Pharmaceutical Research, Vol. 10, No. 12, 1993

Workshop Report[1]

Scaleup of Oral Extended-Release Dosage Forms

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BACKGROUND

Given the lack of extensive information in the published scientific literature, and questions concerning the FDA's Office of Generic Drugs Guide No. 22-90 for immediate-release solid oral dosage forms, recommending minimum batch sizes for bioequivalence studies and a 10-fold limitation on batch size scaleup based on dissolution, the AAPS and the FDA cosponsored a workshop to address this and related issues. This workshop, "Scaleup of Immediate-Release Solid Oral Dosage Forms," was held in December 1991.

A summary report, drawing on the considerable experience of industrial, academic, and regulatory experts, recommended considerable changes from previous regulatory policy as it pertains to batch size for immediate-release solid oral dosage forms. That report, and recommendation, was recently published in the United States (1) and Europe (2).

Because the issues involved in batch size scaleup of modified-release preparations are different and usually more complex than their immediate-release counterparts, a second workshop, entitled "Scaleup of Oral Extended-Release Dosage Forms," was held in Arlington, Virginia, September 8–10, 1992. This workshop was cosponsored by the FDA, USP, and AAPS and the present report describes the issues and outcome of that meeting.

Using an open-forum format, which permits participation by academic, industrial, and government scientists, the specific objectives of the workshop were as follows

(1) Identify critical issues involved in the scaleup process for extended-release drug products.
(2) Define terms that are specific to extended-release dosage forms.
(3) Explore the "state of the art" of manufacturing extended-release dosage forms and delineate the key formulation and process variables which affect scaleup.
(4) Facilitate the development of a data base to support the scaleup of extended-release dosage forms using, where possible, other than *in vivo* studies or limited bioavailability studies.

NOMENCLATURE

A number of terms were defined by a subcommittee of the general committee prior to holding the workshop to assure that all participants employ the same lexicon (see Glossary of Terms, below).

COMPOSITIONAL CHANGES

The effect of compositional changes on the scaleup of immediate-release dosage forms was addressed in the first workshop report (1). After careful consideration, certain compositional adjustments were determined to be acceptable, without further justification. On the whole, these same adjustments would appear to be equally applicable for extended-release batch size scaleup. There is, however, an additional consideration for extended-release dosage forms: the inclusion of a critical release component(s) which enables the extended release of active ingredient. Thus, for extended-release dosage forms, consideration must be given as to whether the component is critical or not critical to drug release.

For noncritical components, changes in composition within the scope of the "Immediate-Release" report are acceptable without additional justification, provided that all final product specifications are met. Changes beyond those recommended for immediate-release dosage forms would be allowable when based on *in vitro* data [if the *in vitro* method had been correlated with *in vivo* data (see *In Vitro/In Vivo* Correlations, below)].

A noncritical component is one which is formulated within the quantitative range given below, is specified in the New Drug Application (NDA/ANDA), and does not affect the release rate of drug from the dosage form. Such determination may be made using a dissolution test which has been correlated with *in vivo* data.

After careful consideration, the ranges given in Table I were determined to be acceptable for compositional purposes, without further justification, as a percentage of the total formula, as long as all final process specification are met. These percentage changes are considered normal

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0724-8741/93/1200-1800$07.00/0

Table I. Allowable Range of Noncritical Components (as % of Total Formula)

Noncritical component	% of total formula (%)
Filler	5
Disintegrant	
Starch	3
Other	1
Binder	0.5
Lubricant	
Ca or Mg stearate	0.25
Other	1
Glidant	
Talc	1
Other	0.1
Film coat	1

changes to aid in processing, not to affect product performance.

Drug Substance is formulated to 100% of label/potency. However, given the total additive effect of excipient changes, the drug substance/total excipient ratio should not change by more than 5%.

Quantitative adjustment of the formulation within these ranges should be viewed as a minor change. On the other hand, changes in excess of these amounts, as well as any qualitative changes other than the deletion of a color, should be viewed as major changes.

