Drug Development and Industrial Pharmacy, 22(1), 25-34 (1996)

Process Validation: A 17-Year Retrospective of Solid-Dosage Forms

Robert A. Nash

Associate Professor, Department of Pharmacy, St. John's University, Jamaica, NY 11439

ABSTRACT

The author takes the reader through the various stages, phases, and steps in the product and process development sequence of solid-dosage form design (tablet and capsule) using process validation principles and practices as a guide. The challenge for the pharmaceutical industry as it approaches the next millennium is to streamline and/or simplify validation requirements without sacrificing product quality and process flexibility. Cost-containment pressures in the future will necessitate the use of more process automation and innovative ways of manufacturing products. In the final analysis, these objectives can best be accomplished with the cooperation of a worldwide regulatory commitment to achieving harmonization goals for both good manufacturing practices and process validation.

INTRODUCTION

After 17 years, process validation apparently is here to stay. But we all knew that it wasn't going away. It is an important derivative of the cGMP regulation itself (1). The cGMP regulation has served both the Food and Drug Administration (FDA) and the pharmaceutical industry well since its inception in 1978. Since that time, new products (many of them tablets and capsules), processes, and methodologies have been developed and all have conformed to the spirit and intent of the original regulation. The process validation concept too has evolved and grown under the umbrella of the cGMP regulation.

In my opinion, and where appropriate, elaborations, interpretations, and new policy directives with respect to process validation and cGMP regulation are best handled by the present system of FDA guidelines and guidance manuals (22,24,26,37,39) and not by proposed future amendments to the present cGMP document (1).

It has been estimated in recent years that the cost of manufacturing drug products has risen by an additional 20–25% percent just to handle process validation requirements. These added costs are mainly the result of number and assay generation, additional nonusable clinical and production batches, more internal investigations, and a mountain range of paperwork to support such activities (40,44).

Now that the development function is a full-time member of the process validation team (development, engineering, manufacturing, and QC/QA), older process validation strategies have had to be redesigned to accommodate preapproval inspection requirements (24). The additional energy expended in process validation restructuring will eventually lead to a more efficient operational system once the team has handled successfully several preapproval and postapproval audit inspections (26), including the accompanying stream of SOPs, reports, and documents.

It has been said that process validation is so costly because most of what we do in connection with validation is unnecessary (21,38,40,44,46). Furthermore, companies have been confused by their consultants as to just what is required by the FDA and their own internal technical operations. The more cynical (with no proof offered) have also said that process validation has made technical operations worse, not better. I seriously challenge the validity of this latter concern.

There is no doubt that there is much confusion as to what constitutes process validation and what does not. Today, the plethora of technical terms and definitions, and the shades of meaning of these various terms debated at conferences on harmonization (42), does not lessen the confusion.

This paper will attempt, using a matrix or continuum format, to depict the various stages or phases necessary in establishing appropriate validation documentation for tablets and capsules. In most cases, we intuitively know these various development stages and what we as technologists need to do. Reinforcing what we already know will be reassuring to the reader.

Recently, one of the major U.S. pharmaceutical companies reissued its 40 mg strength uncoated 900 mg tablet in a smaller 450 mg version. Apparently the message of a more efficient development strategy through the use of process validation principles and practices has not completely gotten through. Perhaps this article can prove helpful in this regard too.

A SURVEY OF VALIDATION CONSIDERATIONS FOR SOLID-DOSAGE FORMS

Today, we use the term *validation* to cover an entire spectrum of cGMP concerns, most of which are essentially facility, equipment, component, procedure, and system or process qualification. The specific protocol-driven term *process validation* should be reserved for the final steps in the product and process development sequence (30).

Nevertheless, elements of the validation concept should be incorporated during each of the various stages of the products and process development continuum. These stages have been summarized as follows:

Preformulation Studies: BPCs
Product Design and Development (Stage I)
Preparation of Clinical and Biobatches (Stage II)
Process Scale-up and Evaluation (Stage III)
Formal Process Validation (Stage IV)

Preformulation Studies: Bulk Pharmaceutical Chemicals

Preformulation testing of the specific active drug substance of interest and key excipients that will be used in the product design stage, alone and in binary combinations with the active drug substance, should be included as a preliminary first step in the product and process development sequence. Reference to several excellent reviews on the subject have been provided:

