A Methodology for the Robust Evaluation of Pharmaceutical Processes under Uncertainty*

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It is becoming widely recognized in the pharmaceutical industry that a more structured approach to process development would benefit the quality of the developed processes to ensure added value to the products in the long term. In this paper, a model-based methodology is proposed for the robust evaluation and development of pharmaceutical processes which realizes the pressures inherent to the industry and that critical decisions need to be made at all stages despite incomplete knowledge of the process. It aims to identify the most relevant process information subject to the availability and quality of the prevailing data at any given stage in the development, so that informed decisions can be made at short notice. Steps towards a multiscenario approach are proposed to resolve stochastic model parameter uncertainties in process sequences and evaluate robust performance indicators. Correlation analysis is used to provide an indication of the critical stage interactions under uncertainty so that potential causes of problems can be identified in a more rigorous manner. The potential benefits of the approach are demonstrated using a two-stage example under two parameter uncertainties. The directions required to complement a general methodology regarding practical application to real problems are indicated.

Increasing emphasis and competition for new pharmaceutical chemicals requires consistent, high quality products in shorter lead times to market. Many of the challenges facing process development are unique to the pharmaceutical industry. Complex organic syntheses of high cost raw materials coupled with implementation of laboratory defined multiphase batch processes into existing multipurpose equipment and a continual need for high quality chemicals for trials often at short notice, combine to pose unique challenges [1]. Additionally, process development is tightly monitored by regulatory legislature and restricted by the substantial economic and time pressures to be first to the market. The implications are that simultaneous process development, scale-up and chemical production must be achieved in an environment in which scale-up of laboratory defined processes proceeds as quickly as possible in a manner of '*learning by doing*' where all the development effort is directed at process feasibility with little resource for optimization. Despite the inevitable trial and error in scale-up processes, a decision needs to be made as to whether the current process knowledge is sufficient to start a pilot plant run with an acceptable expectation of success or whether it would be beneficial to improve the quality of the data prior so that surprises are less frequent. A key element for effective process development is the ability to make the right decisions at early stages, despite uncertain and incomplete information on the process.

The problem posed in this work is concerned with the uncertainty in the process models due to the lack of information for that process at any given stage in development. The pharmaceutical industry acknowledges that building reliable process models would help to save resources in the long term by providing answers to process issues, reducing the trial and error aspect and introducing the opportunity for optimization [2]. However, there is often considerable uncertainty in the inherent physicochemical mechanisms of pharmaceutical processes. Process models and parameters are generated from laboratory experiments in the early stages of the development and may be refined during later stages. There may be no evidence that under the conditions for which this information was established, a larger scale process will exhibit the same behaviour at the operating conditions enforced within existing equipment, which is almost certainly of different design and configuration.

The aim of this work is not a rigorous modelling validation, but rather to identify within simple models where the uncertainties can have a major impact

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on the process sequence. It would be useful to identify whether the quality of the available data and more specifically the uncertainty in the parameters of the subsequent models, can potentially cause problems which may be interpreted in the real process. There appears to be significant potential for a computational tool which may help provide this information to support process development decisions and focus experimental effort *before* the start of scale-up runs.

THEORETICAL

Methods for Uncertainty

Uncertainty and incomplete knowledge is always a problem in the design process. The conventional approach often used in industry is the incorporation of design margins based on empirical over-design factors. More rational systematic approaches to account for uncertainty have been investigated. The concept of flexibility analysis for design optimization was introduced by *Halemane* and *Grossmann* [3], who solved a max-min-max constrained feasibility test problem under nonprobabilistic uncertainty ranges. *Swaney* and *Grossmann* [4] extended this concept to a flexibility index which measures the maximum parameter deviation for which feasibility can be guaranteed. *Straub* and *Grossmann* [5, 6] define a flexibility index subject to stochastic parameter uncertainty measuring the probability of success accounting for hard and soft constraints. Stochastic flexibility analyses for design optimization have also received attention [7]. *Pinto* [8] introduces a cost of parameter uncertainty, used to trade-off resource allocation against the potential benefit of reducing the uncertainty.

Many of these approaches are directed towards the design of continuous systems and some have been extended to dynamic systems, for which literature is more limited. *Terwiesch et al.* [9] review industrial batch modelling and operating practice and suggest approaches for optimization of operating strategy under model uncertainty. These include probabilistic measures of success based on the stochastic flexibility index approach [10], and multiscenario approaches used by *Ruppen et al.* [11] to optimize batch reactor operation under parameter uncertainties. *Dimitriadis* and *Pistikopoulos* [12] use a nonprobabilistic approach and introduce an index quantifying the ability of a design to pass a dynamic feasibility test. *Samsatli et al.* [13] introduce robustness metrics for expectation operators which take into account the one-sided nature of many practical thresholds. These approaches have tended to address optimal operation of single units under uncertainty. Operational windows have indicated an application to multistage processes where windows which guarantee overall feasibility are specified for each stage *a priori* [14, 15].

