
Research Article

Variation Transmission Model for Setting Acceptance Criteria in a Multi-staged Pharmaceutical Manufacturing Process

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Received 8 August 2011; accepted 21 November 2011; published online 23 December 2011

Abstract. Pharmaceutical manufacturing processes consist of a series of stages (e.g., reaction, workup, isolation) to generate the active pharmaceutical ingredient (API). Outputs at intermediate stages (in-process control) and API need to be controlled within acceptance criteria to assure final drug product quality. In this paper, two methods based on tolerance interval to derive such acceptance criteria will be evaluated. The first method is serial worst case (SWC), an industry risk minimization strategy, wherein input materials and process parameters of a stage are fixed at their worst-case settings to calculate the maximum level expected from the stage. This maximum output then becomes input to the next stage wherein process parameters are again fixed at worst-case setting. The procedure is serially repeated throughout the process until the final stage. The calculated limits using SWC can be artificially high and may not reflect the actual process performance. The second method is the variation transmission (VT) using autoregressive model, wherein variation transmitted up to a stage is estimated by accounting for the recursive structure of the errors at each stage. Computer simulations at varying *extent of variation transmission* and *process stage variability* are performed. For the scenarios tested, VT method is demonstrated to better maintain the simulated confidence level and more precisely estimate the true proportion parameter than SWC. Real data examples are also presented that corroborate the findings from the simulation. Overall, VT is recommended for setting acceptance criteria in a multi-staged pharmaceutical manufacturing process.

KEY WORDS: acceptance criteria; multi-staged process; serial worst-case; tolerance interval; variation transmission.

INTRODUCTION

Pharmaceutical manufacturing processes consist of a series of unit processes or unit operations, referred to as stages in this paper, to generate the active pharmaceutical ingredient (API). For example, a process starts with a chemical reaction and is followed by workup, filtration, and crystallization to isolate the API. The quality attributes of the API are affected by the earlier stages. To assure that the final drug product meets its quality requirement, the in-process control (IPC) and the API need to be controlled within their respective specified acceptance criteria.

Several works have been published for calculating acceptance criteria (1–3). These employ some type of a statistical interval (confidence, prediction, and tolerance) to incorporate process average and process variability. These works, however, are applied to only a single-unit operation. Methods applicable to a process with sequential unit operations are of interest.

Per the ICH Q6A Justification of Specifications, one of the sources from which acceptance criteria may be established

is relevant process development data. Process development usually entails exploratory screening, optimization, and robustness studies using factorial experiments. These design-of-experiments (DOEs) type of studies purposely vary input materials and process parameters relevant to a stage to determine their effect on the output. Separate DOE studies are typically performed at each stage for ease of execution. An example process development DOE scheme of a k-staged process is diagrammed in Fig. 1.

The monitored quality attributes are impurities which are either generated from side reaction of the reactants, transformed from one isomer to another, or carried across the stages as inert chemical species. For a well-defined pharmaceutical manufacturing process, the pathways that impurities follow across the stages are known. Hence, it is possible to track a particular impurity at each stage and infer empirical relationships between Y_i and Y_{i-1} and/or PP_{ij} 's, whether the impurity remains untransformed or does undergo some chemical transformation.

Given a dataset generated from a scheme such as Fig. 1, the key question is how should variation from a previous stage be taken into account in setting acceptance criteria for subsequent intermediate stages and ultimately for the final stage? A simplified risk minimization strategy practiced in the industry is referred to in this paper as serial worst case (SWC) approach. This entails determination of maximum output

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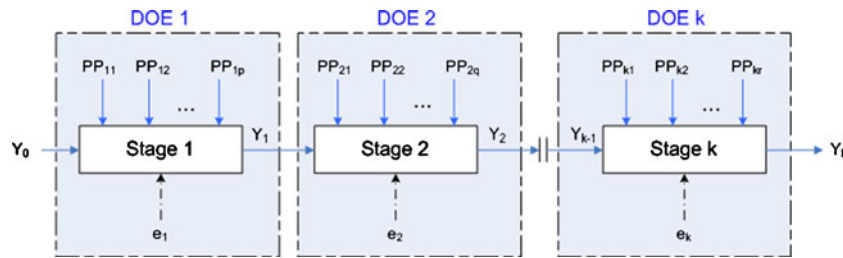


Fig. 1. Diagram of sequential k-staged manufacturing process where separate DOE studies are performed at each stage. Notations: Y_i =monitored quality attribute (e.g., impurity level); PP_{ij} =jth process parameters (e.g., temperature, pressure) studied at i th stage; e_i =error at each stage

level for Y_i that would be expected to be generated at stage i by calculating an upper limit of a statistical interval when input starting materials and process parameters are set at their worst-case settings. Since the monitored quality attribute is an impurity, the higher its output level, the “worse” it is from a safety perspective. The maximum (worst) expected output of stage i is then carried over as input material to stage $i+1$ wherein again the process parameters are fixed at worst-case settings. This procedure is serially repeated from one stage to the next until the final k th stage, hence the name for the approach. The calculated upper limits of statistical intervals at intermediate and final stages are then used as basis for establishing IPC and API acceptance criteria. Although the SWC does result in deriving acceptance criteria with minimized risk of excursion, the calculated limits can be artificially high and may not reflect the actual process performance. An alternate, more realistic approach to SWC is needed to establish statistically-based acceptance criteria for each stage of the process.

Several papers studying variation in product quality attributes as it moves through multiple stages of manufacturing process have been published. The terminologies introduced and the particular industries the works have been applied to are: *variance synthesis* (4,5); *stream of variation* in automotive body assembly (6); *variation transmission* using autoregressive model in automobile manufacturing (7); *variation propagation* using state space model in machining processes (8); and *variation transmission* in ceramic tile manufacturing (9).