1. M. J. Akers, Preformulation testing of solid oral dosage form drugs, Can. J. Pharm. Sci., 11, 1–10 (1976).
2. A. L. Jacobs, Determining optimum drug/excipient compatibility through preformulation testing, Pharm. Manufacturing, 6, 43–45 (1985).
3. H. G. Brittain et al., Physical characterization of pharmaceutical solids, Pharm. Res., 8, 963–973 (1991).
4. Z. T. Chowhan, Excipients and their functionality in drug product development, Pharm. Technol., 17 (9), 72–82 (1993).
5. Z. T. Chowhan, Drug substance, physical properties and their relationship to the performance of solid dosage form, Pharm. Technol., 18 (3), 45–60 (1994).

The basic requirements for most active drug substances and key formulation excipients are covered in the latest edition of the *United States Pharmacopeia and National Formulary* (Mack Publishing Co., Easton, PA). In addition, the FDA has reissued its *Guide to Inspection of Bulk Pharmaceutical Chemicals* (September 1991).

A simple checklist of items that one might consider when conducting preformulation studies with bulk pharmaceutical chemicals (both active drug substances and important or *critical* excipients) is provided in Table 1.

Table 1

Preformulation Studies: Bulk Pharmaceutical Chemicals

Active Drug Substance
Key Excipients
Fillers/diluents
Binders
Disintegrants
Glidants/lubricants
• Chemical and physical compatibility
• Minimum lot-to-lot variability in properties
• Available worldwide from comparable suppliers
Properties for Possible Evaluation
Aspect: Color, odor, taste, solubility
Particle morphology including DSC, TGA, x-ray diff.
Particle size distribution and surface area
Crystal and bulk density and compaction index
Angle of repose and flowability index
Spectrophotometry: UV, FTIR, NMR, OR,
Water content, LOD, and moisture uptake
Microbial limits and heavy metals
HPLC assay and impurity profile

Several factors must be kept in mind before preformulation studies are undertaken:

1. It is imperative that two-way technical communication between the manufacturers of the active drug substance (laboratory and plant) and the pharmaceutical product development laboratories be established. It should start early and be maintained throughout the product and process development life cycle.
2. In addition to potency, purity, and stability considerations of the active drug substance, Product Development is especially interested in the chemical and physical form (free acid or base, salts, esters, amides, polymorphs, solvates, particle size and shape) of the active drug substance. Time spent early in the cycle in getting these particular factors established will often aid and/or simplify the subsequent product and process development program.

Not every item provided or listed in Table 1 must be tested or addressed. One or more items, however, in each of the main categories (aspect, particle morphology and size, compaction and flowability, water content, spectrophotometry and chromatography) should be studied and monitored throughout the product and process development program (32,33).

Since key excipients are well established in most new product and process development programs, the same degree of preformulation scrutiny is often not required. Binary compatibility studies with the active drug substance, however, should be performed to study possible untoward interactions between the actives and the excipients. It should be kept in mind that small or minor changes in physical and possibly chemical properties upon intimate contact in binary studies with key excipients should not automatically rule out the use of a favored excipient without further critical testing.

Stage I: Product Design and Development

Following successful preformulation studies, the active drug substance is transferred to the formulations laboratory for preliminary product design and development studies. In most cases, the drug is admixed with an appropriate diluent/filler and glidant combination and filled into two-piece opaque hard-shell capsules for preliminary stability and subsequent phase one clinical studies vs. matching placebo capsules (16).

On or about the same time, initial studies of a prototype tablet formulation should be started. The key steps in the product design and development sequence are outlined in Table 2. Even though the work is conducted in the research or formulations laboratory using

Table 2

Key Steps in Stage I: Product Design (1 × Laboratory Scale, 1–10 kilos)

Hard-shell capsule (phase one clinical trials) followed by prototype tablet dosage form
Direct compression vs. wet granulation
Maximize chemical and physical stability
Minimize product and process costs
• Product design
• Product characterization
• Product selection
• Process design
Excipients selected from the following lists:
Binder/Diluent/Disintegrant
Alginates, calcium phosphate, cellulose and derivatives, dextrates, gelatin, povidone and derivatives, starch and derivatives, sorbitol, sucrose and derivatives
Glidant/Lubricant
Colloidal silicon dioxide, hydrogenated vegetable oil, mineral oil, PEG, silica gel, sodium lauryl sulfate, stearates, talc

small-scale processing equipment, it is important to gain early experience with colorant systems that have been selected for the final finished tablet product. The use of color will aid in blend uniformity evaluation.

