Pharmaceutical Research, Vol. 10, No. 2, 1993

Workshop Report

Scaleup of Immediate Release Oral Solid Dosage Forms[1]

J. P. Skelly, G. A. Van Buskirk, D. R. Savello, G. L. Amidon, H. M. Arbit, S. Dighe, M. B. Fawzi, M. A. Gonzalez, A. W. Malick, H. Malinowski, R. Nedich, G. E. Peck, D. M. Pearce, V. Shah, R. F. Shangraw, J. B. Schwartz, and J. Truelove

BACKGROUND

For years the Agency has had difficulty developing a regulatory policy, based on solid pharmaceutic principles, for scaling-up solid oral dosage form batch sizes. The published scientific literature does not presently provide a sufficiently rich source of data to enable such regulatory policy formation. Based on problems observed in the area of generic drugs, the Division of Bioequivalance attempted to respond to the growing regulatory need by espousing, in 1989, the employment of a minimum batch size of 100,000 units with the provision for upscaling by 10-fold, on the basis of similar dissolution profiles. This eventually evolved into FDA's Guideline 22-90, which allowed firms routinely to use a batch size of 10% of the proposed production batch, or 100,000 units, whichever was greater.

Problems remained, however, for while Revised GL 22-90 (dated 9-13-90) did not specify that both test and scaled-up batches be produced on the same or even similar equipment, it clearly indicated that was the intent—even requiring, if different pieces of equipment were employed, written explanation as to "why and how the pieces . . . are believed to be comparable." It, also, specifically allowed the use of alternative equipment of the "same design and operating principles, but of a different capacity." Guideline 22-90 required the same standard operating procedures, controls, and manufacturing procedures as had been employed for the test batch. It failed to consider adjustment in magnesium stearate or other material, to obtain the larger size granulation.

On April 30, 1990, the Agency accepted the American Association of Pharmaceutical Scientists (AAPS) offer to provide assistance in accessing such information within industry and academia. The AAPS Task Force charged with responding to the FDA request developed and proposed new scaleup procedures. While these were never officially communicated to FDA by AAPS, the Agency was aware of them by virtue of membership participation on the task force. While these proposed procedures expanded the envelope of knowledge and agreed with the reasonableness of the 10-fold increase specified in GL 22-90 (same equipment design, same operating principles, and same dissolution), they provided for separate procedures for very soluble drugs, drugs having a narrow therapeutic index, and those cases where different equipment designs and operating principles were to be employed. For very soluble drugs, a dissolution profile would be required. Where equipment of different design or operating principle was employed, an *in vivo* bioavailability study might be required.

For these reasons a joint FDA–AAPS workshop on scaleup considerations was held to explore the issue in an open forum with the participation of academia, industry, and government. The purposes were as follows:

- identify issues involved in the scaleup process;
- define terms;
- explore the "state of the art" and delineate the key parameters for formulation and process changes which affect scaleup; and
- facilitate the development of a data base to support scaleup, using other than *in vivo* studies.

Since it would be advantageous for all participants to be using the same lexicon, a number of terms were defined by a subcommittee of the general committee, prior to the holding of the workshop. These are provided in the glossary attached.

COMPOSITIONAL CHANGES

Nonantibiotic drug products are required to be formulated to 100% of labeled drug content, and antibiotics are formulated to potency. These ideal formulations generally are quantitatively expressed in precise amounts. However, with measurement errors, the imprecise conditions of addition, mixing, and other processing variables, such a precise listing is nugatory. Formulations should specify not only the ideal amount, but also the acceptable range for each excipient. After careful consideration, the following ranges were determined to be acceptable for compositional purposes, without further justification, as a percentage of the 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%

[1] This document contains the personal views of the authors or presenters and does not necessarily represent the policies or guidelines of the American Association of Pharmaceutical Scientists (AAPS) or any cosponsoring organization.

0724-8741/93/0200-0313$07.00/0

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

Quantitative adjustment of the formulation within these ranges should be viewed as a relatively 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.

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—is viewed as a major change, unless justified by appropriate scientific rationale.

Excipients

Fillers (Lactose, Phosphates, Cellulosics)

Particle size changes of more than 20%, or a change in physical chemical type (e.g., corn–potato starch, powdered–microcrystalline cellulose, regular–pregelatinized starch), can be viewed as major changes.

Lubricants (Magnesium/Calcium Stearate)

Changes of bulk density greater than 10%, or water content greater than 2%, or particle size of more than 15%, or any morphological change as seen on scanning electron microscopy can be viewed as being a major change. Also, a change in supplier is viewed as a major change.

Disintegration Agents

Changes greater than 25% in particle size or any change in the type of disintegrant (including regular vs pregelatinized starch) is viewed as a major change.

Wet Binders

A change in concentration of a binder in the granulating media greater than 10% is viewed as being a major change. A volume change of less than 20% of the fluid used to granulate is not viewed as major.

SCALEUP EQUIPMENT AND PROCESS

It is generally recognized that many NDAs and ANDAs contain provision for multiple manufacturers of the drug substance(s) and that not all drug substance suppliers, a priori, produce equivalent material. There is, then, a need for material quality control to assure the performance and reproducibility of the finished product. Particle size and distribution, morphology, and intrinsic dissolution of the drug substance are important considerations. Polymorphism, hygroscopicity, surface area, wetability, density (bulk and tapped), compressibility (for dry blending), and powder flow effects should be controlled.