In this paper, the concept of variation transmission (VT) by (7) is combined with tolerance interval calculations as a proposed method to derive acceptance criteria for a multi-staged process. The method is presented in the context of having generated process development data using but not limited to factorial experiments at each process stage. The paper is subdivided into the following: (1) introduction of variation transmission model in a generalized k-staged process; (2) brief review of tolerance interval concept; (3) simulation study and real data examples to compare tolerance intervals calculated using SWC and the proposed VT.

METHODS

Variation Transmission in a k-Staged Process

Consider the diagram of a k -staged manufacturing process depicted in Fig. 1. At each stage, factorial DOE

would have been performed during process development. Assuming the quality attribute of the output (Y_i) is linearly correlated to the input starting material (Y_{i-1}) and the process parameters (PP_{ij} 's), the multiple linear regression equation (Eq. 1) applies:

$$Y_i = \alpha_i + \beta_i Y_{i-1} + \sum_{j=1}^{m_i} \gamma_{ij} PP_{ij} + e_i \quad (1)$$

where subscript i refers to i th stage ($i=1, \dots, k$); subscript j refers to j th process parameter in stage i ($j=1, \dots, m_i$; where m_i is the number of process parameters studied at stage i); α_i is the intercept; β_i and γ_{ij} are the regression coefficients for Y_{i-1} and PP_{ij} predictor variables, respectively. For the purpose of introducing the concept of variation transmission, the simple case where only Y_{i-1} influences Y_i is first presented (i.e., γ_{ij} 's=0). This case may occur in a process robustness study wherein the ranges of the PP_{ij} 's are chosen such that varying the PP_{ij} 's within this range have no statistically significant effect on Y_i . The quality of the input starting material Y_{i-1} almost always influences Y_i based on mass balance principles. Other cases where both Y_{i-1} and PP_{ij} 's influence Y_i and also where neither influences Y_i will be presented later in the [Real Data Examples](#) section.

For the case considered in this section, it can be modeled by a simple linear regression:

$$Y_i = \alpha_i + \beta_i Y_{i-1} + e_i \quad (2)$$

with $Y_0 \sim N(\mu_0, \sigma_0^2)$. Equation 2 is an example of a first-order autoregressive model in which the distribution of Y_i depends only on Y_{i-1} (10). The errors at each stage, e_i 's, are assumed to be independent of each other (recursive error structure) and normally distributed $N(0, \sigma_{i,A}^2)$. The expected value and variance of Y_i are:

$$E(Y_i) = \mu_i = \alpha_i + \beta_i \mu_{i-1} \quad (3)$$

$$V(Y_i) = \sigma_i^2 = \beta_i^2 \sigma_{i-1}^2 + \sigma_{i,A}^2 \quad (4)$$

Equation 4 estimates variation transmitted through the i th stage of the process. The first term ($\beta_i^2 \sigma_{i-1}^2$) on the right-hand side is the variation transmitted to Y_i from stage $i-1$, while the second term ($\sigma_{i,A}^2$) is the variation added at stage i . The regression coefficient (β_i) is a measure of the extent of variation transmission. By using Eq. 4 recursively, the

variation transmitted through the final k th stage can be generalized as:

$$\sigma_k^2 = \beta_k^2 \beta_{k-1}^2 \sigma_{k-2}^2 + \beta_k^2 \sigma_{k-1,A}^2 + \sigma_{k,A}^2 \quad (5)$$

Tolerance Interval

A tolerance interval is an interval expected to contain at least a specified proportion, p , of the population with a specified degree of confidence, $(1-\alpha)$. Since tolerance interval estimates the capability limits of a process manufacturing products in large quantities (11), this type of interval is appropriate for setting acceptance criteria. An upper tolerance limit for a univariate linear regression model of the form shown in Eq. 6 (12) is used in this paper.

$$\begin{aligned} &\text{one-sided}(p, 1 - \alpha) \text{ tolerance interval} \\ &= \left[-\infty, x' \hat{\beta} + k(x)S \right] \end{aligned} \quad (6)$$

where $x' \hat{\beta}$ is the predicted mean in vector notation of the ordinary least squares regression; $k(x)$ is the tolerance factor which is dependent upon proportion p , confidence level $(1-\alpha)$, and sample size n , and can be calculated from (13) or obtained from statistical textbooks; S is an estimate of variability.

Applications of Eq. 6 to set acceptance criteria via SWC and VT differ slightly by virtue of how the respective methods work. To illustrate and contrast the difference, the resulting tolerance interval calculations for the two methods are written out for a $k=3$ process in Table I. For example, using SWC at stage 2, the predicted mean ($\hat{\alpha}_2 + \hat{\beta}_2 TI_{Y1}$) is evaluated at the maximum output level of stage 1 (TI_{Y1}) but S used is variation contributed solely by stage 2 ($\hat{\sigma}_{2,A}$). In essence, the variation from stage 1 is incorporated to stage 2 via the calculated TI_{Y1} (i.e., the maximum or worst-case scenario from stage 1). Using VT at stage 2, the predicted mean ($\hat{\alpha}_2 + \hat{\beta}_2 \hat{\mu}_1$) is evaluated at the predicted mean of stage 1 ($\hat{\mu}_1 = \hat{\alpha}_1 + \hat{\beta}_1 Y_0$) but S used is the total variation transmitted up to stage 2 ($\hat{\sigma}_2 = \sqrt{\hat{\beta}_2^2 \hat{\sigma}_1^2 + \hat{\sigma}_{2,A}^2}$).

Simulation Study

A computer simulation experiment is performed to compare tolerance limits at each of process stages calculated using SWC and VT. The process considered is Fig. 1 with $k=3$ and no effects of process parameters PP_{ij} 's (i.e., γ_{ij} 's=0). Conditions of varying extent of variation transmission ($\beta_i=0.1$ or 1.0) and varying stage variability ($\sigma_{i,A}=0.1$ or 1.0) are simulated. The selected ($\beta_i, \sigma_{i,A}$) combination is assumed to

apply to each of the k stages. Since this work is presented in the context of having performed some process development studies, sample sizes ($n=10, 40, 80$) are used. These values are typical number of experimental units performed during process development of a pharmaceutical drug. The simulated scenarios are tabulated in Table II.