For those components which are critical to the release mechanism, the compositional range of these components must be established on the basis of *in vitro* dissolution which has been shown to correlate with *in vivo* data. Justification of the compositional range should take into account the specific mechanism of release and the manufacturing process.

Drug Substance(s)

All final product specifications must be met.

Changes in particle size, surface area, and/or intrinsic dissolution can have significant effects. Therefore, for drug substances with an aqueous solubility of ≤ 5 mg/mL, a change greater than 10% in mean particle size (distribution remaining approximately the same), surface area, or intrinsic dissolution rate, or for drug substances with an aqueous solubility of >5 mg/mL, a change greater than 25% in particle size (distribution remaining approximately the same), surface area, or intrinsic dissolution rate, are viewed as a major change, unless justified by appropriate scientific rationale.

EQUIPMENT AND PROCESSING

The need for quality control to assure reproducibility of finished product performance for extended-release products is essential. To this end, the unit operations for the scaleup, i.e., milling, blending, granulating, drying, or coating should be maintained. Any changes in process conditions must be justified through a measurement of the impact of measurable variables, such as spray rates, temperatures, rotational speed, air velocity, cooling times, blending times, and feed rates, on the quality and performance of the finished product.

Such changes may be allowed where an appropriately correlated, *in vitro* dissolution test is available (see *in Vitro/in Vivo* Correlations, below) and where the dissolution profile falls within specifications set prior to scaleup. Furthermore, all processing and equipment changes should be validated, all other drug product properties should be within specification, no change in the release mechanism (no change in the operative mechanism such as from erosion to diffusion control) should occur, and there should be no qualitative change in composition as defined above. Some leeway in the amount of release controlling agent may be necessary to allow for efficiencies resulting from the scaleup process. This reflects the importance of having a meaningful *in vitro/in vivo* correlation.

Additionally, minor process and equipment changes are permitted when the product conforms to the same specifications employing a meaningful, predictive, and reliable dissolution test.

IN VITRO/IN VIVO CORRELATIONS

One objective of an *in vitro/in vivo* correlation is to allow dissolution testing to serve as a surrogate for human bioequivalence studies during scaleup or manufacturing site changes of extended-release dosage forms. An *in vitro/in vivo* correlation can also be an aid in setting dissolution specifications for extended-release dosage forms. However, in order to utilize an *in vitro/in vivo* correlation, the adequacy of the *in vitro* method to act as a surrogate for *in vivo* testing must be demonstrated.

Since one can use the same components, material, processes, and equipment to make a product with inappropriate release performance, it is imperative that end-product tests correlated with *in vivo* data be employed. The key issues are (a) the adequacy of the *in vitro* dissolution test to act as a surrogate marker for *in vivo* studies and (b) the robustness of the formulation and process. Each of these need to be demonstrated with data.

The development of a reliable surrogate for extended/modified-release products has been the subject of continuing controversy (3–5). At this point in time, the Committee feels that the "state of the art" has advanced sufficiently such that dissolution, under certain specific conditions, may be used as a sensitive, reliable, reproducible surrogate. Indeed, the value of *in vitro* dissolution specifications as a quality-control measure is dependent upon a relationship to *in vivo* bioavailability. With some minor modification, there is agreement with the approach given in the USP General Chapter on *In Vitro* and *In Vivo* Evaluation of Dosage Forms ⟨1088⟩ (6).

The Workshop Committee recommends the use of the term "point to point" in lieu of the current USP nomenclature "one to one" for level "A" correlations. N.B.: In the new USP proposal this has been changed to "point to point." Level A correlations can be employed to establish the utility of *in vitro* dissolution data as a surrogate for *in vivo* bioavailability data during batch size scaleup of extended-release products. Such correlations should be established, either by defining an *in vivo* "input function" or by an appropriately validated plasma level simulation based on sound pharmacokinetic principles. Further validation of this

correlation and/or justification of the dissolution specification range may be obtained by preparing one or more batches of product with different release rates and determining drug absorption in a small number (e.g., six) of human subjects. Modification of release rates should be accomplished by varying those component and process variables that are likely to be varied during the manufacturing process and using these data to set acceptable target ranges.

