MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY
Vol. 28, No. 7, pp. 841–848, 2002

RESEARCH PAPER

Power of Experimental Design Studies for the Validation of Pharmaceutical Processes: Case Study of a Multilayer Tablet Manufacturing Process

F. Goutte,[1] F. Guemguem,[1] C. Dragan,[1] G. Vergnault,[1] and P. Wehrlé[2,*]

[1]*Process Development and Engineering Department, SkyePharma AG, 51 Eptingerstrasse, CH-4132 Muttenz, Switzerland*
[2]*Pharmaceutical Technology Department, ULP Strasbourg, 74 route du Rhin, BP 24, F-67401 Illkirch, France*

ABSTRACT

Experimental design studies (EDS) are already widely used in the pharmaceutical industry for drug formulation or process optimization. Rare are the situations in which this methodology is applied for validation purposes. The power of this statistical tool, key element of a global validation strategy, is demonstrated for a multilayer tablet manufacturing process. Applied to the Geomatrix® system generally composed of one compression and three granulation processes, time and strictness gains are non-negligible. Experimental design studies are not used in this work for modeling. Introduced at each important step of the process development, they allow for the evaluation of process ruggedness at pilot scale and specifications for full production. A demonstration of the complete control of key process parameters is given, identified throughout preliminary studies.

Key Words: Validation; Experimental design; Pharmaceutical process; Multilayer tablet; Granulation; Compression

INTRODUCTION

Nowadays, with the current regulatory constraints, modern pharmaceutical designers cannot be satisfied with formulation and process development methods that lead to uncertain and potentially non-validatable results (e.g., ''trial and error'' approach or ''one factor at a time'' method). State

*Corresponding author. Fax: +33390244314; E-mail: wehrle@aspirine.u-strasbg.fr

DOI: 10.1081/DDC-120005630
0363-9045 (Print); 1520-5762 (Online)

www.dekker.com

organization pre-approval inspections recently emphasized the argument of process justification.[1] It is therefore increasingly apparent that a more rigorous scientific approach to the design and implementation of process validation is required to identify, optimize, and control critical process parameters. Experimental design studies (EDS) are then the most efficient tools to address these goals. Experimental design studies are already widely used in the pharmaceutical industry for drug formulation or process optimization. Recently, this methodology has been applied for validation.[2–5] The present study used EDS as a validation tool to assess the effect of critical process parameters on isosorbide-5-mononitrate 60 mg modified release multilayer tablet performance.

GENERAL METHODOLOGY

Experimental Design Studies and Process Development

The general flow chart of the process development (Fig. 1) shows that if EDS are introduced at each important step of process development, they allow the evaluation of process ruggedness and setting of consistent in-process and product specifications.

Process Definition

Process definition and optimization must be achieved before validation. Key process parameters must be identified. A screening EDS[6] can then be employed. Screening experimental design studies permit the identification of key parameters among those suspected to influence product characteristics, but do not quantify interactions between these factors. Generally, this screening work is based on past experience and on knowledge of the product. Thus, a potential candidate for the nominal manufacturing process is defined but can still be slightly modified after the EDS. The process is then replicated at least three times to assess its reproducibility and to estimate the experimental uncertainty. This estimation enables a determination of the significance of the factor effects calculated during the EDS. Finally, factors highlighted as influential or significant are investigated with complementary trials to define the maximum and minimum settings that will be considered as level −1 and +1 in the validation