The specific steps followed in the simulation are: (a) specify arbitrary values for intercepts ($\alpha_i=1$) and input starting material quality ($Y_0=5$) in Eq. 2; (b) select ($\beta_i, \sigma_{i,A}$) combination applied to each of the k stages; (c) simulate Y_i 's at each ($\beta_i, \sigma_{i,A}$) combination using the RANNOR random number generator function in SAS taking into account the autoregressive relationship (i.e., output in stage 1 becomes input for stage 2, etc.); (d) perform ordinary least squares regressions (Eq. 2) at each stage; (e) construct upper one-sided ($p=0.99, 1-\alpha=0.95$) tolerance intervals at each stage for SWC and VT using formulas in Table I; (f) repeat steps c to e 2,000 times.

The metrics for the simulation study are: (1) *confidence coefficient*, which is empirically derived as the fraction of constructed tolerance intervals that correctly contain at least the true proportion ($p=0.99$) of the simulated population and (2) *average tolerance interval length*. The method with confidence coefficient that is closer to the true confidence level and with shorter average tolerance interval length is deemed the better method.

Real Data Examples

Three cases of varying scenarios on extent of variation transmission and on stage variability as well as different number of process stages and correlation (or lack thereof) of Y_i with Y_{i-1} and/or PP_{ij} 's are presented to further illustrate the simulation findings. The description of each case is presented in more detail in the next section along with the calculations using Eq. 1 and the formulas in Table I.

RESULTS

Simulation Study: Confidence Coefficient

Figure 2 presents the simulated confidence coefficients as process stage progresses ($Y_1 \rightarrow Y_2 \rightarrow Y_3$). The results are given for the two methods (SWC and VT) and three sample sizes ($n=10, 40, 80$) tested. The four panels correspond to the different ($\beta_i, \sigma_{i,A}$) combinations. Using the normal approximation to the binomial, if the true confidence level is 0.95, a simulated confidence level based on 2,000 iterations has only a 0.025 probability of being less than 0.94. A reference line at 0.94 is drawn in the plots.

Table I. Tolerance Interval (TI) Calculations for $k=3$ Staged Process Using Serial Worst-Case (SWC) and Variation Transmission (VT)

Stage	SWC	VT
1	$TI_{Y1} = (\hat{\alpha}_1 + \hat{\beta}_1 Y_0) + k \hat{\sigma}_{1,A}$	$TI_{Y1} = (\hat{\alpha}_1 + \hat{\beta}_1 Y_0) + k \hat{\sigma}_{1,A}$
2	$TI_{Y2} = (\hat{\alpha}_2 + \hat{\beta}_2 TI_{Y1}) + k \hat{\sigma}_{2,A}$	$TI_{Y2} = (\hat{\alpha}_2 + \hat{\beta}_2 \hat{\mu}_1) + k \hat{\sigma}_2$
3	$TI_{Y3} = (\hat{\alpha}_3 + \hat{\beta}_3 TI_{Y2}) + k \hat{\sigma}_{3,A}$	$TI_{Y3} = (\hat{\alpha}_3 + \hat{\beta}_3 \hat{\mu}_2) + k \hat{\sigma}_3$

Table II. Simulated Scenarios Varying β_i and $\sigma_{i,A}$ with Each Combination Sampled at $n=10, 40$, and 80

Extent of variation transmission (β_i)	Variability at each stage ($\sigma_{i,A}$)	
	0.1	1.0
0.1		
1.0		