Where dissolution rate is independent of testing conditions in the physiological range (i.e., pH, surfactant, ion content, enzyme content, agitation, etc.), Level A correlations may be used directly as a surrogate for batch size scaleup in lieu of additional *in vivo* studies. Where dissolution rate is dependant upon testing conditions, the curve obtained by deconvolution of the human plasma concentration–time curve obtained from the bioavailability/bioequivalence study should be compared to the *in vitro* dissolution curves obtained under various dissolution conditions. Once the dissolution conditions which correlate best with the deconvolution curve are found, validation of these conditions should be performed. This may be accomplished by preparing one or more batches of product with differing dissolution rates (prepared as above), measured using the dissolution conditions that correlated best with the *in vivo* data and determining the absorption characteristics of these batches in a small number (e.g., six) of human subjects. If the correlation is consistent, it is considered validated.

If a dosage form fails to meet a Level A correlation, Level B or C may still be utilized, or any other scientifically valid approach to correlations using multipoint dissolution determinations. Where it is not possible to obtain a Level A correlation, "mapping" is an alternate means of validating *in vitro* dissolution specifications relative to *in vivo* bioavailability data (7). It involves two processes. (i) The critical variables (compositional and processing) must be established for the specific dosage form. The range in each variable that is expected during normal manufacturing should be established and this range correlated with dissolution rates using a suitable *in vitro* dissolution procedure. The composite *in vitro* dissolution data for all critical variables should be used to establish the upper and lower values for the dissolution specifications. (ii) In order to establish that batches made at the upper and lower dissolution specifications are bioequivalent the batches at these extremes should be tested *in vivo* (with an adequate number of subjects) using prevailing FDA criteria. If the two batches representing the upper and lower specifications are bioequivalent, it is assumed that all batches within these specifications are also bioequivalent. The "recommended decision tree" in Fig. 1 should aid the reader in this concept.

SITE CHANGES AND POSTAPPROVAL CHANGES

After much discussion, the Committee concluded that the concerns and concepts addressed by this series of "Scaleup Workshops" also relate to manufacturing site changes and postapproval changes.

GLOSSARY OF TERMS

The following definitions of terms commonly used in the scaleup of pharmaceuticals have been generated by the program committee for the purpose of aiding speakers and participants alike in better understanding the concepts and points raised at the subject conference. This Glossary of Terms represents only the opinion of those who formulated it and has no statutory significance (except for those definitions taken from the CFR as noted).

Absorption Rate. Fraction of dose in a dosage form absorbed per unit of time as defined by the Wagner–Nelson, the Loo–Reigelman, or another deconvolution method.

Absorption "Window." The part of the gastrointestinal (GI) tract where drug is absorbed at significantly higher rates than in other sections of the GI tract. Usually the window is expressed as a location within the GI tract. Alternately, one can express a window as a time element over which the drug can be absorbed from the dosage form as it passes through the GI tract.

Active Moiety. The molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance. Source: *Federal Register,* Vol. 54, No. 130, July 10, 1989, p. 28930.

Batch. A specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture. Source 21 CFR 210.3 (b) (2), April 1, 1991, edition.