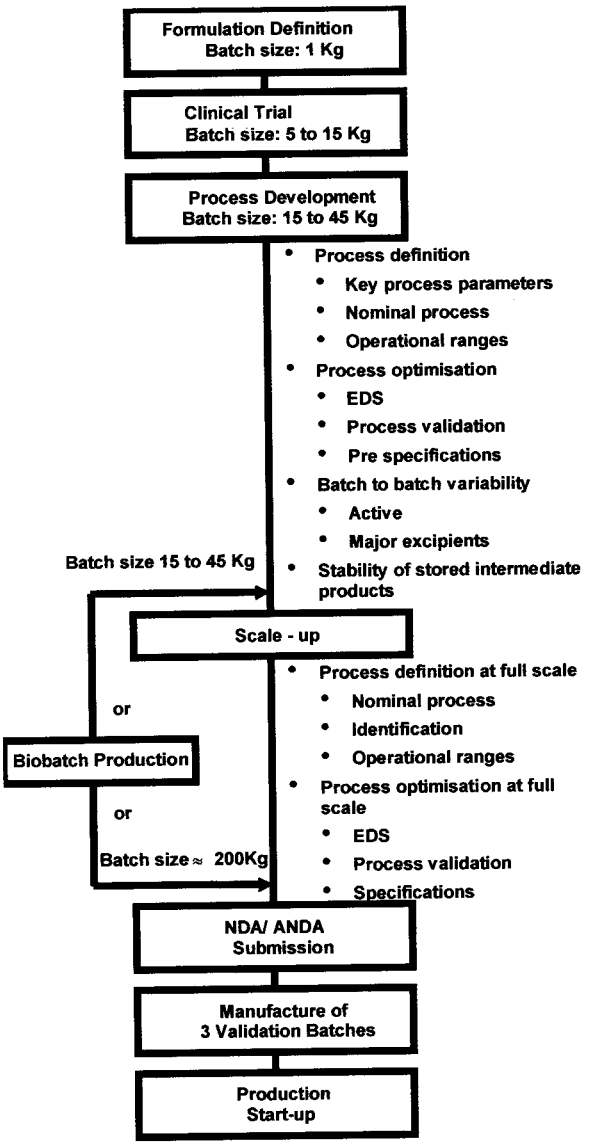

Figure 1. Flow chart of the manufacturing process development.

EDS. These ranges will represent a basis for defining potential pre-specifications for process settings. Nevertheless, if limit values are set as nominal parameters, the ruggedness of the manufacturing process can be weakened.

Process Validation

The validation work is established with the design of an experimental plan. Based on previous

experiences, parameters studied during wet granulation and tablet compression were chosen. Experiments have been performed in extreme conditions during the process definition step. The key process parameters previously identified are therefore defined as factors and will be varied from level −1 (low limit) to level +1 (high limit). A mathematical model can then be postulated, based on the number of experiments (as numerous as corresponding to the best precision) and depending on the financial cost of the study planned (raw material quantity, working time, facilities available, etc.). Moreover, the model definition must estimate some interactions. The significance of a factor can be obscured or expanded in the process of setting another parameter. Nevertheless, the number of interactions that can be studied is dependent upon the number of experiments. For easily understandable financial reasons, full factorial designs cannot be performed. Compared to the classical full factorial design, the fractional factorial design, widely used in this work, is an economical option, which permits the collection of relevant information when higher-order interactions, not being realistic, are not of interest. This type of EDS leads then to making a choice and ignoring some potential interactions. Thus, these omissions create a bias in the analyses and are a potential source of error. Nevertheless, as asserted previously, the assumption of interaction between three factors is not realistic.

Thus, the estimation of the influence or significance of the studied factors allows recommendations to be made. The optimization of the manufacturing process is then finalized considering the results of the EDS. The nominal manufacturing process candidate is therefore validated or optimized.

MATERIALS AND EQUIPMENT

An experimental design study was developed to assess the effect of critical process parameter performance on isosorbide-5-mononitrate Geomatrix™ 60 mg multilayer tablets. The Geomatrix™ technology[7–9] is based on the use of different types (swellable and erodible) of hydroxypropyl methylcellulose (HPMC) polymer grades incorporated at various concentrations within different layers of the tablet (Fig. 2). The various grades of polymers are characterized by their degree of substitution on the cellulose back bone, giving for each a specific hydration and swelling behavior. By combining active-containing and support (non-active-containing) layers, each incorporating various concentrations and grades of HPMC, the ability to modify the release profile of the active ingredient from the drug product is achieved.[9] The multilayer tablets are produced using well-characterized excipients listed in different pharmacopeias. The active premix isosorbide-5-mononitrate/lactose (70/30 w/w trituration) is supplied by Dinamite Dipharma S.p.A., Italy. Hydroxypropyl methylcellulose (Methocel® K15M Premium, Methocel® E10M CR Premium), lactose monohydrate (200 mesh lactose powder), glyceryl behenate (Compritol® 888 ATO), povidone (Plasdone® K29), magnesium stearate, colloidal silicon dioxide (Aerosil® 200) are supplied by Dow Chemicals (USA), Gervais Danone (Germany), Gattefossé (France), BASF (Germany), and Merck AG (Germany), respectively.