The pharmaceutical industry is beginning to recognize the need for a systematic approach to sustain the development of higher quality processes using less resources in shorter times [2, 16], to rely not only on human expertise but integrating this knowledge with computational tools so that these decisions can be based on a wider range of structured information. In this article a methodology for model-based pharmaceutical process development is proposed in view of the steps towards the utilization of a multiscenario approach to generate the data for the critical evaluation of batch process sequences under model parameter uncertainty.

Methodology

The available information concerning a process needs to be structured in a flexible computational tool to support design decisions regarding the viability of a process under incomplete knowledge. With simple models of a proposed sequence of operations and characteristic data on the parameter uncertainties, a general methodology for a model-based approach to pharmaceutical process development (Fig. 1) can be used to identify the critical parameters, stage interactions, and potential problems in the integrated process and focus attention to improving the model definition.

A sensitivity analysis identifies the most significant parameters to reduce the size of the multiscenario problem. Solution of the multiscenario problem can yield expectation operators measuring conventional aspects of a process (*e.g.* a quality objective or variance) or more specific robustness metrics (*e.g.* expected extent of violation [13]). Expectation is the resolution of the uncertain parameter space by multiple integration of the product of the joint uncertain parameter probability distribution and some quality function, over the number of uncertain parameters (see Appendix I).

In this article the multiscenario problem is posed as an evaluation in which it is assumed the conditions are based on an initial process definition derived from laboratory experiments. Alternatively an optimization problem may be posed which could be formulated as either a nominal or a multiscenario optimal control problem in which some measure of robustness is incorporated.

Identification of a high risk of unacceptable performance, denoted by failure of key expectation thresholds, leads to an important process development decision. The primary limiting factor may be due to the poor quality of the model parameters or the limitations of the proposed operations and existing equipment. To support this decision, an indication of the critical parameter is obtained using a correlation analysis based on the information generated in the multiscenario problem. The context of criticality depends on the objectives of the process development. It would be desirable to be able to predict what reduction in