In addition to excipient screening and selection, it is important to gauge processing parameters that will be more fully explored during the future process scale-up phases. These processing factors include flowability, compaction and compressibility of powders and granules, content uniformity of powder and granule blends and finished tablets, moisture uptake, in-vitro dissolution release profiles, and subsequent full-scale stability testing. Product that is used in human clinical trials will, of course, conform to good laboratory, good clinical, and good manufacturing practice requirements (22,23).

Stage II: Preparation of Clinical and Biobatches

After the (1×) "go" laboratory batch has been determined to be both physically and chemically stable based on accelerated, elevated temperature testing (i.e., 1 month at 45°C or 3 months at 40°C or 40°C/80% relative humidity), the next step (Stage II) is to scale the product and its process to (10×) pilot-laboratory size batch(es).

The (10×) pilot-laboratory size batch represents the first replicated scale-up of the designated formula. The size of the pilot-laboratory batch will usually range between 10 and 100 kg, 10 and 100 liters, or 10,000 and 100,000 units. Often these pilot-laboratory batches are used in clinical trials and bioequivalency studies. According to the FDA, the minimum requirement for a biobatch is 100,000 units (28,39).

These pilot-laboratory batches are usually prepared in small pilot equipment within a designated cGMP-approved facility. The number and size of these pilot-laboratory batches may vary in response to one or more of the following factors:

1. Equipment availability
2. Active drug substance availability
3. Cost of raw materials
4. Inventory requirements for both clinical and nonclinical studies

Process development (process qualification) or process capability studies are normally started in this important second stage of the scale-up sequence. The scope of Stage II process development is presented in Table 3 and consists essentially of *product optimization* and *process characterization* studies. Unit operations are selected for the development of either a tablet (coated or noncoated) or capsule (hard shell or soft-gel) process (17). Those unit operations that are considered to be *critical* are determined through an analysis of the process variables and their respective measured responses in each unit operation (see Table 4) (3,4,5,8,9,11,12).

Table 3

Key Steps in Stage II: Process Development (10× Pilot-Laboratory, Clinical, 10-100 kg)*

First Product and Process Scale-Up Experience in a GMP Facility

- Product Optimization
  Establish formula rationale and boundary conditions for active and excipients
- Process Characterization
  Define unit operations, process variables and response parameters
  Define critical process variables and response parameters using simple experimental designs
  Establish provisional control limits for critical process variables and their response parameters based on process replication
- Maintain Product Stability

Unit Operations for Solid-Dosage Form Development Include:

- Granulation
- Drying
- Sizing
- Blending/Mixing
- Encapsulation/Tablet Compression
- Coating

*Biobatch should be at least 100,000 units.

In order to get a handle on the critical control parameters and their unit operation, constraint analysis techniques (30) followed by fractional factorial designs (45) (see Table 5) are used to challenge the tentative control limits (so-called worst-case analysis) established for the process at this intermediate stage.

In my opinion, Stage II (10×) process development represents the "heart and soul" of the prospective validation, preapproval inspection program. Time and effort spent to qualify the process at the 10× stage will often simplify the work that follows during Stages III and IV.

Von Doehren et al (11) and Chowhan (27) have written separate articles on the various stages of solid-dosage form process development as it relates to technology transfer and process validation. Their respective approaches to the topic have been integrated and added to in the present paper (see Tables 2–4, 6, and 7).

Table 4

Control Parameters for Consideration in Solid-Dosage Form Development

Unit Operation	Process Variables (X's)	Measured Responses (Y's)
Granulation (power type)	Load	Power consumption
	Speed (main/chopper)	
	Liquid addition rate	
	Granulation time	
Drying	Load	Moisture content
	Inlet temperature	Bulk density
	Airflow rate	
	Drying time	
Sizing (screening)	Load	Particle size distribution
	Screen size	Bulk density
	Speed	
	Feed rate	
Blending (mixing)	Load	Blend uniformity
	Speed	
	Mixing time	
Encapsulation	Fill volume	Capsule weight
	Tamper setting	Moisture content
	Speed	Dissolution
	Glidant (type and amount)	Content Uniformity
		Potency
Tablet Compression	Press speed	Tablet weight
	Feed rate	Moisture content
	Precompression force	Hardness/friability
	Compression force	Thickness
		Dissolution/Disintegration
		Content Uniformity
		Potency
Coating (film type)	Load	Weight gain
	Pan speed	
	Spray rate	
	Airflow	
	7–23 possible variables	11–16 possible responses