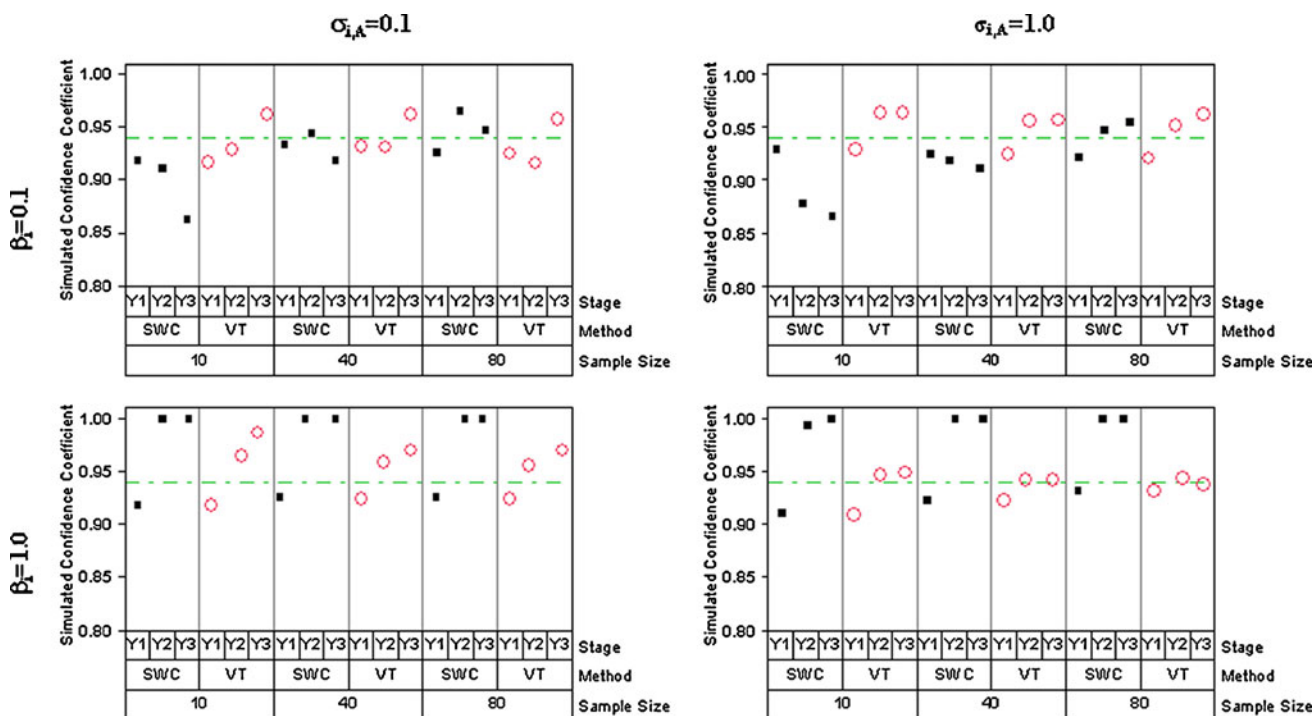


Fig. 2. Plot of simulated confidence coefficients as process stage progresses ($Y_1 \rightarrow Y_2 \rightarrow Y_3$) for method (VT=variation transmission, SWC=serial worstcase) and sample size (n) in each of $(\beta_i, \sigma_{i,A})$ simulated scenarios. The reference line at 0.94 is the simulated confidence level

At low extent of variation transmission ($\beta_i=0.1$) for both levels of variability ($\sigma_{i,A}=0.1$ and 1.0), the simulated confidence coefficients for SWC at smaller sample sizes ($n=10$ and 40) fall further below 0.94 as stage progresses (Fig. 2, upper left and right panels). VT approaches the simulated confidence level for all $\sigma_{i,A}$ and n levels as stage progresses. At large size ($n=80$), the confidence level of both methods improve and become comparable to each other.

At high extent of variation transmission ($\beta_i=1.0$), SWC exceeds 0.94, approaching or even reaching 1.0 for both $\sigma_{i,A}$ levels as stage progresses (Fig. 2, lower left and right panels). VT also exceeds 0.94 at low variability ($\sigma_{i,A}=0.1$) but not as severely as SWC; the exceedance is attenuated as sample size is increased. At high variability ($\sigma_{i,A}=1.0$), VT effectively maintains simulated confidence level with results approaching 0.94 as stage progresses for all sample sizes.

Simulation Study: Average Tolerance Interval Length

Figure 3 presents the average tolerance interval lengths as process stage progresses. The average TI length is re-scaled by subtracting from it the “true” 99th percentile of the simulated $N(\alpha_i + \beta_i Y_{i-1}, \sigma_i^2)$ population. The smaller this difference is, the more precise the estimate of the true proportion parameter. This re-scaling makes it easier to graphically compare the two methods across the four $(\beta_i, \sigma_{i,A})$ simulated scenarios.

At low extent of variation transmission ($\beta_i=0.1$), the average TI lengths of SWC are longer than VT although only slightly (Fig. 3, upper left and right panels). The difference from the true proportion parameter is widened as stage progresses, more so with SWC than with VT. As expected, increased sample size improves the precision of the estimates. These trends are similar between $\sigma_{i,A}=0.1$ and $\sigma_{i,A}=1.0$, only differing by an order of magnitude in the Y -axis scale.

At high extent of variation transmission ($\beta_i=1.0$), the average TI lengths of SWC are drastically much longer than VT (Fig. 3, lower left and right panels). The disparity between the two methods becomes even more pronounced as stage progresses. Again, improved precision is achieved by increasing sample size. Just like in $\beta_i=0.1$ scenario, trends between $\sigma_{i,A}=0.1$ and $\sigma_{i,A}=1.0$ are similar in $\beta_i=1.0$ scenario except for scaling of Y -axis by an order of magnitude.

Taking together the results of the confidence coefficients and average TI lengths for the scenarios tested, SWC is verified to be a conservative method—it exceeds the simulated confidence level, even reaching 1.0 as stage progresses, and it gives longer tolerance limits thus less precise estimates of true proportion parameter. In contrast, VT is more effective in maintaining the simulated confidence level and provides more precise estimates of true proportion parameter. These contrasts in performance are especially observed when extent of variation transmission is high and process stage variability is also high.

Real Data Examples

In this section, real data examples are presented to further illustrate setting acceptance criteria using the SWC and VT methods. The data comes from actual retrospective historical data and/or prospective DOE studies that have been slightly modified for proprietary reasons. The identities of the chemical impurities measured in these studies are blinded for confidentiality.

Case 1 is a three-staged process wherein the output of a stage, Y_i , appears to be influenced solely by its input material, Y_{i-1} . This is similar to the hypothetical case considered in the simulation, only the estimates of σ_i 's and $\sigma_{i,A}$'s vary from stage to stage. Case 2 is a two-staged process wherein Y_i also