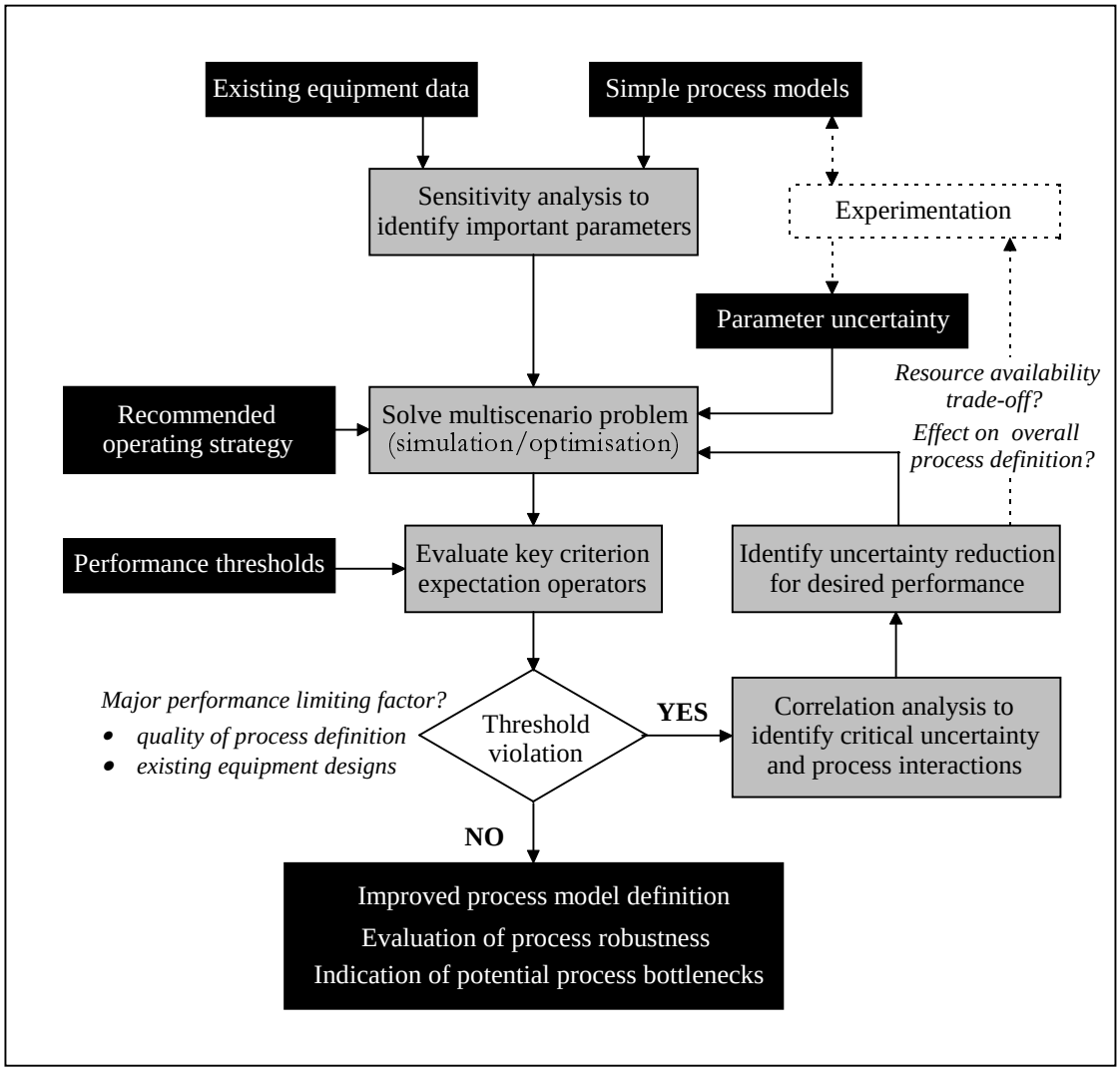

Fig. 1. A general methodology for a model-based approach to pharmaceutical process development under uncertainty.

which uncertainty gives the greatest decrease in adverse effect on the process with respect to the final objective so that a better end product can be expected. It would also be important to reduce the uncertainty which ultimately results in a better defined process and a more confident understanding of the interactions with respect to the current models of the overall process. A reduction in variance would indicate the former, assuming the available models are reasonably reliable. However these objectives may conflict and a decision can be based on the trade-off.

The correlation analysis aims to improve the understanding of the uncertain system by identifying the interactions of the integrated system under uncertainty in a systematic manner. Despite the limitation of the correlation analysis in determining only approximate qualitative linear relationships, it is considered adequate to provide sufficient indication of the critical interactions, for the requisite level of investigation. The expectation shows the effect quantitatively. Analysis of certain relationships (Fig. 2) can provide this information. Steps (*i*) and (*v*) directly indicate the critical uncertain parameters, θ_{mc}, and stage variables, $x(t_s)_{\mathrm{c}.s}$, to the final objective, Q. Step (*ii*) gives the critical final stage variables comprising Q, from which critical upstream variables are identified, Step (*iii*). Step (*iv*) relates the degree of relation between $\theta_{m.s}$ and $x(t_s)_{\mathrm{i}.s}$, for each stage, s. While it would be reasonable to assume that reducing the uncertainty in the earliest stage may provide a clearer definition of the process as propagation of the uncertainty through the stages *via* the interactions is decreased, the correlation analysis can be used to deduce the critical stage.

Identification of the critical parameter, θ_{mc}, creates a focus for design of experiments towards a specific process mechanism in the relevant stage. First, an indication to the uncertainty reduction in θ_{mc} required to meet the desired performance thresholds is achieved through an optimization which finds the new constricted θ_{mc} limits about the original mean, μ. Trade-offs between expected performance and uncer-

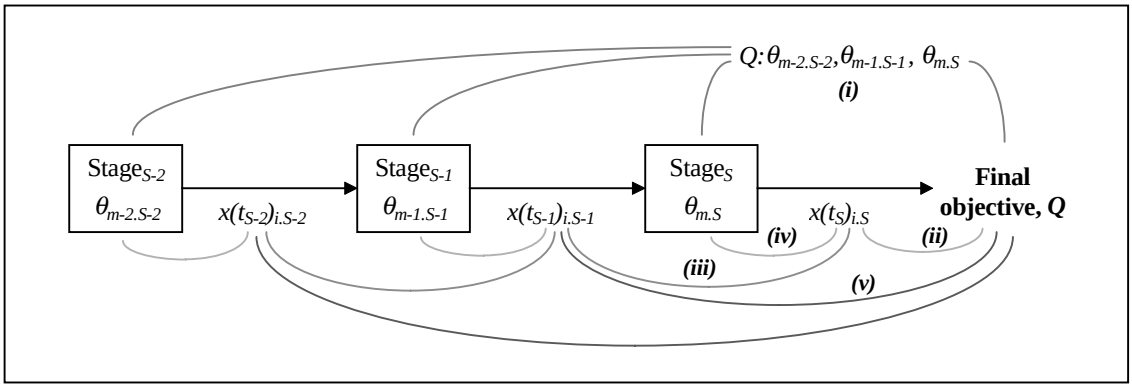

Fig. 2. Correlated interactions for an integrated process sequence.

tainty reduction may be generated. This information provides a basis for the decision, indicated in Fig. 1, regarding resource allocation towards additional experimentation for the improvement of the process model definition with respect to the critical mechanism. The outcome of the experiments should provide a more accurate definition of the critical parameter or a revised model structure, enhancing the overall model definition in an efficient and effective manner made possible by the model-based approach.

