The BCS approach outlined in this guidance can be used to justify biowaivers for highly soluble and highly permeable drug substances (i.e., class 1) as well as highly soluble and low permeable drug substances (i.e., class 3) in IR solid oral dosage forms that exhibit rapid or very rapid in vitro dissolution using the recommended test methods. The recommended methods for determining solubility, permeability, and in vitro dissolution are discussed below.

Solubility

The solubility class boundary is based on the highest strength of an IR product that is the subject of a biowaiver request. A drug substance is considered *highly soluble* when the highest strength is soluble in 250 mL or less of aqueous media within the pH range of 1–6.8 at 37°C ± 1°C. The volume estimate of 250 mL is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with an 8-fluid ounce glass of water.

Permeability

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans, and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, other systems capable of predicting the extent of drug absorption in humans can be used (e.g., in situ animal, in vitro epithelial cell culture methods). A drug substance is considered to be *highly permeable* when the systemic BA or the extent of absorption in humans is determined to be 85% or more of an administered dose based on a mass balance determination (along with evidence showing stability of the drug in the GI tract) or in comparison to an intravenous reference dose.

Dissolution[7]

An IR drug product is considered *rapidly dissolving* when a mean of 85% or more of the labeled amount of the drug substance dissolves within 30 minutes, using *United States Pharmacopeia* (USP) Apparatus 1 at 100 rpm or Apparatus 2 at 50 rpm (or at 75 rpm when appropriately justified (see section III.C.) in a volume of 500 mL or less (or 900 mL when appropriately justified) in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

An IR product is considered *very rapidly dissolving* when a mean of 85% or more of the labeled amount of the drug substance dissolves within 15 minutes, using the above-mentioned conditions.

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[7] See also the draft guidance for industry *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*. When final, this guidance will represent the FDA's current thinking on this topic.