It is also possible to get a waiver for a higher strength based on the similarity of dissolution profiles provided the following conditions are met: (a) clinical safety and/or efficacy data on the proposed dose and the need for the higher strength, (b) linearity of the pharmacokinetics over the therapeutic dose range, and (c) the higher strength is compositionally proportionally similar to the lower strength that has bioavailability data.

The guidance [3] defines "proportionally similar" in the following ways:

- All active and inactive ingredients are in exactly the same proportion between different strengths (e.g., a tablet of 50 mg strength has all the inactive ingredients, exactly half that of a tablet of 100 mg strength and twice that of a tablet of 25 mg strength).
- Active and inactive ingredients are not in exactly the same proportion between different strengths as stated above, but the ratios of inactive ingredients to total weight of the dosage form are within the limits defined by the SUPAC-IR and SUPAC-MR guidances up to and including Level II.
- For high-potency drug substances, where the amount of the active drug substance in the dosage form is relatively low, the total weight of the dosage form remains nearly the same for all strengths (within ±10% of the total weight of the strength on which a bio-study was performed), the same inactive ingredients are used for all strengths, and the change in any strength is obtained by altering the amount of the active ingredients and one or more of the inactive ingredients. The changes in the inactive ingredients are within the limits defined by the SUPAC-IR and SUPAC-MR guidances up to and including Level II.

Biopharmaceutics Classification System

The Biopharmaceutics Classification System (BCS) categorizes drug substances into four classes: High Solubility/High Permeability (Class I), Low Solubility/High Permeability (Class II), High Solubility/Low Permeability (Class III), and Low Solubility/Low Permeability (Class IV). A drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1 to 7.5. A drug is considered highly permeable when extent of absorption (fraction of dose absorbed, not systemic bioavailability) in humans is determined to be greater than 90% of an administered dose based on a mass balance determination or in comparison with an intravenous reference dose. An IR drug product is also characterized as a "rapidly dissolving" product when not less than 85% of the labeled amount of the drug substance dissolves within 30 min using USP Apparatus I at 100 rpm or USP Apparatus II at 50 rpm in a volume of 900 mL or less of each of the following media: (a) acidic media, such as 0.1 N HCl or USP simulated gastric fluid without enzymes; (b) a pH 4.5 buffer; and (c) a pH 6.8 buffer or USP simulated intestinal fluid without enzymes. If the drug product meets the BCS criteria for Class I, meaning that the drug substance is highly soluble and highly permeable, and the drug product is rapidly dissolving, it is quite likely that the rate-limiting step for drug absorption is gastric emptying. In this instance, the requirements for in vivo bioavailability or bioequivalence