The methodology needs be flexible enough for use throughout progressive stages of development, incorporate new data as it becomes available from experiments or scale-up runs, track the progressive reduction in uncertainty and promote process alternatives. Its purpose is to aid engineers in the identification of potential process bottle-necks by examining 'what if' scenarios where process interactions may be difficult to predict by intuition, so that process development is achieved in a manner of *learning before doing* as opposed to the current trend of *learning by doing*. An example is used to identify the potential of the methodology with regard to the stated criteria.

Example

The proposed methodology is illustrated using a simple example of a two-stage batch reactor sequence (Fig. 3). Each stage is assumed to be isothermal, well mixed with instantaneous addition of feeds (A into Stage 1, D and final contents of Stage 1 into Stage 2). The reactions are liquid phase of constant volume, elementary and irreversible according to the reaction scheme below

$$\text{Stage 1. } (\text{rx}_1 \text{ and } \text{rx}_2)\text{: A} \xrightarrow{k_1} \text{B} \xrightarrow{k_2} \text{C} \qquad (A)$$

$$\text{Stage 2. } (\text{rx}_3)\text{: B} + 2\text{D} \xrightarrow{k_3} \text{E } \textit{desired reaction} \qquad (B)$$

$$(\text{rx}_4)\text{: C} + 2\text{D} \xrightarrow{k_4} \text{F } \textit{undesired reaction} \qquad (C)$$

In Stage 1, component A reacts to form the desired intermediate B in rx_1, but a consecutive reaction rx_2 converts B to an undesired intermediate C. On completion of Stage 1, the reaction mixture is passed to Stage 2 where B reacts with reactant D, rx_3, to form the desired product E whilst parallel reaction rx_4 forms impurity F. The reaction conditions (Fig. 3), are assumed to be derived from a workable process, defined by chemists in the laboratory. Although sub-optimal under these conditions, the concentration of B in Stage 1, C_{B1}, is close to a maximum and the chemist's targets of reactant conversions, $X_{\text{A}} \geqq 99$ % and $X_{\text{D}} \geqq 98$ %, are achieved. However at the larger scale the process objectives change and a purity threshold of product E, $P_{\text{E}} \geqq 80$ %, is recommended on completion of Stage 2 due to the known limitations of proposed downstream purification operations.

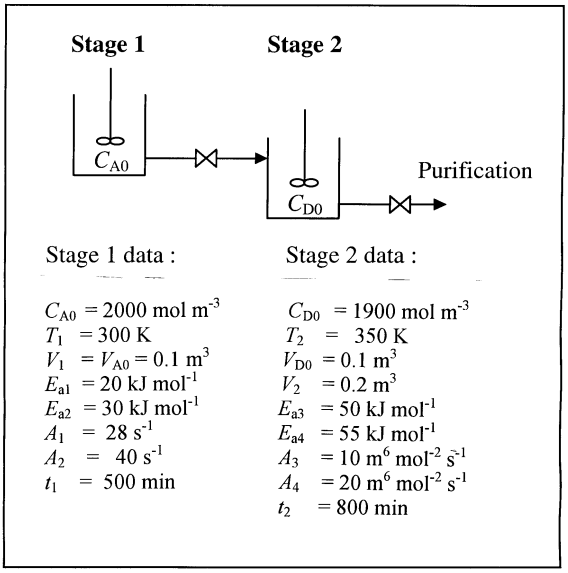

Fig. 3. Two-stage batch reactor sequence for Example.

Simple models of both stages are available (see Tables 2 and 3, Appendix II) for which the values of the experimentally derived activation energies are uncertain. A sensitivity analysis indicates that only deviations in E_{a2} and E_{a3} affect the process significantly. E_{a2} and E_{a3} are assumed to be independent and characterized by normal probability distributions, N(30000, 3000) and N(50000, 5000), respec-

tively, within a $\sigma_1.\sigma_2$ joint distribution limit. The multiscenario stochastic problem posed is an evaluation, where the conditions are assumed to be fixed at those recommended by the chemists. It is desired to evaluate the process with respect to the expected value of P_E over the entire uncertainty space and the expected extent of P_E threshold violation in the case of sub-grade performance (see Appendix I). 7th order Gaussian quadrature (49 scenarios for 2-dimensional uncertainty) is used to solve the multiscenario problem.