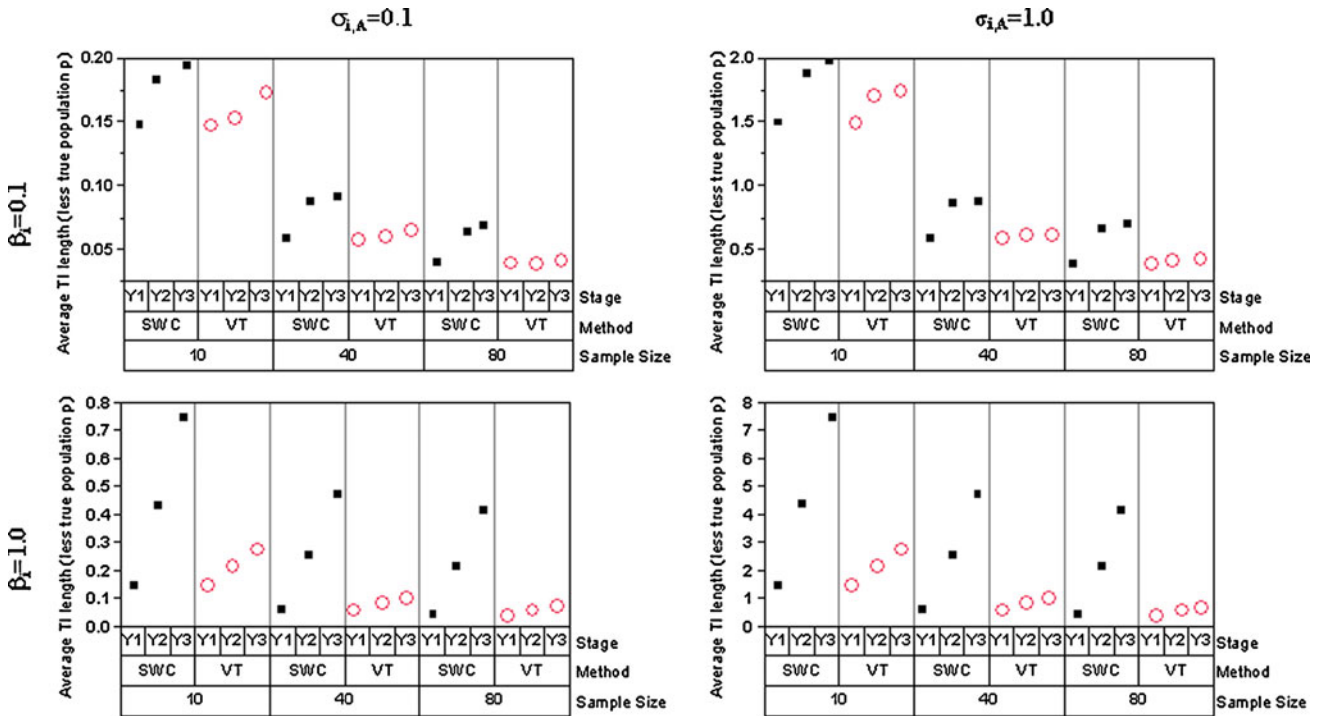


Fig. 3. Plot of average tolerance interval lengths (less the true proportion p values of the simulated population) for process stages progresses ($Y_1 \rightarrow Y_2 \rightarrow Y_3$) for method (VT variation transmission; SWC serial worst case) and sample size (n) in each of $(\beta_i, \sigma_{i,A})$ simulated scenarios

appears to be influenced by Y_{i-1} . In addition, two process parameters PP_{21} and PP_{22} also appear to influence the output of stage 2, Y_2 . Case 3 is a three-staged process wherein for stages 1 and 3, the outputs Y_1 and Y_3 appear to be correlated with their input materials, Y_0 (upon log-transformation) and Y_2 , respectively. However for stage 2, neither its starting material Y_1 nor any of its PP_{ij} 's appear to influence the output Y_2 . This may occur, for example, in robustness studies wherein the goal is to demonstrate that within the selected range of the input parameters, there is no significant effect on the output. This may also occur when the process is

inherently variable such that any signal due to systematic sources of variation could not be detected.

In all of these three cases, when systematic sources of variation (Y_{i-1} and PP_{ij} 's) appear significant, they are modeled in Eq. 1 as fixed effects. Modeling them as random effects is probably more reflective of how these factors behave in real applications. For example, the chemical impurity of interest Y_0 contained in the starting material supplied by a vendor is likely distributed as a normal random variable, $N(\mu_0, \sigma_0^2)$. Likewise, the setting at which a process parameter PP_{ij} is actually operated may also have some random distribution (e.g., uniform or

