivalence have been extensively studied in drugs, formulation factors that influence bioavailability and bioequivalence in nutritional supplements are largely unknown.

- With the growth in Bioanalytical capacity in the mid-1950s, available data indicated that compromised product performance, as expressed in BA measures, might be more readily detected. These data led to national and international efforts to define BA and BE and to determine appropriate procedures for their assessment. In the United States, the Congressional Office of Technology Assessment issued a key report that recommended the importance of BA and BE studies and indicated further steps to ensure that this information became part of the drug development and regulatory processes. Many recommendations of this report were subsequently adopted by FDA and were published in 1977 as regulations entitled Part 320—Bioavailability and Bioequivalence Requirements, which contain subparts A (General Provisions) and B (Procedures for Determining the Bioavailability or Bio-equivalence of Drug Products).

- The focus of these regulations was on BA and pharmacokinetic information needed for submission in a New Drug Application (NDA) and to some extent on evidence of BE (relative BA). With passage of the 1984 Drug Price Competition and Patent Term Restoration amendments to the Food, Drug and Cosmetic
Act, BE took on added importance for generic drugs. As defined in implementing regulations, an applicant submitting an Abbreviated New Drug Application (ANDA) under Section 505(j) of the Act (excepting Suitability Petitions submitted under 505(j)(2)(c) of the Act) must demonstrate both pharmaceutical equivalence (PE) and BE between the generic product and listed innovator reference drug product. With acceptance of this documentation by FDA, along with other information, the generic product is deemed bio-equivalent, therapeutically equivalent, and interchangeable with the listed reference drug product.

- The fundamental tenet underpinning the logic is similar to that described later for generic product testing. First, it is assumed that the time-dependent drug concentrations in blood from an early formulation are intimately linked with the effects. Second, if a new formulation exhibits the same time-dependent drug concentrations (rate and extent of drug absorption), the new formulation is deemed "bioequivalent" and, by inference, has the same safety and efficacy.

- Topiramate is a sulfamate-substituted monosaccharide. Topiramate tablets are available as 25 mg tablets for oral administration.

- Topiramate is a white to off-white powder. Topiramate is most soluble in alkaline solutions containing sodium hydroxide or sodium phosphate and having a pH of 9 to 10. It is freely soluble in acetone, chloroform, dimethyl sulfoxide, and ethanol. The solubility in water is 9.8 mg/mL. Its saturated solution has a pH of 6.3. Topiramate has the molecular formula C12H21NO8S and a molecular weight of 339.37. Topiramate is designated chemically as 2,3:4,5,-Di-O-isopropylidene-β-D-fructopyranose sulfamate and has the following structural formula:

1. Topiramate 25 mg (brand name Topamax) is a medication originally developed for the treatment of migraine. Presently, Topiramate is widely used to relieve pain, especially neuropathic pain. Topiramate is well tolerated in most patients, has a relatively mild side-effect profile, and passes through the body un metabolized.