RESULTS AND DISCUSSION

The results for the initial evaluation under uncertainty (Table 1) show that the expected value of P_E is 1.5 % below the desired threshold with an expected violation of 4.1 % in the uncertain parameter regions of sub-grade performance. The significant results of the correlation analysis under both uncertainties for the failure scenarios (Fig. 4) indicate a stronger relation between E_{a2} and P_E than E_{a3} and P_E. The potential problem is portrayed by the uncertainty in E_{a2}, considering its strong relation with C_{B1}, C_{C1} with the analysis indicating the criticality of the interactions between C_{B1}, C_{C1} and the desired product C_{E2} and impurity C_{F2}. With respect to the final objective, P_E, the most critical stage completion variables are C_{B1}, C_{C1} and C_{E2}, C_{F2}. However, it can also be seen in Fig. 4 that the critical variables of Stage 1 are strongly correlated to the respective stage uncertainty which is not the case for Stage 2, indicating the greater adverse effect of the uncertainty in Stage 1 on the overall process. It can be inferred that a reduction in the E_{a2} uncertainty, over E_{a3}, would achieve better expected results.

Table 1. Expectation Operators for Example

	Initial evaluation
$E(P_E)$	0.788
$E_{viol}(P_E)$	0.041
$E_{var}(P_E)$	0.007

A 32 % reduction in the uncertainty of E_{a2} achieves the desired expected value threshold of 80 % purity and reductions in the expected threshold violation and variance of 33 % and 61 %, respectively. The relative effects of the uncertainty reduction in E_{a2} or E_{a3} on the expected value and threshold violation indicators are apparent in the trade-off curves in Figs. 5*a* and *b*. It is clear that reducing the uncertainty in E_{a2} as opposed to E_{a3}, a distinct advantage is available regarding the expectation objectives of product purity performance, $E(P_E)$, and increased confidence in both the adverse performance, $E_{viol}(P_E)$, and in the model definition of the overall process, $E_{var}(P_E)$. Correlation analysis identifies the change in the critical interactions which result from this reduction in uncertainty.

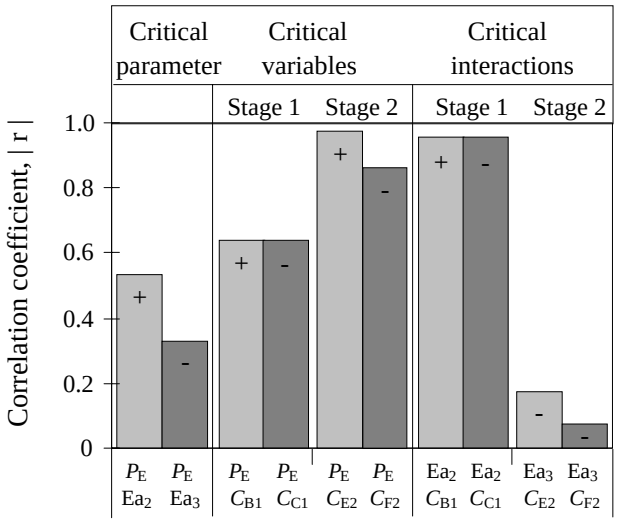

Fig. 4. Critical correlation coefficients for failure scenarios of Example.

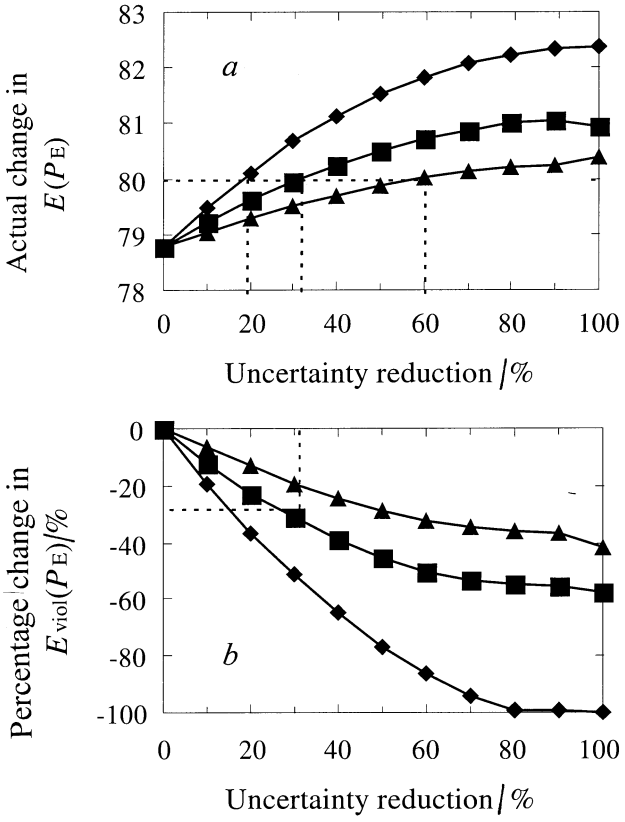

Fig. 5. Uncertainty reduction trade-off curves. ■ E_{a2} uncertainty reduction, ▲ E_{a3} uncertainty reduction, ♦ E_{a2} and E_{a3} uncertainty reduction. *a*) Actual change in $E(P_E)$, *b*) percentage change in $E_{viol}(P_E)$/%.