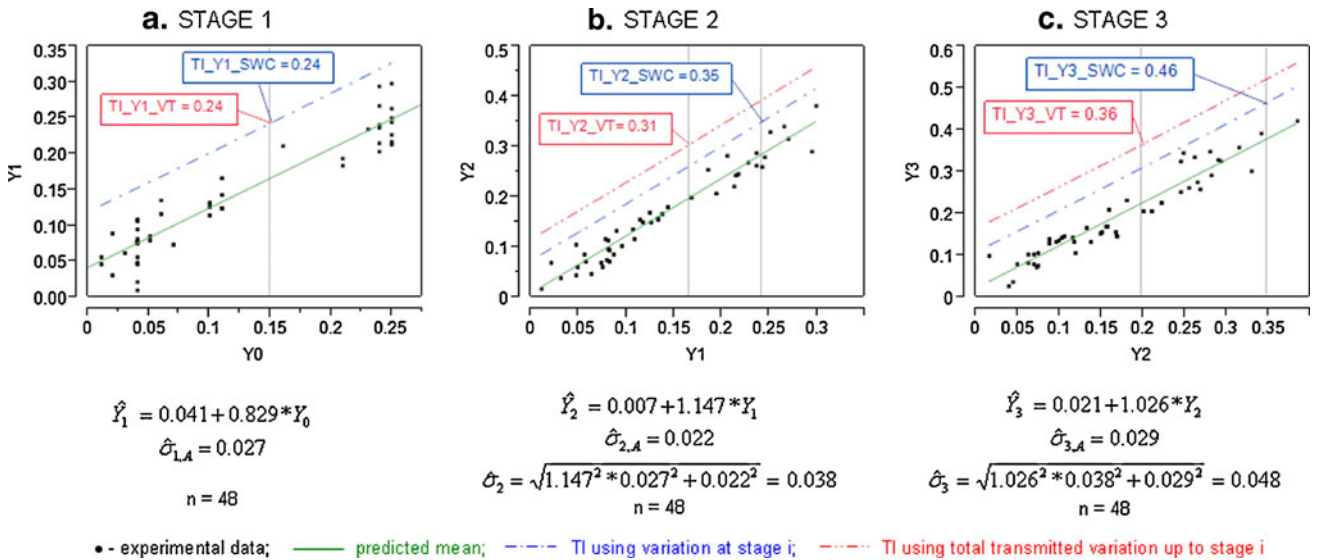
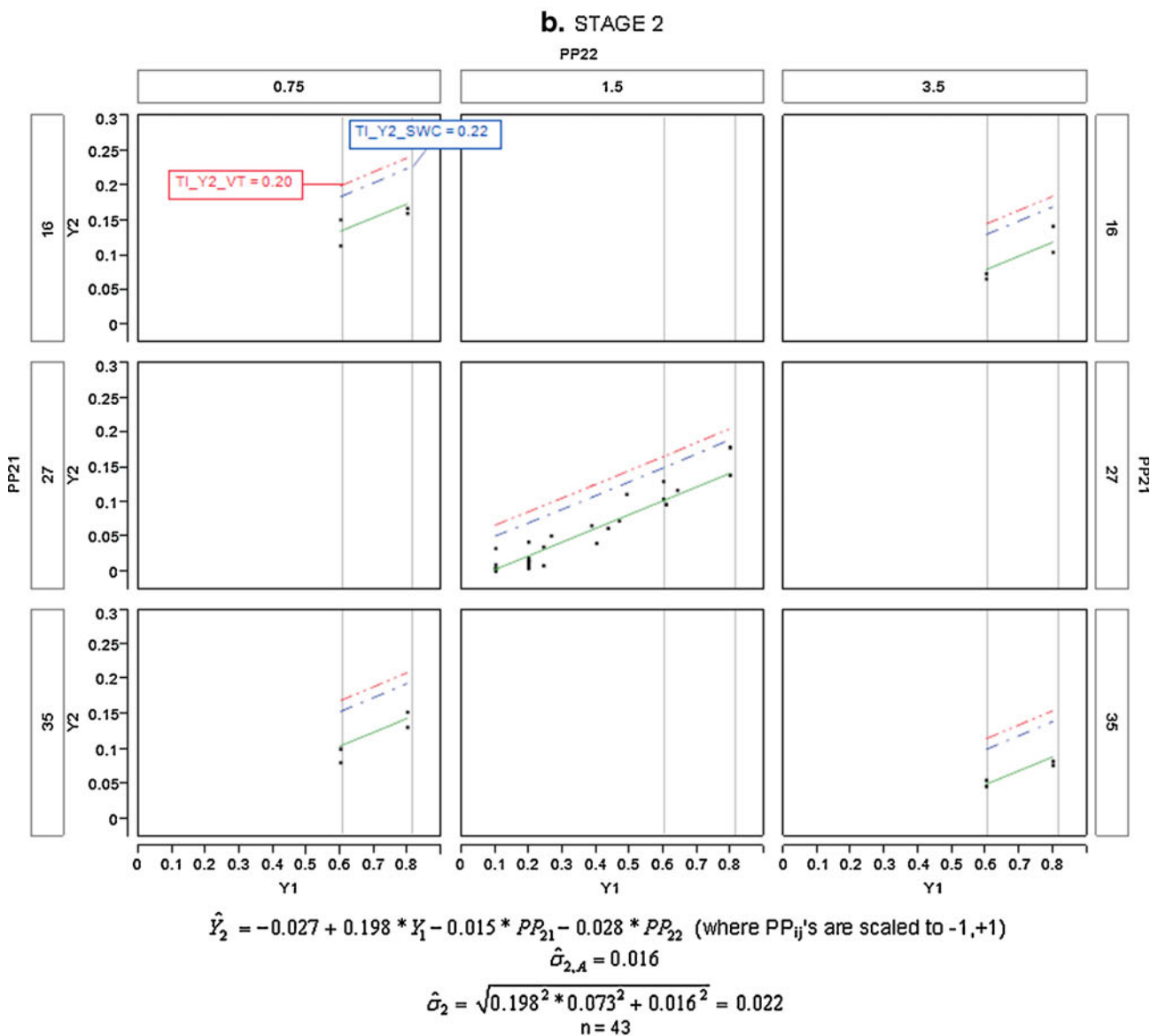
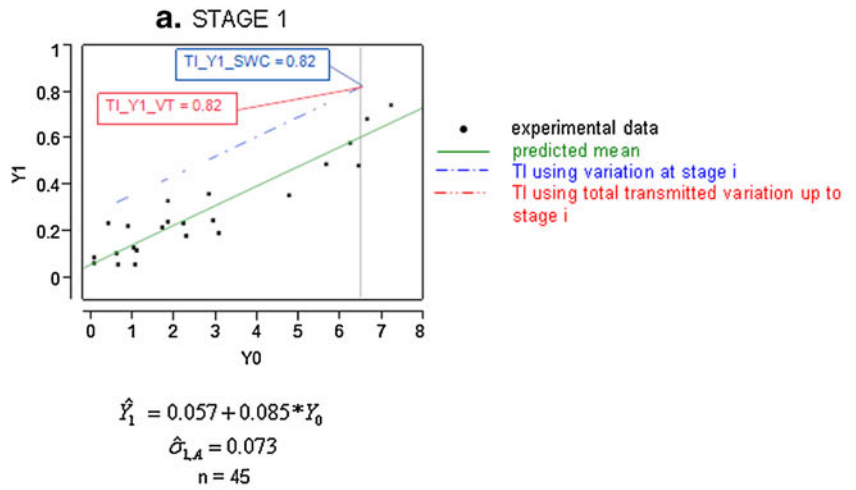


Fig. 4. Case 1 example: High extent of variation transmission, low-stage variability. Three-staged process where Y_i 's appear correlated solely with respective Y_{i-1} 's



• - experimental data; — predicted mean; - - - TI using variation at stage i; ···· TI using total transmitted variation up to stage i
Fig. 5. Case 2 example: Low extent of variation transmission, low-stage variability. **a** Stage 1 of a two-staged process where Y_1 appears correlated with Y_0 . **b** Stage 2 of a two-staged process where Y_2 appears correlated with Y_1 and process parameters PP_{21} and PP_{22}

triangular) within its normal operating range. The scope of the current paper, however, is on how to account for random sources of variation in each stage, $\sigma_{i,A}$. Therefore, in evaluating the expected stage output Y_i , the systematic sources of variation are fixed at their worst-case scenarios (Y_0 at input material specification; PP_{ij} at the setting that gives the highest level of Y_i), in keeping with the overall risk minimization strategy. For accounting for the stochastic nature of the systematic sources of variation, the reader is referred to these papers (3,14,15).