Fahrner (36), in his excellent paper on the new role for pilot plants in product development, raises the following issues:

- There is too much preliminary or applied research and not enough time is devoted to the proper development of the process.
- Often there is a lack of a suitable manufacturing strategy during the early phases of the program, which often results in poorly planned technology transfer and an inappropriate division of responsibility with respect to the overall program.
- Most laboratory processes are rarely scalable, since piloting is a scaled-down version of manufacturing not a scaled-up version of the laboratory batch.

In his paper, Fahrner makes the case for a separate pilot facility (process development function) to bridge the communication gap between R&D and production.

Stage III: Process Scale-up and Evaluation

The technical transfer of the product and process from the traditional Product Development function to either a separate Process Development (Pilot Plant) function or Production itself is normally carried out at

Table 5

*New Fractional Factorial Design for Development**

	Seven Variables, Eight Trials Key Variables**							
Trials	X_1	X_2	X_3	X_4	X_5	X_6	X_7	Sums
1	–	–	–	–	–	–	–	0/7
2	–	–	–	+	–	–	–	1/6
3	–	–	+	–	–	+	–	2/5
4	+	+	–	–	+	–	–	3/4
5	+	+	–	–	–	+	+	4/3
6	+	–	+	+	+	–	+	5/2
7	–	+	+	+	+	+	+	6/1
8	+	+	+	+	+	+	+	7/0
SUMS	4/4	4/4	4/4	4/4	4/4	4/4	4/4	28/28

*Adapted from C. D. Hendrix, What every technologist should know about experimental design, CHEMTECH (March 1979).
**Key variables are randomly assigned "X_{no}" value

the (100×) pilot-production batch stage (Table 6). The creation of a separate pilot plant or Process Development unit has been favored in recent years because this particular organizational structure is ideally suited to carry out key process qualification and/or process validation studies in a timely manner (18,23,41).

The objective of the pilot-production batch is to scale the product and its process by another order of magnitude (100×). For most solid-dosage forms it represents a full production scale batch in standard production equipment. The technical transfer documents should include the technical package normally required for preapproval inspection:

1. Preformulation information
2. Product development report
3. Product stability report
4. Analytical methods report
5. Proposed manufacturing formula, manufacturing instruction, in-process and final product specifications at the 100× batch size

The objectives of prevalidation trials at Stage III (100× Pilot-Production) is to *qualify* and *optimize* the process in full-scale production equipment and facilities. Stage IV (Table 7) formal, protocol-driven, three-batch validation studies should never be designed to fail. In my experience, lack of success during formal validation can often be traced to failure in establishing proper and sufficient process capability and process qualification information during the previous stages.

Rushing through the first (100×) pilot-production batch in order to get on with formal validation should be discouraged. Small problems that often arise during (100×) scale-up should be addressed immediately and not ignored since "Murphy's Law" is always operational. Often such problems are best addressed by returning to the laboratories (10×) for supplemental process characterization and qualification studies.

Many companies, however, go directly to three-batch formal validation without Stage III prevalidation work

Table 6

Stage III: Process Scale-up and Evaluation (100× Pilot-Production Batches)

- Full-Scale Batch (100×) 100–1000 kilos
- For Possible Clinical/Future Commercial Use
- Evaluate Critical Process Parameters
  Product and process is scaled to another order of magnitude (100×)
- Process Optimization
  Mixing/blending times
  Drying times
  Milling operations
  Press speed/compression force
  Encapsulation speed/tamping settings
  Speed/airflow/spray settings/temperature
- Process Qualification (Prevalidation batch(es)
  Determine process capability
  Challenge in-process control limits
- Maintain Product Stability

Table 7

Stage IV: Formal Process Validation (100× Production Batches)

- Complete product development program and report
- Prepare protocol for prospective process validation
- Complete preapproval inspection requirements

Conduct three-batch formal process validation
Establish reproducibility for mixing/blending and compression or encapsulation operations

- Establish, process documentation
  Preformulation report
  Analytical methods validation report
  IQ/OQ and cleaning validation reports
  Formula development report
  Process feasibility report
  Manufacturing bioequivalency report
  Product development report
  Process validation protocol
  Process validation report
  Product stability report

and often complete formal trials *prior* to preapproval inspection. The downside of this alternative strategy is that finished production batches often sit in the warehouse beyond their approved expiry dating period. There is no one ideal way of completing the pilot scale-up and validation sequence other than depending on prior experience with related products and processes when it comes to a choice of strategies.