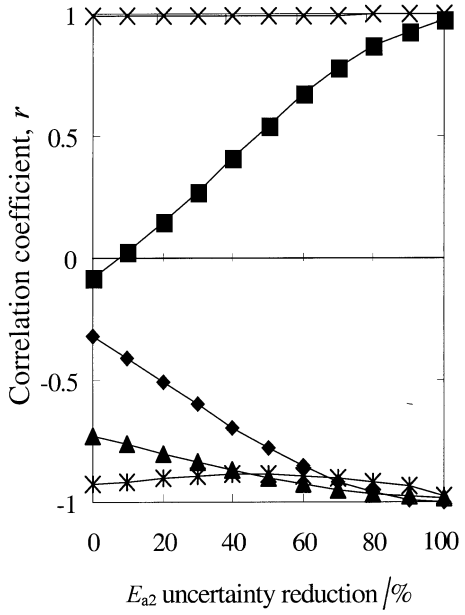

Fig. 6. Effect of E_{a2} uncertainty reduction on $P_E : C_{i2}$ correlation coefficients. ♦ $P_E : C_{B2}$, ■ $P_E : C_{C2}$, ▲ $P_E : C_{D2}$, × $P_E : C_{E2}$, ∗ $P_E : C_{F2}$.

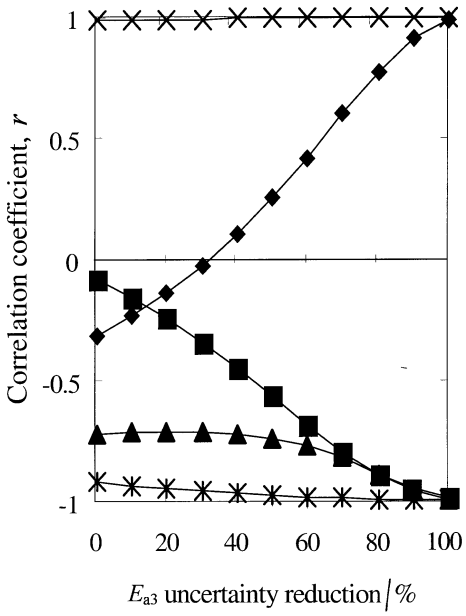

Fig. 7. Effect of E_{a3} uncertainty reduction on $P_E : C_{i2}$ correlation coefficients. ♦ $P_E : C_{B2}$, ■ $P_E : C_{C2}$, ▲ $P_E : C_{D2}$, × $P_E : C_{E2}$, ∗ $P_E : C_{F2}$.

It makes sense that the potential problem caused by the uncertainty in E_{a2} is eliminated, since C_{E2} is still critical to P_E (C_{F2} is not) but is not strongly related to either the Stage 1 or Stage 2 uncertainty. E_{a3} appears to be marginally the critical parameter. Uncertainty reduction in both E_{a2} and E_{a3} provides significantly superior performance but would require more experimentation. The results appear to corroborate the prediction of the critical parameter from the correlation analysis.

Analysis of stepwise reductions in each uncertainty indicates that reduction in one uncertainty leads to a reduced correlation with the final objective but an increase in the correlation with the remaining uncertainty. Not so intuitive is the identification of how the behaviour of the critical interactions changes with respect to each reduction. As uncertainty in either E_{a2} or E_{a3} is reduced and the system approaches uncertainty in only one dimension, the relationship between P_E and the Stage 2 variables appears to approach linearity indicated by the correlation coefficients converging to 1 or -1 (Figs. 6 and 7). Considering the nature of the objective function (see Table 3, Appendix II) this behaviour may not be surprising. Since a stronger correlation to P_E (converging to 1 or -1) in the Stage 2 variables is observed at all levels of uncertainty reduction in E_{a2} over E_{a3} (Figs. 6 and 7), it may be surmised that less refinement of the E_{a2} parameter is required to give an equivalent level of confidence in the given definition of the overall process. The opposite response between the correlations of C_{B2} and C_{C2} to P_E under E_{a2} or E_{a3} uncertainty reduction can be attributed to the correlations of C_{B1} and C_{C1} converging to 0 but diverging to 1 and -1 for each respective reduction. This is intuitive considering the reaction scheme.

The ability to provide such insight in more complex systems would be useful in the decision-making process (Fig. 1). It is important to note the possibility a reduction in uncertainty will not give an improvement in all the performance indicators, depending on the shape of the feasible region inside the uncertainty space. However, the need for a more accurate process model and in particular the critical stage are identified. This must be the ultimate aim of a model-based approach to process development in the long term, so that behaviour can be confidently predicted, problems ascertained *a priori* and optimization can become a more realistic target.