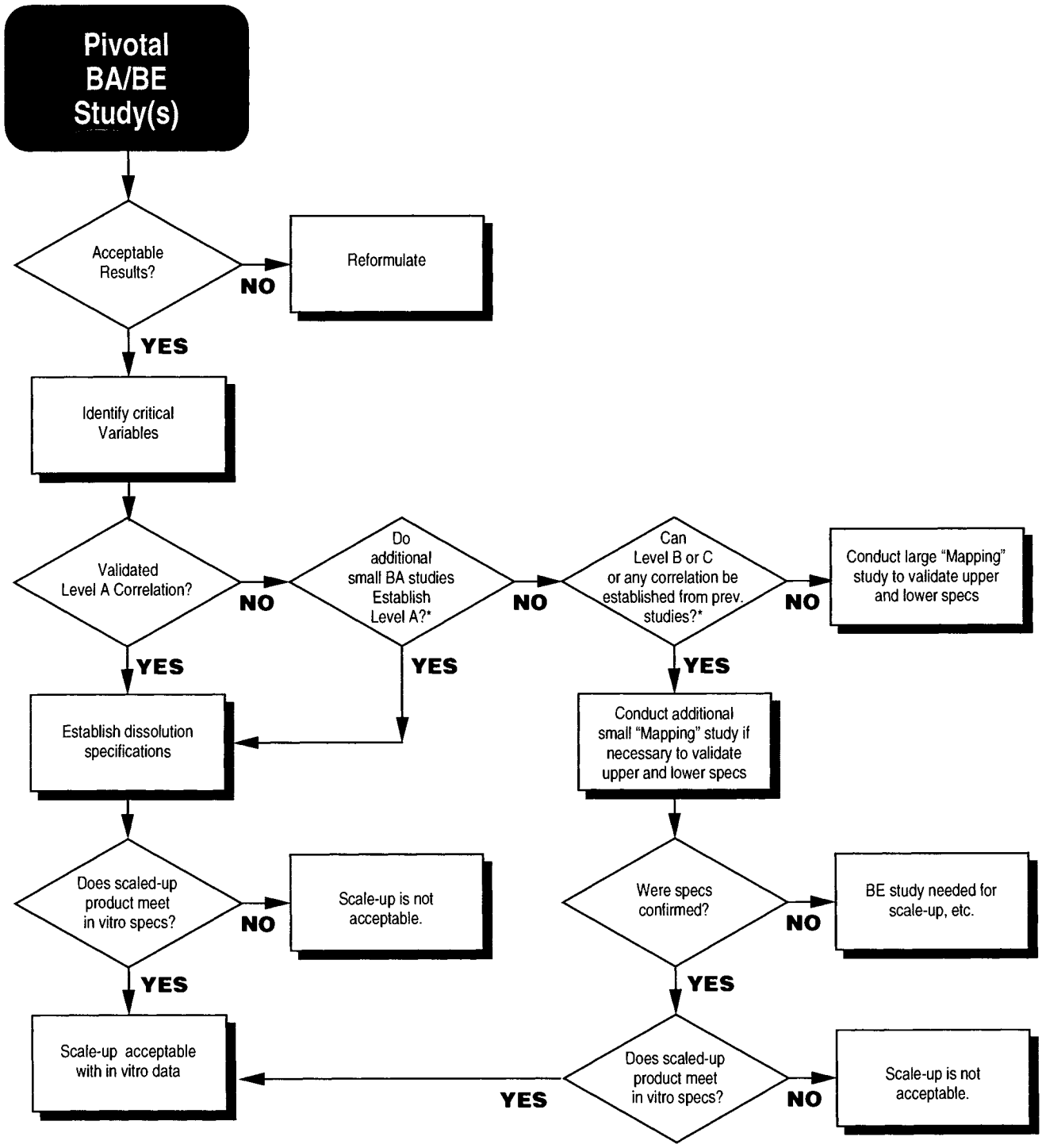
Batch Formula (Composition). . . . A complete list of the ingredients and their amounts to be used for the manufacture of a representative batch of the drug product. . . . All ingredients should be included in the batch formula whether or not they remain in the finished product. Source: *Drug Product Guideline,* FDA.

Beads/Pellets/Multiparticulate System. Dosage form in which the drug contents have been divided into multiple units. These units may be contained in a capsule, compressed into a tablet, or dispersed in a liquid.

Bioavailability. The rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action. Source: 21 CFR 320.1 (a), April 1, 1991, edition.

Biobatch. The lot of drug product formulated for purposes of pharmacokinetic evaluation in a bioavailability study. This lot is typically 10% as large as a production lot or at least 100,000 units.

Bioequivalent Drug Products. Pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied. Source: 21 CFR 320.1 (e), April 1, 1991, edition.



* These studies may also serve as a "Mapping" study.

Fig. 1. Recommended decision tree for scaleup of solid, oral extended-release products.

Challenge Condition. An extreme in the anticipated manufacturing condition or batch formula that is purposely generated in order to determine the ability of the finished product to meet specifications.