Figures 4, 5, and 6 show the experimental data, the predicted mean of the fitted regression model (solid line generated from Eq. 1), and the constructed tolerance intervals (dashed lines) using formulas in Table I for SWC and VT methods. Estimates of the variation at each stage ($\hat{\sigma}_{i,A}$), and the total transmitted variation up to a stage ($\hat{\sigma}_i$ from Eq. 4) are also presented. Reference lines on X-axis are drawn corresponding to the levels at which to evaluate the input material Y_{i-1} to obtain the Y_i tolerance interval.

For case 1 (Fig. 4), the slopes of the regression lines at each stage are all large ($\hat{\beta}_i \geq 0.829$). This exemplifies the high extent of variation transmission scenario in the simulation. The variabilities at each stage are relatively small ($\hat{\sigma}_{i,A} \leq 0.029$). The reference line in stage 1 (Fig. 4a) is 0.15 corresponding to Y_0 specification. The predicted mean $\hat{\mu}_1|_{Y_0=0.15} = 0.166$ and the calculated $TI = 0.24$. This value is identical for both SWC and VT methods at stage 1 since it is assumed that the total transmitted variation up to the first stage equals the variation at that stage (i.e., $\hat{\sigma}_1 = \hat{\sigma}_{1,A}$). For stage 2 (Fig. 4b) using SWC, Y_1 is evaluated at the worst-case output of stage 1 ($TI_{Y1_SWC} = 0.24$) and using variation at stage 2 ($\hat{\sigma}_{2,A} = 0.022$), the calculated $TI_{Y2_SWC} = 0.35$. For stage 2 using VT, the Y_1 is evaluated at the predicted mean output of stage 1 ($\hat{\mu}_1 = 0.166$) and using the total transmitted variation up to stage 2 ($\hat{\sigma}_2 = 0.038$), the calculated $TI_{Y2_VT} = 0.31$. This procedure is repeated for stage 3 (Fig. 4c) and the calculated TI 's are 0.46 and 0.36, for SWC and VT, respectively. For this case scenario of high extent of variation transmission with low stage variability, the calculated TI at the final process stage using VT is 0.1 lower than SWC.

For case 2 (Fig. 5), the slopes are relatively small ($\hat{\beta}_i \leq 0.198$) and stage variability are also small ($\hat{\sigma}_{i,A} \leq 0.073$). The reference line in stage 1 (Fig. 5a) is 6.5 corresponding to Y_0 specification. At stage 2, PP_{21} and PP_{22} along with Y_1 appear to significantly influence Y_2 . Figure 5b groups the observations according to the PP_{2j} settings (center points for historical data and low-high factorial settings for DOE data). PP_{2j} 's are fixed at settings that give the highest value of Y_2 ($PP_{21} = 16$ and $PP_{22} = 0.75$) as a risk minimization strategy. For stage 2 using SWC, Y_1 is evaluated at the worst-case output of stage 1 ($TI_{Y1_SWC}|_{Y_0=6.5} = 0.82$) and using $\hat{\sigma}_{2,A} = 0.016$, the calculated $TI_{Y2_SWC} = 0.22$. For stage 2 using VT, Y_1 is evaluated at the predicted mean output of stage 1 ($\hat{\mu}_1|_{Y_0=6.5} = 0.607$) and using $\hat{\sigma}_2 = 0.022$, the calculated $TI_{Y2_VT} = 0.20$. In this case of low extent of variation transmission and low stage variability, the calculated TI at the final process stage using VT is 0.02 lower than SWC.

For case 3 (Fig. 6), the $\hat{\beta}_i$'s are 0.043, 0, and 0.924 for stages 1, 2, and 3, respectively, and the $\hat{\sigma}_{i,A}$'s are all relatively low (≤ 0.025). The reference line in stage 1 is $LN(1) = 0$ corresponding to natural-log-transformation of $Y_0 = 1$ specification (Fig. 6a). The apparent lack of correlation between Y_2 and Y_1 ($\hat{\beta}_2 = 0$) or with any of the process parameters PP_{2j} 's ($\hat{\gamma}_{2j}'s = 0$) in stage 2 (Fig. 6b), may occur, as discussed earlier, during process robustness studies or in a highly variable process. With $\hat{\beta}_2 = 0$, the total transmitted variation up to stage 2 using Eq. 4 is $\hat{\sigma}_2 = \sqrt{\hat{\beta}_2^2 * \hat{\sigma}_1^2 + \hat{\sigma}_{2,A}^2} = \sqrt{0^2 * 0.025^2 + 0.022^2} = 0.022$. This means that $\hat{\sigma}_1$ has "zero" extent of transmission into stage 2 and only $\hat{\sigma}_{2,A}$ comprises $\hat{\sigma}_2$. Since the regression model in stage 2 is no better than the overall mean of the Y_2 observations ($\hat{Y}_2 = \bar{Y}_2 = 0.057$), the predicted mean will be 0.057 whether Y_1 is evaluated at $TI_{Y1_SWC} = 0.20$ or at $\hat{\mu}_1 = 0.133$. Because of this and since $\hat{\sigma}_2 = \hat{\sigma}_{2,A}$, then the calculated $TI_{Y2} = 0.12$ is identical for SWC and VT. For stage 3 (Fig. 6c) using the SWC method, Y_2 is evaluated at the worst-case output of stage 2 ($TI_{Y2_SWC} = 0.12$) and