Whilst the considered example is of elementary complexity and the results could be seen to be intuitive, considerations of real process sequences are not. The multiphase batch processes inherent to the pharmaceutical industry mean that even using simple models, the stage interactions and effect on the final end product will often be impossible to predict across varying production scales and different equipment. Further work will be directed at integrating multiphase models into the process sequence, implementation of different formulations of the multiscenario problem (*e.g.* robust optimal control), and increasing the efficiency of the multiscenario solution which could potentially become an excessively large problem under more uncertainties.

CONCLUSION

The need for a more structured approach to the development of pharmaceutical processes is acknowledged with respect to the industrial pressures. The potential of the approach is assessed using a simple two-stage example with uncertainty in two parameters. Solution of the stochastic multiscenario problem gives the expected key performance indicators for which the correlation analysis conclusively indicated the correct prediction of the critical limiting parameter. It was also possible to identify the important stage interactions under the prevalent uncertainty in an efficient manner, using the data generated from the multiscenario problem. It is concluded that the methodology has the capacity to provide useful information but further work is required to confirm the multiscenario approach regarding practical application to real problems. A more efficient method to resolve the uncertainty may be necessary to ensure a tractable robust optimal control problem in which a larger sequence of models and more uncertainties can be accommodated.

SYMBOLS

k	reaction rate constant, mol m^{-3} s^{-1} for k_1 and k_2; m^6 mol^{-2} s^{-1} for k_3 and k_4	
r	correlation coefficient	
rx	elementary reaction	
t_S	stage completion time	min
A_1, A_2	pre-exponential factor	s^{-1}
A_3, A_4	pre-exponential factor	m^6 mol^{-2} s^{-1}
C	component concentration	mol m^{-3}
C_0	initial component concentration	mol m^{-3}
E	expected value	
E_a	activation energy	kJ mol^{-1}
E_{viol}	expected violation	
E_{var}	expected variance	
P	purity	%
T	temperature	K
V	reaction volume	m^3
μ	mean	
θ	uncertain parameter	
σ	standard deviation	

Indices (sets for Example are shown)

c	criticality identifier
i	variable identifier, i ∈ {A, B, C, D, E, F}
l	reaction identifier, $l \in \{1, 2, 3, 4\}$
m	uncertain parameter identifier, $m \in \{1, 2\}$
s	stage identifier, $s \in \{1, 2\}$

REFERENCES

1. Basu, P. K., *Chem. Eng. Prog. 94*, 75 (1998).
2. Basu, P. K., Mack, R. A., and Vinson, J. M., *Chem. Eng. Prog. 95*, 82 (1999).
3. Halemane, K. P. and Grossmann, I. E., *AIChE J. 29*, 425 (1983).
4. Swaney, R. E. and Grossmann, I. E., *AIChE J. 31*, 621 (1985).
5. Straub, D. A. and Grossmann, I. E., *Comput. Chem. Eng. 14*, 967 (1990).
6. Straub, D. A. and Grossmann, I. E., *Comput. Chem. Eng. 17*, 339 (1993).
7. Pistikopoulos, E. N. and Ierapetritou, M. G., *Comput. Chem. Eng. 19*, 1089 (1995).
8. Pinto, J. C., *Chem. Eng. Sci. 53*, 2029 (1998).
9. Terwiesch, P., Agarwal, M., and Rippin, D. W. T., *J. Proc. Cont. 4*, 238 (1994).
10. Terwiesch, P., Ravemark, D., Schenker, B., and Rippin, D. W. T., *Comput. Chem. Eng. 22*, Suppl., S201 (1998).
11. Ruppen, D., Benthack, C., and Bonvin, D., *J. Proc. Cont. 5*, 235 (1995).
12. Dimitriadis, V. D. and Pistikopoulos, E. N., *Ind. Eng. Chem. Res. 34*, 4451 (1995).
13. Samsatli, N. J., Papageorgiou, L. G., and Shah, N., *AIChE J. 44*, 1993 (1998).
14. Samsatli, N. J., Papageorgiou, L. G., and Shah, N., *Comput. Chem. Eng. 23*, Suppl., S887 (1999).
15. Woodley, J. M. and Titchener-Hooker, N. J., *Bioprocess Eng. 14*, 263 (1996).
16. Shah, N., Samsatli, N. J., and Sharif, M., *5th Int. Conf. FOCAPD*, Paper I05, 1 (1999).

