18.5.1 SUPAC-SS

In May 1997, the FDA released a guidance for industry entitled "SUPAC-SS—Nonsterile Semisolid Dosage Forms—Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation" (1). The guidance relies on IVR testing to assure product sameness between pre-change (approved, reference) product and post-change (SUPAC-related changes, test) product. Release rates are considered similar when the ratio of the median release rate for the post-change (test) product over the median release rate for the pre-change (reference) product is within the 90% confidence interval limits of 75% to 133.33%. The product performance IVR test is used to assess product sameness for the product after SUPAC. The release rate is regarded as a "final quality control" test that can signal possible inequivalence in performance, thus comprising in the aggregate a number of physicochemical tests that might be performed individually.

18.5.2 Waivers for Lower Strength

For solid oral dosage forms, biowaivers for generic products are generally granted in situations where the formulations of lower-strength product(s) are proportionately similar and the dissolution profile is also similar [21 CFR 320.22 (d) (2)]. Using these same principles, bioequivalence waivers for lower strengths of topical dermatological drug products might also be granted based on IVR rate measurements. To request a biowaiver for lower strength, the product must meet the following criteria: Formulations of the two strengths should differ only in the concentration of the active ingredient and equivalent amount of the diluent. No differences should exist in manufacturing process and equipment between the two strengths. For a generic application, that is, an abbreviated new drug application (ANDA) the reference listed drug (RLD) should be marketed at both higher and lower strengths. In vitro drug release rate studies should be measured under the same test conditions for all strengths of both the test and RLD products. The IVR rate ratio of the two strengths of reference product and the two strengths of the test product should be similar.

18.5.3 Regulatory Application of In Vitro Drug Release

Another important application of IVR testing is the biowaiver for generic drug products. Recently, the FDA released several product-specific draft guidelines for topical drug products that utilize microstructure determination and IVR as a measure of bioequivalence, for example, guidance for acyclovir ointment 5% (5) and for cyclosporine ophthalmic emulsion (6). These developments may result in the use of IVR tests as a routine product performance test for semisolid dosage forms as the dissolution test is for oral dosage forms and may also be used for biowaiver under certain conditions.

18.5.4 Topical Drug Classification System

The Topical Drug Classification System (TCS) is a science-based approach to simplifying the regulatory pathway for topical drugs (7). TCS classification is similar to the well-established BCS. TCS considers the qualitative (Q1) and quantitative (Q2) composition of inactive ingredients between the test (generic) product and reference (brand name) product and the microstructure arrangement with rheological properties (Q3) of topical semisolid products. The IVR reflects the combined effects of several physicochemical characteristics, particle or droplet size, viscosity, the microstructure arrangement of the matter (Q3), and the state of aggregation of the dosage form (1). Based on composition (Q1 and Q2) and IVR similarity, the topical drug products are classified as TCS class 1, 2, 3, or 4. Under the proposed classification, topical drug products under TCS class 1 and TCS class 3 are eligible for biowaiver; topical drug products under TCS class 2 and TCS class 4 are not eligible for biowaiver and will require appropriate in vivo bioequivalence (BE) studies for drug