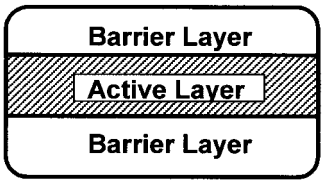

Figure 2. Geomatrix® multilayer tablet.

Standard manufacturing processes were also employed. The two support layers, having the same formulation of isosorbide-5-mononitrate tablets, are produced by manufacturing two distinct granulations for compression (active layer and inactive support layer). Each granulation was begun with a premix in a suitable high-shear mixer followed by wet granulation employing purified water as granulation fluid. Each granulation was dried in a fluid bed dryer before dry milling followed by final blending with lubricants. Multiple batches of the support layer are typically produced since the final tablets contain two support layers. During tablet compression, three granulations were independently fed into a multilayer rotary tablet press for compression of the three-layered tablet in which the support layers are sandwiched with the active-containing layer.

Standard equipment was used for production of the multilayer tablets: high-shear mixer (PMA 65 L and 150 L, Aeromatic-Fielder AG, Switzerland), fluid bed dryer (WSG 30, 100 L bowl, Glatt-AG,

Switzerland T/SG2; 50 L bowl, Aeromatic-Fielder, AG, Switzerland), oscillating bar mill (MGI 205, Frewitt SA, Switzerland), bin blender (Alucon Bulk VA 10S14, Alucon Bulk Systems GmbH, Germany), and rotary multilayer press (HT-AP-55-LSU-3 L, Elisabeth-Hata, USA).

Evaluation of granulations and tablets was performed with: infrared balance (Mettler LP16, Mettler Toledo AG, Switzerland), vibratory siever (Vibro, Retsch GmbH, Germany), jolting volumeter (Stav 2003, Jel Apparatebau AG, Switzerland), flowability tester (AMSI-GLAS, Switzerland), hardness tester (Pharma Test, Erweka Apparatebau GmbH, Germany), friability tester (Erweka TA, Erweka Apparatebau GmbH, Germany), and dissolution apparatus (Sotax AT7, Sotax AG, Switzerland).

RESULTS

Optimization and Validation of the Active Layer Granulation Process at Pilot Scale

A six-trial [$\frac{3}{4}2^{(4-1)}$] factorial fractional design including a triplicate of the nominal process was applied (Tables 1 and 2). Some key process parameters have only two levels available (e.g., size of milling screen designed for the chosen equipment). Thus, the nominal value is chosen to be one of the limits, taking into account the future full-scale process. This fractional design allows estimation of, with a minimum number of experiments (nine granulations), the effect of the four defined factors (granulation liquid percentage, massing step time, outlet air target temperature during the drying step, and milling screen aperture) as well as the interaction between the amount of granulation liquid and the outlet temperature. Each granulation was compressed into isosorbide-5-mononitrate 60 mg Geomatrix™ tablets with the compression manufacturing process (nominal candidate), in order to assess the impact of the dependent variables (factors) on the final product quality. Thus, numerous responses, classified in four categories, were evaluated for each trial: granulation physical characteristics (e.g., flowability, bulk density, ability to settle: $V_{10} - V_{500}$, particle size distribution); extensometric responses (e.g., cohesion index, lubrication index, ejection strength, plasticity,

Table 1

Factors and Experimental Levels: Active-Layer Granulation

Factor	Low Level (−1)	Nominal	High Level (+1)
Granulation liquid amount (%)[a]	11	11	15
Massing time (sec)	30	60	120
Target drying outlet air temperature (°C)	32	36	40
Dry mill screen size (mm)	0.80	1.25	1.25

[a]Percentage (w/w) of theoretical batch size.

Table 2

Experimental Design for the Validation of the Active-Layer Granulation Process

Experiment Number	Granulation Liquid (%)	Massing Time (sec)	Temperature (Drying) (°C)	Screen Size (mm)
1	15	120	40	0.80
2	11	120	40	1.25
3	15	120	32	0.80
4	11	120	32	1.25
5	15	30	40	1.25
6	11	30	40	0.80
Nominal candidate replication				
7	11	60	36	1.25
8	11	60	36	1.25
9	11	60	36	1.25

elasticity); tablet characteristics (e.g., weight variation, hardness, friability, thickness); and analytical results (e.g., content uniformity, dissolution profile).