APPENDIX I

Mathematical Approach

For the evaluation problem the general expression for an expectation operator of some quality Q or function of Q over n scenarios and m uncertain parameters θ, is

$$E(Q) = \int_{m\in\Theta} J(\theta_m) Q(\dot{x}, x, y, t, \theta_m) \mathrm{d}\theta_m = \\ = \sum_{n=1}^{N} j_n Q(\dot{x}_n, x_n, y_n, t, \theta_{mn}) \qquad (1)$$

where x are differential state variables, $\dot{x}$ are their derivatives, y are the algebraic variables, and t is time. A Gaussian—Legendre quadrature scheme is used to approximate the multiple integral of eqn (*1*). It discretizes the parameter space, Θ, and assigns weighted probabilities, j, from a joint distribution function, J. Most conventional measures may be expressed as an expectation function in this way. In the Example, expected violation from a quality threshold, Q_{th}, is used. For the evaluation problem it is given by [13]

$$E_{viol}(Q) = \int_{m\in\Theta} J(\theta_m) b[Q(\dot{x}, x, y, t, \theta_m) - Q_{th}] \mathrm{d}\theta_m \qquad (2)$$

where b is a binary variable denoting the one-sided aspect of pass or failure of the threshold. In the optimization problem $E(Q)$ or $E_{viol}(Q)$ could be the objective function or a constraint with u and ν, the time-dependent and time-invariant control variables, components of Q. Control can either be optimized over the

entire uncertainty space in a 'here and now' recourse problem or it can be assumed to be adjustable across the uncertainty space in a 'wait and see' problem.

The correlation analysis is based on estimating linear relationships between system variables and parameters, in the form of correlation coefficients. The standard expression for the correlation coefficient between random variables, X and Y, is

$$r_{X,Y} = \frac{\mathrm{cov}(X,Y)}{\sqrt{\mathrm{var}(X)\,\mathrm{var}(Y)}} \qquad (3)$$

where $-1 \leqq r_{XY} \leqq 1$ and the covariance, cov, and variances, var, are based on standard discretized expressions for which the probabilities are assigned from the quadrature scheme. The uncertain parameters are random and the process variables, as functions of the uncertain parameters, are as well.

APPENDIX II

Model equations for Example (see Fig. 3 for parameter values).

Table 2. Example: Stage 1 Model Equations

Model 1, $t \in [0,\ t_1]$	Initial conditions
$\frac{\mathrm{d}C_\mathrm{A}}{\mathrm{d}t} = -k_1(T_1)C_\mathrm{A}$	$C_\mathrm{A}(0) = C_{\mathrm{A}0}$
$\frac{\mathrm{d}C_\mathrm{B}}{\mathrm{d}t} = k_1(T_1)C_\mathrm{A} - k_2(T_1)C_\mathrm{B}$	$C_\mathrm{B}(0) = 0$
$\frac{\mathrm{d}C_\mathrm{C}}{\mathrm{d}t} = k_2(T_1)C_\mathrm{B}$	$C_\mathrm{C}(0) = 0$
$k_1(T_1) = A_1 \mathrm{e}^{\frac{E_{\mathrm{a}1}}{RT_1}}$ $k_2(T_1) = A_2 \mathrm{e}^{\frac{E_{\mathrm{a}2}}{RT_1}}$	

Table 3. Example: Stage 2 Model Equations

Model 2, $t \in [t_1,\ t_2]$	Initial conditions
$\frac{\mathrm{d}C_\mathrm{A}}{\mathrm{d}t} = 0$	$C_\mathrm{A}(0) = C_\mathrm{A}(t_1)$
$\frac{\mathrm{d}C_\mathrm{B}}{\mathrm{d}t} = -k_3(T_2)C_\mathrm{B}C_\mathrm{D}^2$	$C_\mathrm{B}(0) = C_\mathrm{B}(t_1)$
$\frac{\mathrm{d}C_\mathrm{C}}{\mathrm{d}t} = -k_4(T_2)C_\mathrm{C}C_\mathrm{D}^2$	$C_\mathrm{C}(0) = C_\mathrm{C}(t_1)$
$\frac{\mathrm{d}C_\mathrm{D}}{\mathrm{d}t} = -2k_3(T_2)C_\mathrm{B}C_\mathrm{D}^2 - 2k_4(T_2)C_\mathrm{C}C_\mathrm{D}^2$	$C_\mathrm{D}(0) = C_{\mathrm{D}0}$
$\frac{\mathrm{d}C_\mathrm{E}}{\mathrm{d}t} = k_3(T_2)C_\mathrm{B}C_\mathrm{D}^2$	$C_\mathrm{E}(0) = 0$
$\frac{\mathrm{d}C_\mathrm{F}}{\mathrm{d}t} = k_4(T_2)C_\mathrm{C}C_\mathrm{D}^2$	$C_\mathrm{F}(0) = 0$
$k_3(T_2) = A_3 \mathrm{e}^{\frac{E_{\mathrm{a}3}}{RT_2}}$ $k_4(T_2) = A_4 \mathrm{e}^{\frac{E_{\mathrm{a}4}}{RT_2}}$	
$P_\mathrm{E} = \frac{C_\mathrm{E}}{C_\mathrm{A} + C_\mathrm{B} + C_\mathrm{C} + C_\mathrm{D} + C_\mathrm{E} + C_\mathrm{F}}$	