APPARATUS AND DISSOLUTION CONDITIONS

For immediate-release products, the most commonly used dissolution apparatus are the USP Apparatus 1 (basket) and USP Apparatus 2 (paddle). Usually, the Apparatus 1 is operated at 100 rpm and the Apparatus 2 at 50 rpm. However, it was suggested that the Apparatus 2 is operated at 75 rpm to reduce coning (Dressman 2005). By itself, the rotation speed would not be expected to affect the extent of dissolution of a low solubility drug because solubility is a thermodynamic property. However, once the solubility is addressed via selection of pH and surfactant, selection of the appropriate rotation speed raises similar issues to those found for higher solubility drugs. The rotation speed can be set on the basis of matching *in vivo* hydrodynamics, selecting the most sensitive speed, or selecting the speed that minimizes variability in the test method. In a recent article (Mirza et al. 2005), the effect of hydrodynamics on both low solubility and high solubility drugs were evaluated, and the low solubility drug was slightly more sensitive to perturbations. In this article, the low solubility drug was still able to dissolve greater than 90% in 45 min in a media of 1000 mL borate buffer, pH 8.0, containing 0.1% Tween® 80.

Other USP apparatus, the reciprocating cylinder (USP Apparatus 3) and the flow-through cell (USP Apparatus 4), are not commonly used for release testing but may be valuable for use in a biorelevant dissolution method during product development. The Apparatus 3 is believed to have hydrodynamic flow patterns that are more representative to those found *in vivo* (Yu et al. 2002). The flow-through cell allows removal of dissolved drug that would saturate media in other closed apparatus and thus gets much closer to the *in vivo* situation that a truly low solubility drug encounters.

ACCEPTANCE LIMIT

After dissolution conditions are identified for a dissolution test, the dissolution specification is not complete until an acceptance limit is set. Three categories of dissolution test acceptance limits for immediate-release drug products are described in the 1997 FDA Guidances for Industry for immediate-release (Food and Drug Administration CDER 1997) and sustained-release drug products (FDA Center for Drug Evaluation and Research 1997).

- *Single-point specifications*: As a routine quality control test (for highly soluble and rapidly dissolving drug products).
- *Two-point specifications*: For slowly dissolving or poorly water-soluble drugs (BCS Class II), a two-point dissolution specification, one at 15 min to include a dissolution range (a dissolution window) and the other at a later point (30, 45, or 60 min) to ensure 85% dissolution, is recommended to characterize the quality of the product.
- *Profile comparison.*

Although the FDA guidance for IR dissolution (Food and Drug Administration CDER 1997) suggests that a two-point limit be used for low solubility drugs, in practice almost all low solubility drugs in IR formulations have a single-point acceptance limit.

For regulatory approvals of new drug applications (NDAs)/abbreviated new drug applications (ANDAs) for solid oral dosage forms, sponsors are required to develop appropriate *in vitro* dissolution testing. For NDAs, the dissolution specifications are currently based on acceptable clinical, pivotal bioavailability, and/or bioequivalence batches. For ANDAs, the dissolution specifications are generally the same as that of the reference-listed drug (RLD). The specifications are then confirmed by testing the dissolution performance of the generic drug product from an acceptable bioequivalence study batch(es). If the dissolution of the generic product is substantially different from that of the RLD but the product is bioequivalent in an *in vivo* study, a different dissolution specification for the generic product may be set (Food and Drug Administration CDER 1997).