The effects of the process factors are calculated by multiple regression (Nemrod® software, L.P.R.A.I., Marseille, France). Figures 3 and 4 are convenient graphics on which the standardized effects of each process variable and interaction are represented according to the direction of response variable variation (positive or negative). The given values correspond therefore to half of the studied response variable variation when the studied factor has a variation from level −1 to level +1. Experimental error was estimated in triplicate, allowing calculation of a standard deviation for the factor effects. The 95% confidence interval was consequently calculated for each factor and is represented in Figs. 3 and 4 by upper and lower confidence limits (dotted lines). Each main effect (and/or interaction) plotted inside these limits is statistically not different from zero and therefore not significant ($\alpha = 0.05$).

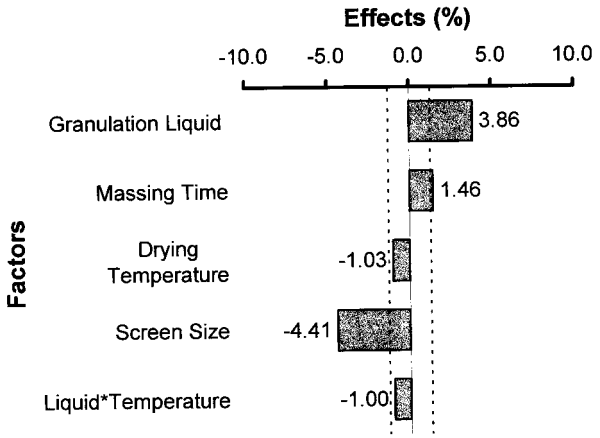

Figure 3. Mean variation of the granulometric fraction above 500 μm.

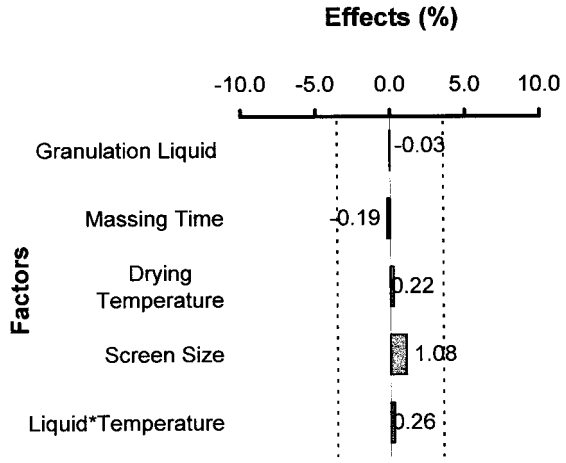

Figure 4. Mean variation of percentage of drug released after 7 hr.

The analysis of the responses obtained shows different levels of effects. Only the significant ones are summarized. Important variations are logically noticed with the pharmacotechnical parameter responses. Thus, granulation liquid percentage and milling screen aperture are considered as significant factors (Fig. 3) on the granulometric fraction above 500 μm measured on final active granulations. Due to its influence during the compression step, this response is defined as the most characteristic response to qualify the granulation. The bulk density significantly increases with the increase in amount of granulating liquid. Logically, the ability to settle, $V_{10} - V_{500}$, is also affected by the granulation liquid. None of the studied factors influence the flowability. Likewise, the extensometric responses as well as almost all the tablet characteristics (friability, thickness) do not vary according to the factor variations. Only the tablet crushing strength is affected by the factors, but the observed variations were not proved relevant. Particularly, the interaction between the amount of granulating liquid and the drying temperature (liquid × temperature) was found statistically significant, but this interaction corresponds to a very low level of variation (±5 N).

The statistical analysis of the analytical results (content uniformity, drug released) did not allow significant factor effect identification. These results demonstrate therefore that, despite a variation of granulation and tablet physical characteristics, the dissolution profile results (e.g., mean variation of the drug release percentage after 7 hr of dissolution; Figs. 4 and 7) were unaffected by the studied process parameter variations.

The analysis of the results obtained allows recommendations (Table 3) for setting the studied factors. A balance between the advantages and disadvantages estimated with the statistical tool permits confirmation of the nominal manufacturing process candidate and also validation of the granulation process.