Additionally, the process should be controlled by employment of a validation protocol which defines the critical parameters and also establishes the acceptance criteria for the granulation or blend, which may include sieve analysis, flow, density, uniformity, compressibility, moisture content, etc.

In the milling, blending, granulating, and/or drying processes, the operating principles of the equipment employed should be defined, and the variables determined. The impact and mechanism of measurement on in-process variables should be defined. Time, temperature, work input of equipment, blend/granulation volume, and granulation rate should be determined. Changes in the volume of the granulating fluid should be expected during scaleup but should be scientifically rationalized. The parameters selected should be appropriate for the process and may include, for tablets: the compression force/dissolution profile, content uniformity, and weight variation. (The compression parameters may be critical.) For capsules, the particle size of the blend, sieve analysis, or other characterization of the blend/granulation, (e.g., bulk density, a top volume, etc.), capsule fill weight, and content uniformity may be important.

Previously, some tablet coating procedures were demonstrated to have caused a significant reduction in tablet dissolution and, thereby, to have adversely affected product bioavailability. However, most coating processes employed today do not adversely affect dissolution. Where the process is controlled, stability is unchanged, and a discriminating dissolution test is available, the coating process should not be viewed as impacting batch-size scaleup (scale-down). The parameters that should be controlled are the coating solution (i.e., viscosity and sedimentation rate), spray rate, air flow as cubic feet per minute, nature of the adhesive/cohesive interaction of the substrate, coating temperature, and pan speed.

In those cases where the manufacturing process has been controlled and validated as specified in the foregoing discussion, batch scaleup, changes in site of manufacture, allowance for equipment change (where the operating principle is the same), minor formulation changes, etc., should be determined on the basis of the comparability of both the blend/granulation and the final product, as assured by (a) appropriate tests, (b) specifications, (c) process validation, and (d) comparative accelerated stability.

End-process testing requirements need to be determined on the basis of the drug's bioavailability problem potential. For highly soluble, well-absorbed, highly permeable drugs, gastric emptying is rate determining for drug absorption, if dissolution is sufficiently rapid. On the other hand, for very slightly soluble drugs with a high permeability, dissolution is likely the critical variable controlling drug absorption. Since solubility in the fluids of the gastrointestinal tract cannot be separated from dose, the dose/solubility or volume of dissolution, rather than intrinsic solubility, should be considered as the important parameter.

In order to obtain meaningful results, *in vitro* dissolution

testing must be conducted under specific, sensitive, physiologically meaningful conditions. For our purposes, we consider official USP Method I employing a speed of rotation of 100 rpm and official USP Method II employing a speed of rotation of 50 rpm as meeting these conditions. Separate tests should be conducted using up to 900 mL of 0.1 *N* HCl, 900 mL of H_2O, or other appropriate media.

Dissolution Requirements

Case A: High Permeability, High Solubility

Drugs with a dose/solubility volume of less than or equal to 250 mL are defined as high-solubility drugs. High permeability may be defined as those drugs with an extent of absorption into the intestinal tract greater than 90% in the absence of luminal instability. Dissolution of 85% in 30 min in 900 mL of 0.1 *N* HCl may be all that is required. Failure to meet Case A automatically defaults to Case B.

Case B: High Permeability, Low Solubility or High Solubility, Low Permeability

These are the same as for Case A, but the drugs must have a dissolution profile [15, 30, 45, 60, 120, 180 min (or until either 90% is dissolved, or an asymptote is reached)] in media of differing pH's, with a 95% confidence interval encompassing the "reference batch" (previous market formulation batch having a known bioavailability or defined clinical efficacy). Profiles should be obtained in water, 0.1 N HCl, and USP buffer media at pH 4.5, 6.5 and 7.5. A surfactant may be used if it was in the original application, or can be otherwise justified.

Case C: Low Permeability, Low Solubility

Because of the expected sensitivity of absorption to *in vivo* dissolution, *in vivo* data are required.

RECOMMENDATIONS

Validated scale up/scale down processes which assure: (i) comparability of the in-process powder blends or granulations by means of particle size analysis, moisture content, and content uniformity by appropriate tests; (ii) comparability of the finished product as determined by dissolution limit or profile (Case A or B), content uniformity, weight variation and other tests where appropriate; and (iii) stability should not be limited by batch size. Scale up/scale down processes meeting (i) through (iii), achieved on processing equipment employing similar operating principles, are considered minor and may be filed in the Annual Report. Others may require FDA preclearance and should be discussed with the FDA. All stability requirements for NDAs and ANDAs apply. The scaled-up batch should be stable at labeled storage conditions for the life of the product.

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).

Active Moiety. The molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, a salt (including a salt with hydrogen or coordination bonds), or another 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. Provide a complete list of the ingredients and their amounts to be used for the manufacture of a representative batch of the drug product. Submit a separate batch formula for each formulation 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.

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.

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.

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.

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

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.

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

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

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. CDER has defined "major changes" as they apply to supplements as follows: "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.

Minor Change. CDER has defined "minor changes" as they apply to supplements as follows: "Examples of reformulation changes that are generally considered to be 'minor' include a change in: the size or shape of a tablet; the flavor or preservative; the coating procedure (film/sugar); the source of the inactive ingredients; the source of the active ingredient (providing adequate chemical/physical tests are presented); and an addition of a lower or higher strength tablet/capsule where the ratio of ingredients is the same as the dosage form on which the bioequivalence study was conducted." Source: *Federal Register,* Vol. 54, No. 69, April 12, 1989, p. 14687.

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 is 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).

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.

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

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

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

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.

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.*