Stage IV: Formal Process Validation

In the normal course of events and following a successfully completed preapproval inspection, formal, three-batch process validation will be carried out in accordance with the protocol approved during the preapproval inspection. The primary objective of the formal process validation exercise is to establish process reproducibility and consistency. The program is not designed to challenge upper and lower control limits (so-called worst-case analysis) of critical process variables. Such upper and lower control limit challenging is normally conducted during the Stage II (10× size) process characterization, optimization, and qualification program using suitable and reasonable experimental designs (Table 5).

The documentation to be established before, during, and after formal process validation is outlined in Table 7. The protocols and the subsequent formal validation studies are designed to establish uniformity among the three batches with respect to granulation, blend, finished tablet and finished capsule stages (22,24,26,34,37,39, 47).

In that respect the following test data and results are used to show process reproducibility and consistency among validation batches:

1. Particle or granule size distribution
2. Bulk density
3. Moisture content
4. Hardness
5. Thickness
6. Friability
7. Weight uniformity
8. Potency uniformity
9. Disintegration/dissolution profile
10. Product stability

Not every one of the 10 listed items or categories has to be addressed or followed both during in-process and final product testing. Nevertheless, sufficient testing must be carried out to establish process reproducibility and to demonstrate, with a high degree of certainty, that the product and process are in a state of control.

Whenever possible, formal validation studies should continue through packaging and labeling operations (in whole or in part), so that machinability and stability of the finished product can be established and documented in the primary container-closure system.

CHANGE CONTROL

Procedures with respect to establishing change control should be in place before, during, and after the completion of the formal validation program. A change control system maintains a sense of functionality as the process evolves and also provides the necessary documentation trail that ensures the process continues in a validated, operational state even when small noncritical adjustments and changes have been made to the process.

Such minor, noncritical changes in *materials, methods,* and *machines* should be reviewed by the validation team (Development, Engineering, Production, and QA/QC) to assure all that process integrity and process *comparability* have been maintained and documented before the specific requested change can be approved by the head of the Quality Control Unit.

The change control system, based on an approved standard operating procedure(s) (SOPs), takes on added importance as the vehicle or instrument through which innovation and process improvements can be made more easily and more flexibly without prior formal review on the part of the NDA (new drug application) and ANDA (abbreviated new drug application) reviewing function of the FDA. If more of the supplemental procedures with respect to the Chemistry and Manufacturing Control sections of NDAs and ANDAs could be covered through annual review documentation procedures, with appropriate safeguards, process validation could become more pro-innovative (25,38,41,42,44).

OUT OF SPECIFICATIONS

Probably the single most important technical issue facing the industry at the present time is the question: What constitutes process or batch failure in terms of an out-of-specification (OOS) assay value? The concept of product and/or process failure appears two places in the cGMPs (1).

According to section 211.165 (f), "Drug products *failing* to meet established standards or specifications and other relevant quality control criteria shall be rejected." In section 211.192 it also states, "Any unexplained discrepancy (including a percentage of theoreti-

cal yield exceeding the maximum or minimum percentages established in master production and control records) or the *failure* of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific *failure* or *discrepancy*. A written record of the investigation shall be made and shall include the conclusions and follow-up."

The key to establishing product and/or process failure is to *verify the accuracy, relevance, and reproducibility of deviant assay value(s), test result(s), and recorded number(s)* that are reported (35,43). All companies should have SOPs in place that cover the verification of deviant numbers in the quality control laboratories and investigations and reports that prove the deviance of the test result, plus a second set of SOPs covering follow-up actions, for example:

1. Written procedure for full investigation when not a verified laboratory error
2. Scientific criteria for retesting and resampling during the formal investigation
3. Description and results of the formal investigation into possible causes of the OOS result(s)
4. Results of all testing involved during the investigation
5. A scientific basis and justification for discarding any OOS test result and accepting the batch in question
6. Final determination of conformity to appropriate specifications and justification of the actions taken
7. Signature of individual(s) responsible for final decision(s) and the action(s) taken

Even though the responsibility for batch acceptance or rejection lies with the head of the Quality Control Unit, again the help of the Validation Team should prove useful in going through the process of OOS investigation and arriving at some recommendation for action taken.