Coating. The application of a substance or substances to the exterior of a particle or finished dosage form for the purpose of protecting the ingredients from air, moisture, or light, masking of unpleasant tastes and odors, improvement of appearance, and/or control of the site of drug release in the gastrointestinal tract. Source: *U.S.P. XXII.*

Colonic Delivery. Drug release from a dosage form which occurs primarily in the large intestine.

Correlation. Having a connection to one another, or a mutual relationship.

Critical Compositional Variable. An ingredient in the final dosage form whose primary function is to extend the release of the active drug substance from the dosage form.

Critical Processing Variable. A specific step, unit process, or condition of a unit process which can ultimately control a specific performance variable critical to the ultimate and predictable performance of the dosage form and its drug.

Delayed Release. Releases a drug (or drugs) at a time other than promptly after administration. Source: *U.S.P. XXII.*

Diffusion Barrier. Is built due to coating and embedding and becomes a factor controlling the rate of drug release. Source: *Extended-Release Dosage Forms,* CRC Press, Inc., Boca Raton, FL, 1987.

Diffusion Control. A membrane or matrix which controls the rate of diffusion of drug molecules from a region of higher concentration to one of lower concentration.

Drug Product. A finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. Source: 21 CFR 314.3 (b), April 1, 1991, edition.

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. Source: 21 CFR 314.3 (b), April 1, 1991, edition.

Enteric Coated. Intended to delay the release of the medication until the dosage form has passed through the stomach. Enteric-coated tablets are delayed-release dosage forms. Source: *U.S.P. XXII.*

Erosion Mechanism. The process by which a dosage form loses its mass. For example, by the rate of dissolution, or chemical breakdown of the components.

Extended Release. Allows a reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g., as a solution or a prompt drug-releasing, conventional solid dosage form). (Note: Differs from the *U.S.P. XXII* definition in not having the requirement of "*at least a twofold* reduction in dosing frequency.")

First-Order Release. Drug release from the dosage form either *in vitro* or *in vivo* where the rate of release is proportional to the amount of drug in the dosage form.

Formulation. A listing of the ingredients and composition of the dosage form and its method of manufacture.

Gastrointestinal Transit Time. The time material takes to move through the gastrointestinal tract from mouth to anus.

Identical. "Exactly alike or equal" (Webster).

Immediate Release. The release of the drug from a conventional dosage form allowing the drug to dissolve in the GI contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

***In Vitro–In Vivo* Correlation.** The establishment of a relationship between a biological property or a parameter derived from a biological property produced by a dosage form and a physicochemical property or characteristic of the same dosage form. Source: *Pharmacopeial Forum*, May–June 1993.

Level A Correlation: A point-to-point relationship between *in vitro* and *in vivo* dissolution. The *in vitro* dissolution curve for the dosage form is superimposable on the *in vivo* dissolution curve obtained by deconvolution of the plasma concentration–time data.

Level B Correlation: The mean *in vitro* dissolution time of the dosage form compares to either the mean *in vivo* residence time or to the mean *in vivo* dissolution time.

Level C Correlation: The mean *in vitro* dissolution time of a dosage form ($T_{50\%}$, $T_{90\%}$, etc.) correlates with a single pharmacokinetic parameter (such as AUC, C_{max}, and/or T_{max}).

***In Vitro* Release.** Drug release from a dosage form as measured in an *in vitro* dissolution apparatus.

***In Vivo* Release.** Release of drug from a dosage form as measured by pharmacokinetic studies in humans (patients or healthy volunteers).

Ion-Exchange Release Mechanism. The process by which drug substance is released from a dosage form by the exchange process of ions from the external environment with either the drug in ionic form or other ionic substances within the dosage form.

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

Lot. A batch, or a specific identified portion of a batch, having uniform character and quality within specified limits or, in the case of a drug product produced by continuous process, a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits. Source: 21 CFR 210.3 (b) (10), April 1, 1991, edition.

Major Change. "Examples of reformulations that may be considered to be major include a change in: certain inactive ingredients; the order of mixing of ingredients; the amount of certain inactive ingredients; batch size; and most changes in controlled release dosage forms." Source: *Federal Register,* Vol. 54 No. 69, April 12, 1989, p. 14687.