Hence, with only nine experiments the granulation manufacturing process was validated. Docu-

Table 3

Recommendation for Process Setting: Granulation

Process Variable	Recommended Setting	Advantages	Disadvantages
Granulation liquid	11% (medium)	• Decrease: massing load and drying duration • Increase: massing wet density and particle size <63 μm	• Decrease: final bulk density • Increase: $V_{10} - V_{500}$ value
Massing time	1 min (medium)	• Decrease: massing product temperature	• Decrease: crushing strength
Drying temperature	36°C (medium)	• Decrease: drying time and drying product temperature • Increase: drying yield and final yield	• Decrease: crushing strength
Screen size	1.25 mm (medium)	• Decrease: sizing duration and particle size >500 μm and >250 μm • Increase: final yield	• Increase: particle size > 1.0 mm

mented evidence was established that provides a high degree of assurance that the chosen process will consistently produce a product meeting its predetermined specifications and quality attributes.[10] These ranges constitute a good approach for the final specifications which will be defined with replications of the final nominal manufacturing process using different batches of active substance and matrix-forming ingredients.

Optimization and Validation of the Compression Process

Preliminary prototypes were produced to define a potential nominal manufacturing process. The critical parameters were identified as the press turntable speed, the first and second layer, as well as the main compression forces. An eight-trial [$2^{(4-1)}$] factorial fractional design including a triplicate of the nominal process is applied. Thus, only 11 prototypes are produced to perform this process validation study (Table 4).

Table 4

Experimental Design for the Validation of the Compression Process

Experiment Number	Turret Speed (rpm)	First-Layer Pressure (kg)	Second-Layer Pressure (kg)	Compression Force (kg)
1	25	50	50	600
2	35	50	50	1800
3	25	100	50	1800
4	35	100	50	600
5	25	50	200	1800
6	35	50	200	600
7	25	100	200	600
8	35	100	200	1800
Nominal candidate replication				
9	30	75	100	1100
10	30	75	100	1100
11	30	75	100	1100

Expected correlations are found between independent and dependent variables. The impact of the main compression force and of the turret speed on the tablet crushing strength (Fig. 5) are highly significant. Thus, the tablet crushing strength response increases when the turret compression speed or the main compression force is increased. Moreover, these two significant factors are defined as independent due to the lack of significance noticed with the studied interaction (speed × compression force).

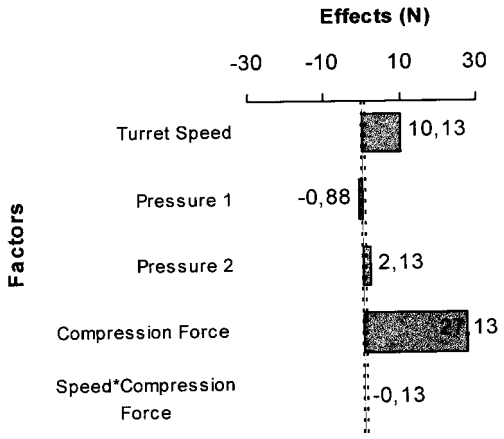

Figure 5. Mean variation of crushing strength.

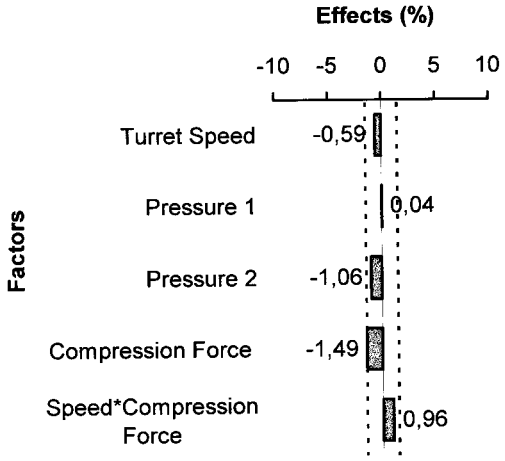

Figure 6. Mean variation of drug released after 7 hr.