THE VALIDATION TEAM

Formal process validation assignments should be carried out by those individuals with both the necessary *training* and *experience* to perform such duties. The specifics of how a dedicated validation team, group, or committee is organized to conduct process validation assignments is beyond the scope of this paper and should be left to the individual pharmaceutical company to establish (31).

Table 8

Specific Responsibilities of Each Organizational Structure Within the Scope of the Process Validation Concept

Engineering	**Install**, qualify, and certify plant, facilities, equipment, and support systems.
Development	**Design**, optimize, and qualify manufacturing process within design limits, specification, and/or requirements. In other words, provide product development and process capability documentation.
Manufacturing	**Operate** and maintain plant facilities, equipment, support system, and the specific manufacturing process within its design limits, specifications, and/or requirements.
QC/QA	Help provide approvable validation protocols and assist with process validation by monitoring sampling, **testing**, challenging, auditing, and **verifying** the specific manufacturing process and its environment for compliance with design limits, specifications, and/or requirements.

Suffice it to say, Table 8 outlines my approach to *core* membership on the validation team and the team's specific missions and responsibilities with respect to new product and process development. Some companies may not have their own in-house engineering function. In such cases traditional outside engineering services can be obtained. In other companies validation is a separate corporate function or concern, whereas in some companies other organizational functions such as regulatory affairs, analytical development, computer services, and bulk pharmaceutical chemical operations may be included in discussions and in carrying out certain validation assignments.

In the final analysis, process validation is more than three good manufactured batches and organized, documented common sense. It is the key to successful solid-dosage form design, development, and manufacture as the U.S. pharmaceutical industry approaches the next millennium.