Manufacturing Site Change. The relocation of the manufacturing process for a drug substance or dosage form from a noncontiguous building to another.

Matrix System. The specific case of drug embedding in insoluble excipients in order to achieve extended release according to the square root law of Higuchi. The term also applies to a matrix built of hydrophilic substances which, in contact with water, form a gel of high viscosity. Source: *Extended-Release Dosage Forms,* CRC Press, Inc., Boca Raton, FL, 1987.

Meaningful Dissolution Method. An *in vitro* dissolution test which has been demonstrated to be directly correlatable with *in vivo* absorption.

Modified Release. Drug-release characteristics of time course and/or location chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions or promptly dissolving dosage forms. Source: *U.S.P. XXII.*

New Chemical Entity. (1) A chemical which has not been adequately characterized in the literature with regard to its physical and chemical properties (not to be confused with "New Molecular Entity"). Source: *Drug Substance Guideline,* FDA.

(2) A drug that contains no active moiety that has been approved by FDA in any other application submitted under

section 505 (b) of the act. Source: *Federal Register,* Vol. 54, No. 130, July 10, 1989, p. 28930.

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. Source: 21 CFR 310.3 (g).

New Molecular Entity. (1) The active moiety not yet marketed in the United States by any drug manufacturer either as a single entity or as part of a combination product. Source: *Staff Manual Guide,* FDA Bureau of Drugs, Guide BD 4829.

(2) A term used by the FDA to describe the subject of a drug application (IND or NDA) classified as Chemical Type 1 (i.e., an active moiety not yet marketed in the United States). Source: *Drug Substance Guideline,* FDA.

Operating Principle. Rules or concepts governing the operation of the system.

Optimization. A combination of empirical and mathematical modeling and evaluation with an end point of establishing the best fit of the dependent variables of a pharmaceutical product (formula composition and manufacturing process).

Osmotic Release. Release mechanism by which the drug substance is displaced from the dosage form by osmotic inhibition of fluids from the environment.

Pharmaceutical Equivalents. Drug products that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Pilot Batch. The batch prior to final product scaleup to commercial-scale batch sizes that is used in the pivotal bioavailability study and upon which final product specifications are set.

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

Range. The extent to which or the limits between which (acceptable) variation exists or is possible. Source: *The Random House College Dictionary.*

Release Mechanism. The process by which the drug substance is released from the dosage form. Typically the definition contains the energy source or pictorially describes the way the drug is released.

Release Rate. Fraction of dose in dosage form released per unit or time as defined by *in vitro* or *in vivo* testing.

Repeat Action. Designed to release initially the equivalent of a usual single dose of drug, then another single dose of the drug at some later time. Source: *Sustained and Controlled Release Drug Delivery Systems,* J. R. Robinson, 1978.

Representative. Corresponding to or replacing some other species or the like; exemplifying a group or kind; typical. Source: *The Random House College Dictionary.*

Reservoir Device. A dosage form where the drug substance is enclosed within a rate-controlling membrane envelope.

Same. Agreeing in kind, amount; unchanged in character or condition. Source: *The Random House College Dictionary.*

Scaleup. The process of increasing the batch size.

Similar. Having a general likeness.

Statistical (Process) Control. Monitoring of the quality of a finished product by application of statistical methods in all stages of production.

Stomach-Emptying Time. Mouth-to-small intestine transit time.

Targeted Release. Release directed toward or at the site of action for the drug.

Validation. "Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes." Source: *Guideline on General Principles of Process Validation,* May 1987, Office of Compliance.

"A validated manufacturing process is one that has been proved to do what it purports or is represented to do. The proof of validation is obtained through collection and evaluation of data, preferably, beginning from the process development phase and continuing through into the production phase. Validation necessarily includes process qualification (the qualification of materials, equipment, systems, building, personnel), but it also includes the control of the entire processes for repeated batches or runs." Source: *Program Guidance Manual for FDA Inspectors.*

Zero-Order Release. Release of drug from a dosage form at a constant rate independent of the amount of drug in the dosage form.

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