copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guidance and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the guidance follows:

Immediate Release Solid Oral Dosage Forms; Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing; In Vivo Bioequivalence Documentation; Guidance

### I. Purpose of Guidance

This guidance provides recommendations to sponsors of new drug applications (NDA's), abbreviated new drug applications (ANDA's), and abbreviated antibiotic applications (AADA's) who intend, during the postapproval period, to change: (1) The components or composition; (2) the site of manufacture; (3) the scale-up/scale-down of manufacture; and/or (4) the manufacturing (process and equipment) of an immediate release oral dosage formulation.

This guidance is the result of: (1) A workshop on the scale-up of immediate release drug products conducted by the American Association of Pharmaceutical Scientists in conjunction with the United States Pharmacopoeial Convention and the Food and Drug Administration (FDA); (2) research conducted by the University of Maryland at Baltimore on the chemistry, manufacturing, and controls of immediate release drug products under the FDA/ University of Maryland Manufacturing Research Contract; (3) the drug categorization research conducted at the University of Michigan and the University of Uppsala on the permeability of drug substances; and (4) the Scale-Up and Post Approval Changes (SUPAC) Task Force which was established by the Center for Drug Evaluation and Research (CDER) Chemistry, Manufacturing, and Controls Coordinating Committee to develop guidance on scale-up and other postapproval changes.

The guidance defines: (1) Levels of change; (2) recommended chemistry, manufacturing, and controls tests for each level of change; (3) in vitro dissolution tests and/or in vivo bioequivalence tests for each level of change; and (4) documentation that should support the change. For those changes filed in a "changes being effected supplement" (§ 314.70(c) (21 CFR 314.70(c))), FDA may, after a review of the supplemental information, decide that the changes are not approvable. This guidance thus sets forth application information that should be provided to CDER to assure continuing product quality and performance characteristics of an immediate release solid oral dose formulation for specified postapproval changes. This guidance does not comment on or otherwise affect compliance/inspection documentation that has been defined by CDER's Office of Compliance or FDA's Office of Regulatory Affairs. This guidance does not affect any postapproval changes other than the ones specified. For changes not addressed in this guidance, or for multiple changes submitted

at one time or over a short period of time, or where the number of batches recommended for stability testing is not specified, sponsors should contact the appropriate CDER review division or consult other CDER guidances/guidelines to obtain information about tests and application documentation.

The regulations in § 314.70(a) state that applicants may make changes to an approved application in accordance with a guideline, notice, or regulation published in the Federal Register that provides for a less burdensome notification of the change (for example, by notification at the time a supplement is submitted or in the next annual report). This guidance permits less burdensome notice of certain postapproval changes within the meaning of § 314.70(a).

For postapproval changes for immediate release dosage forms that affect components and composition, scale-up, site change, and manufacturing process or equipment changes, this guidance supersedes the recommendations in section 4.G of the Office of Generic Drugs Policy and Procedure Guide 22–90 (September 11, 1990). For all other dosage forms and changes, this guidance does not affect the recommendations in Guide 22–90.

#### II. Definition of Terms 1

#### A. Batch

A specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits (21 CFR 210.3(b)(2)).

### B. Contiguous campus

Continuous or unbroken site or a set of buildings in adjacent city blocks.

#### C. Dissolution testing

Case A: Dissolution of Q=85 percent in 15 minutes in 900 milliliters (mL) of 0.1N hydrochloride (HCl), using the United States Pharmacopeia (U.S.P.) <711> Apparatus 1 at 100 revolutions per minute (rpm) or Apparatus 2 at 50 rpm.

Case B: Multi-point dissolution profile in the application/compendial medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached for the proposed and currently accepted formulation.

Case Č: Multi-point dissolution profiles performed in water, 0.1*N* HCl, and U.S.P. buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90 percent of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used with appropriate justification.

## D. Drug product

A drug product is a finished dosage form (e.g., tablet, capsule, or solution) that

contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b)). A solid oral dosage form includes tablets, chewable tablets, capsules, and soft gelatin capsules.

#### E. Drug substance

An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure of any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)).

#### F. Equipment

Automated or non-automated, mechanical or non-mechanical equipment used to produce the drug product, including equipment used to package the drug product.

#### G. Formulation

A listing of the ingredients and composition of the dosage form.

### H. Justification

Reports containing scientific data and expert professional judgment to substantiate decisions.

### I. New drug substance

Any substance that, when used in the manufacture, processing, or packing of a drug, causes that drug to be a new drug, but does not include intermediates used in the synthesis of such substance (21 CFR 310.3(g)).

## J. Operating principle

Rules or concepts governing the operation of the system.

#### K. Pilot scale

The manufacture of either drug substance or drug product by a procedure fully representative of and simulating that used for full manufacturing scale.

For solid oral dosage forms, this is generally taken to be, at a minimum, one-tenth that of full production, or 100,000 tablets or capsules, whichever is larger (see the Federal Register of September 22, 1994, 59 FR 48754–48759).

#### L. Process

A series of operations and/or actions used to produce a desired result.

# M. Ranges

The extent to which or the limits between which acceptable variation exists.

#### N. Same

Agreeing in kind, amount; unchanged in character or condition.

# O. Scale-up

The process of increasing the batch size.

### P. Scale-down

The process of decreasing the batch size.

### Q. Similar

Having a general likeness.

<sup>&</sup>lt;sup>1</sup>See Workshop Report: Skelly, et al., "Scale-up of Immediate Release Oral Solid Dosage Forms," *Pharmaceutical Research*, 10(2):313–316; and the Federal Register of September 22, 1994, 59 FR 48754–59.