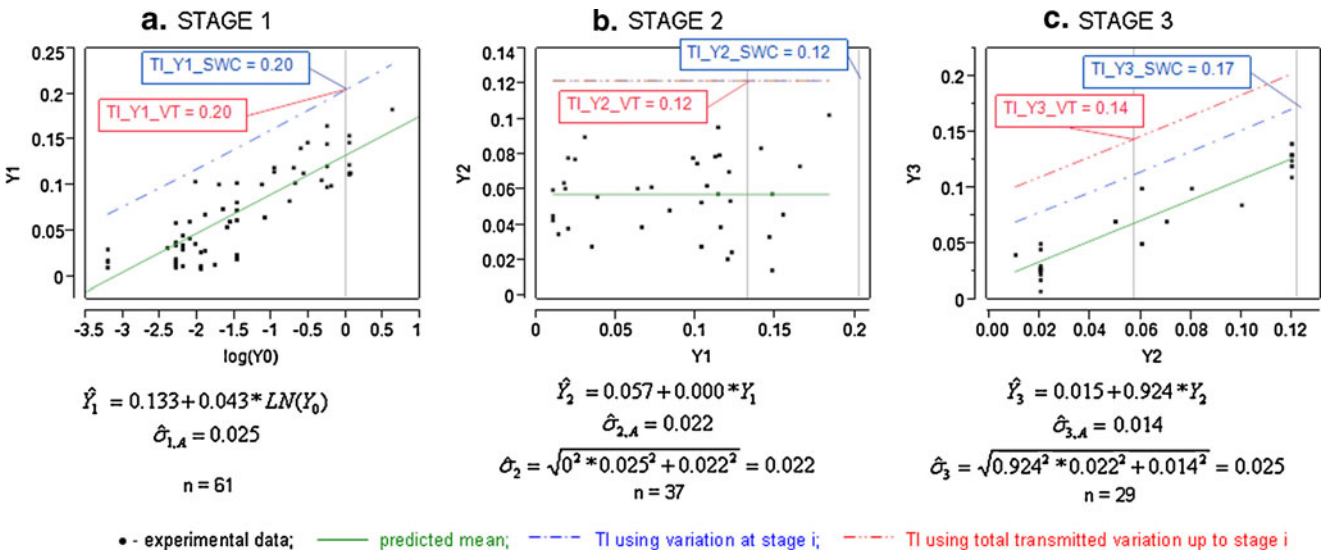


Fig. 6. Case 3 example: Variable (low, "zero," and high) extent of variation transmission, low-stage variability. Three-staged process where Y_1 and Y_3 appear correlated with respective input materials but Y_2 does not appear correlated with Y_1 or any PP_{2j} 's

using $\hat{\sigma}_{3,A} = 0.014$, the calculated $TI_{Y_3_SWC} = 0.17$. For stage 3 using the VT method, Y_2 is evaluated at the predicted mean output of stage 2 ($\hat{\mu}_2 = \bar{Y}_2 = 0.057$) and using $\hat{\sigma}_3 = 0.025$, the calculated $TI_{Y_3_VT} = 0.14$. For this case of variable (low, "zero," and high) extent of variation transmission with low stage variability, the calculated TI at the final process stage using VT is 0.03 lower than SWC.

DISCUSSION

Simulation results indicate that at low extent of variation transmission, at both low- and high-stage variability, and at small sample size, SWC performs poorly relative to VT. With increased sample size, the two methods become practically comparable with the average TI lengths of VT only slightly shorter than those of SWC. This trend is corroborated in the low (or variable) extent of variation transmission, low-stage variability real data examples (cases 2 and 3); VT is only slightly shorter than SWC by 0.02 or 0.03.

The superiority of VT over SWC is especially demonstrated in simulation of high extent of variation transmission and high stage variability. In this scenario, VT more effectively maintains the nominal confidence level and more precisely estimates the true 99th percentile parameter than SWC. The real data example case 1 involves high extent of variation transmission but with low-stage variability. The calculated tolerance limit for VT is 0.1 shorter than SWC and had the stage variability been high, this difference would have been much bigger.

An impurity is introduced in the pharmaceutical drug manufacturing process either from its initial level in the starting material or as a by-product of chemical reaction. If the efficiency of the process in reducing/eliminating this impurity is low (*i.e.*, poor purging), its level going into a stage will approximately remain unchanged from the previous stage. This chemical specie mass balance is a manifestation of high extent of variation transmission which is not uncommon in pharmaceutical drug manufacturing process. The high extent of variation transmission, specifically coupled with high-stage variability, is where the industry practice method SWC performs particularly poorly as shown in the simulation. Setting impurity control limits that exceed the true capability of the process, even by small exceedances, as can be the case using SWC, may have critical implications on the safety of the drug in human patients. Thus, it becomes more imperative to set a more realistic basis for setting control limits by properly accounting for transmission of variation through a multi-staged process using the VT method.

Generalization of Calculation Procedure

The variation transmission concept presented in the simulation and real data examples can be generalized into practical, procedural steps for setting acceptance criteria: (1) screen for the pertinent sources of variations at each stage of a multi-staged process using available studies (*e.g.*, process development data including retrospective historical database and/or prospective factorial DOE studies), (2) estimate effects of systematic and random sources of variation at each stage from the fitted regression model (Eq. 1), (3) estimate

total variation transmitted up to stage i using Eq. 4, (4) calculate upper one-sided tolerance limits for each quality attribute at each stage using Eq. 6 wherein S is estimated from step 3, (5) use the calculated tolerance limits as the basis for setting acceptance criteria in the intermediate and the final stages.

CONCLUSION

This paper addresses the question of how variation in previous stages of a multi-staged pharmaceutical manufacturing process can be appropriately accounted for in subsequent stages. The end goal is establishing a method for setting statistically-based acceptance criteria for intermediate and final stages of the process. Computer simulations are used to compare serial worst case (SWC) and variation transmission (VT) approaches in terms of maintaining the simulated confidence level and estimating the true proportion parameter. When the extent of variation transmission is low, SWC performs poorly but with increased sample size, it is practically comparable with VT. When the extent of variation transmission is high and especially when stage variability is high, VT is the superior method. The real data examples which considered various cases of extent of variation transmission, stage variability, and apparent correlation (or lack thereof) of output with input and/or process parameters corroborate the findings from the simulation. Therefore, variation transmission (VT) approach is recommended for setting acceptance criteria in a multi-staged pharmaceutical manufacturing process.

ACKNOWLEDGMENTS

The author thanks Dr. Jorge Quiroz for helpful discussions regarding the concept and methodology presented in this paper.

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