Table 5

Recommendation for Process Setting: Compression

Process Variable	Recommended Setting	Advantages	Disadvantages
Turret speed	30 rpm (medium)	• Decrease: pressure variation on layer 2 and 3	Decrease: crushing strength
First-layer pressure	75 kg (medium)	• No variation in response	No variation in response
Second-layer pressure	100 kg (medium)	• No variation in response	No variation in response
Main compression force	1100 kg (medium)	• Prevent the tooling from a fast wearing down	Decrease: crushing strength

No significant variations of the analytical responses (content uniformity, drug release) are noticed. More particularly, the percentage of drug released after 7 hr is constant (Fig. 6) and the dissolution profile itself is not affected by the process variations. Therefore, recommendations for the compression step can be given (Table 5).

CONCLUSION

Each of the main process steps has been analyzed using modern mathematical and statistical tools. The critical parameters being defined, the ruggedness of the process was demonstrated at pilot scale by covering and studying a large experimental field using the experimental design methodology. The quantified and statistically tested effects were found to be efficient to define recommendations for each main step of the process and preliminary specifications for the in-process controls and finished product. Finally, the 17 experiments corresponding to 15 different operating conditions (experimental design for the active layer granulation process: six experiments, experimental design for the compression process: eight experiments, nominal candidate replicate: three experiments) have proved the constant quality of the final product, as summarized by the reproducibility of its drug dissolution profile in vitro (Fig. 7). This global strategy has appeared powerful not only to control the whole process

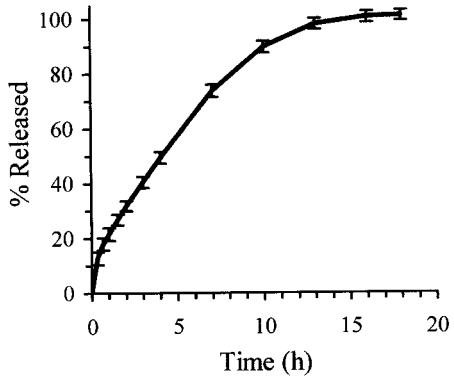

Figure 7. Dissolution profiles of the experimental design study ($n = 6$ tablets), gray lines: individual profiles ($n = 6$ tablets) for each of the 17 designed conditions, black line: mean of the 17 profiles, bars: standard deviation.

but also to collect a complete and rational database for the building of validation evidence.

REFERENCES

1. EMEA (European Agency for the Evaluation of Medicinal Products). Note for Guidance on Process Validation. EMEA/CVMP/598/99, London, September 1999.
2. Anderson, M.J.; Anderson, P.J. Design of Experiments for Process Validation. Med. Dev. Diag. Ind. **1999**, *20* (1), 193–199.
3. Wehrlé, P.; Stamm, A. Statistical Tools for Process Control and Quality Improvement in the Pharmaceutical Industry. Drug Dev. Ind. Pharm. **1994**, *20* (2), 141–164.
4. Faure, A.; York, P.; Rowe, R.C. Process Control and Scale-up of Pharmaceutical Wet Granulation Processes: A Review. Eur. J. Pharm. Biopharm. **2001**, *52* (3), 269–277.
5. Rekhi, G.S.; Nellore, R.V.; Hussain, A.S.; Tillman, L.G.; Malinowski, H.J.; Augsburger, L.L. Identification of Critical Formulation and Processing Variables for Metoprolol Tartrate Extended-Release (ER) Matrix Tablets. J. Contr. Rel. **1999**, *59* (3), 327–342.
6. Lewis, G.A.; Mathieu, D.; Phan-Tan-Luu, R. Factor Influence Studies, Applications of Full and Fractional Designs at 2 Levels. In *Pharmaceutical Experimental Design*, 1st Ed.; Swarbrick, J., Ed.; Marcel Dekker, Inc: New York, 1999; Vol. 92, 108–150.
7. Conte, U.; LaManna, A.; Colombo, P. Tablets with Controlled-Rate Release of Active Substances. US Patent 5,422,123, 1995.
8. Conte, U.; Maggi, L. Multi-Layer Tablets as Drug Delivery Device. Pharm. Technol. Eur. **1998**, *10* (2), 18–25.
9. Conte, U.; Maggi, L. Modulation of the Dissolution Profiles from Geomatrix® Multi-Layer Matrix Tablets Containing Drugs of Different Solubility. Biomaterials **1996**, *17*, 889–896.
10. Shaw, A. Guideline on General Principles of Process Validation. FDA. Course offered by the Center for Professional Advancement in March of 1994. www.fda.gov/cder/guidance/pv.htm (accessed Sept. 2001).