REFERENCES

1. Fed. Reg. 43(190), Human and Veterinary Drugs, Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding, Sept. 29, 1978, pp 45014-45089.
2. A. Chao, Validation of Oral Dosage Forms: An Industrial Viewpoint, Academy of Pharm. Sci., Midwest Regional Meeting, Chicago, May 21, 1979.
3. R. A. Nash, Process validation for solid dosage forms, Pharm. Technol., 3 (6), 105-107 (1979).
4. B. Spiller, Process Validation of Solid Dosage Forms, PA Manufacturers' Control Seminar, Cherry Hill, NJ, Oct. 11, 1979.
5. PMA Seminar on Validation of Solid Dosage Form Processes, May 11-13 1980, Atlanta, GA.
6. Validation of Manufacturing Processes, Fourth European Seminar on Quality Control, Sept. 25, 1980, Geneva, Switzerland.
7. T. H. Riggs, Principles of process validation, MD & DI, 3 (5), 31-34 (1981).
8. P. L. Simmons, Solid process validation, Pharm. Eng., 1 (4), 38-39, 41 (1981).
9. R. A. Nash, Process validation: Solid dosage forms, Drug Cosm. Ind., 129 (3), 38-44 (1981).
10. T. E. Byers, Validation burden or benefit, Drug Cosm. Ind., 122 (6), 43 (1982).
11. P. J. von Doehren, F. St. John Forbes, and C. D. Shively, An approach to the characterization and technology transfer of solid dosage form processes, Pharm. Technol., 6 (9), 139-156 (1982).
12. Validation in Practice, H. Sucker, ed., Wissenschaftliche Verlagsegesellschaft mbH, Stuttgart, 1983.
13. Pharmaceutical Process Validation, B. T. Loftus and R. A. Nash, eds., Marcel Dekker, Inc., New York, 1984.
14. E. M. Fry, General principles of process validation, Pharm. Eng., 4 (3), 33-36 (1984).
15. J. D. Nally, Validation guidelines—industry's perspective, Pharm. Eng., 4 (3), 21-27, 30 (1984).
16. S. Bolton, Process validation for hard gelatin capsules, Drug Cosm. Ind., 134 (3), 42-48, 85-87 (1984).
17. I. R. Berry, Process validation for soft gelatin capsules, Drug Cosm. Ind., 134 (4), 26-35 (1984).
18. H. L. Avallone, Primary elements of validation of solid oral and topical dosage forms, Pharm. Eng., 5 (1), 14-18 (1985).
19. R. A. Nash, A validation experiment in solids blending, Pharm. Eng., 5 (4), 28-32 (1985).
20. PMA Validation Advisory Committee, Process validation concepts for drug products, Pharm. Technol., 9 (9), 78-82 (1985).
21. J. R. Sharp, The problems of process validation, Pharm. J., Jan. 11, 43-45 (1986).
22. FDA, Guideline on General Principles of Process Validation, May 11, 1987 (FDA, Rockville, MD 20857).
23. H.L. Avallone, Development and scale-up of pharmaceuticals, Pharm. Eng., 10 (4), 38-41 (1990).
24. FDA, Pre-approval Inspection/Investigations Guidance Manual, 7346, 832, Oct. 1, 1990.
25. K. G. Chapman, A history of validation in the United States, part I, Pharm. Technol., 15 (10), 82-96 (1991).
26. FDA, Post Approval Audit Inspections Guidance Manual, 7346, 843, May 1992.
27. Z. T. Chowhan, Development of a new drug substance into a compact tablet, Pharm. Technol., 16 (9), 58-67 (1992).
28. H. L. Avallone and P. D'Eramo, Scale-up and validation of ANDA/NDA products, Pharm. Eng., 12 (6), 36-39 (1992).
29. R. A. Nash and S. M. Zilli, Mixing of acetaminophen and lactose in a V-shaped blender: An example of a total mixture, Pharm. Eng., 12 (6), 54-62 (1992).
30. Pharmaceutical Process Validation, 2nd ed., revised and expanded, I. R. Berry and R. A. Nash, eds., Marcel Dekker, Inc., New York, 1993.
31. R. A. Nash, A response to recent GMP-validation interpretations, Clin. Res. and Reg. Affairs, 10, 253-264 (1993).
32. J. P. Skelly et al., Scaleup of immediate release oral solid dosage forms, Pharm. Res., 10, 313-316 (1993).
33. J. P. Skelly et al., Scaleup of oral extended-release dosage forms, Pharm. Res., 10, 1800-1804 (1993).
34. WHO, Good Manufacturing Practices for Pharmaceutical Products—Guidelines on the Validation of Manufacturing Processes, Geneva, Switzerland, 1993.
35. C. L. Burgess, The ever-changing standards of cGMP: United States v. Barr Laboratories, Inc., Clin. Res. and Reg. Affairs, 10 (3), 137-157 (1993).
36. R. Fahrner, New role for pilot plants in product development, Biopharm., 6 (3), 34-37 (1993).
37. FDA, Guide to Inspections of Dosage Form Drug Manufacturers cGMPs, Oct. 1993.
38. J. Akers, Simplifying and improving process validation, J. Parenteral Sci. Technol., 47, 281-284 (1993).
39. FDA, Guide to Inspections of Oral Solid Dosage Forms Pre/Post Approval Issues for Development and Validation, January 1994.
40. M. H. Anisfeld, Validation—How much can the world afford? Are we getting value for money? PDA J. Pharm. Sci. Technol., 48, 45-48 (1994).
41. G. Bala, An integrated approach to process validation, Pharm. Eng., 14 (3), 57-64 (1994).
42. K. Tomamichel et al., Pharmaceutical quality assurance: Basics of validation, Swiss Pharm., 16 (3), 13-23 (1994).

43. S. Bolton, When is it appropriate to average and its relationship to the Barr decision, Clin. Res. and Reg. Affairs, 11, 171–179 (1994).
44. J. Agalloco, Validation: An unconventional review and reinvention, PDA J. Pharm. Sci. Technol., 49, 175–179. (1995).
45. Statistical Design and Analysis in Pharmaceutical Science, Validation, Process Controls and Stability, S-C Chow and J-P Liu, eds., Marcel Dekker, Inc., New York, 1995. Interpretations, Clin. Res. Reg. Affairs, 10, 253–264 (1993).
46. J. R. Sharp, Validation—How much is required? PDA J. Pharm. Sci. Technol., 49 (3), 111–117 (1995).
47. C. DeSain and C. V. Sutton, Process development that supports process validation, Pharm. Technol., 19 (10), 131–136 (1995).