

## **MONTE CARLO SIMULATIONS FOR RISK ANALYSIS IN PHARMACEUTICAL PRODUCT DESIGN**

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### **ABSTRACT**

Risk Analysis is one of the essentials of Process Analytical Technology (PAT) being adopted in the Pharmaceutical Industry as per the new guidance of the FDA. Under PAT, the quality is designed into a Pharmaceutical product, rather than established by testing of a finished batch. The traditional spreadsheet analysis of quality outcomes does not give any probability information on quality. In PAT, the critical product quality variables are identified from the historic data. Crystal Ball® software is run on critical parameters to build Monte Carlo simulation models. The simulation model provides probability data for almost all possible outcomes by analyzing the statistics of simulations. The probability of quality in the final product can be predicted with confidence.

### **1 INTRODUCTION**

Pharmaceutical development and manufacturing has not changed its fundamental paper-based infrastructure for decades. The regulatory requirements were not very encouraging to make such a change. Until recently, the Pharmaceutical Industry and FDA were not falling into line with respect to utilizing innovations into manufacturing processes to bring the Pharmaceutical sector into the twenty-first century. The US Pharmaceutical Industry currently spends approximately \$90 billion on manufacturing (Helfrich, 2005). By improving manufacturing efficiency by 5%, the industry could save over \$4.5 billion annually.

Leading pharmaceutical companies, generic and contract manufacturing organizations have prioritized programs designed to eliminate the routine, non-value-added tasks through automation. The foremost Pharmaceutical companies are now adopting a new approach to automating compliance by utilizing innovative technologies and building quality into the products. Under the new paradigm, the focus is to reduce risk and to provide higher productivity and improved quality. The automations allow us to manage data across the entire Pharmaceutical Industry-within a plant itself (intraplant) and from plant to plant (interplant).

The uncertainty regarding a situation indicates risk, which is the possibility of loss, damage, or any other undesirable event. Low risk strategies translate to a high probability of success, profit, or some form of gain. The 2004 risk-based regulatory approaches under Process Analytical Technology (PAT) recognize the level of scientific understanding of formulations and manufacturing process factors affecting the product and quality performance and the capability of process control strategies to prevent and mitigate the risk of producing a poor quality pharmaceutical product.

The objective of PAT is to improve understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products, it should be built in or it should be by design. The increased emphasis of PAT on building quality into products allows us to have more focus on multi-factorial relationship among raw materials, manufacturing processes, and their impact on quality. This is a basis to understanding the relationship among various critical process and formulation factors and developing effective risk mitigation strategies. A desired goal of PAT is to design and develop processes that will ensure a predefined quality at the end of the manufacturing process. To obtain this target all critical sources of variability are identified and explained; the variability is managed by the process and product quality attributes which can be accurately and reliably predicted over the design space established for the materials used, process parameters and manufacturing conditions.

The formulation of a drug involves complex coordination of a variety of physical, chemical, and biological factors and processes (Willis, 2004). Thus, any practical efficiency improvements will incorporate a knowledge base that contains a scientific understanding of how these variables interrelate and a means of applying this knowledge to different formulation scenarios. The design-of-experiment (DOE) evaluations are critical to the success of PAT.

By analyzing current methodologies and results in a systematic and statistical manner, pharmaceutical manufacturers will build a database of practical experiences that will enable them to simulate and test new processes. This informatics-based approach will allow Pharmaceutical companies to identify the variables that are most critical to the final desired product and its behavior, to decide where they need to insert controls into the process, and discover the factors that control sample degradation.

## **2 CONTENT UNIFORMITY**

Content Uniformity is a measure of the variations in the amount of active ingredient in individual units comprising a batch (Murphy, 2003). It is not always possible to obtain absolute homogeneous mixing of the drug with the excipients. Factors such as different densities, different particle sizes and different shapes contribute to different settling tendencies and flow characteristics, which causes variations in the content uniformity. In the formulation of Product A, we use API, Dextrate, Silicon Dioxide and Magnesium Stearate. Dextrate acts as excipient or filler and is directly compressible tablet diluents, while Silicon dioxide acts as a glident and Magnesium Stearate is a lubricant. The 500 mg strength Product A is made in batches of 260,000 tablets. We made about 125 batches in 2006, some of which failed because of out of specification Content Uniformity.

The blending of active pharmaceutical ingredients (APIs) with various excipients is a common step in the solid dosage form manufacturing process. Typically, the API in the compressed blend is analyzed in the finished dosage form for potency and content uniformity. For existing formulations, we ensure that both the active and excipients are uniformly distributed throughout the solid dosage form. But each pharmaceutical product has a distinctive blend of API and excipients and thus each blending operation is also unique. The homogeneity of the blend is critical in defining the uniformity of dosage units within a batch of tablets, especially in the case of direct compression products. Pharmaceutical Scientists recognize that it is unlikely that content uniformity of the dosages form is achieved unless the blend is mixed to a uniform level (Brush, et al., 2006). In a recent proprietary study, 48% of the variations in manufacturing processes were attributed to blending as a major cause.

Blend uniformity is addressed in the Current Good Manufacturing Practices (cGMP) regulations and drug approval programs. Section 211.110 of cGMP requires manufacturers to establish control procedures that include adequacy of mixing to assure uniformity and homogeneity. The regulations, however, do not specify the blend testing approach, nor the particulars as to the acceptance criteria, limits, or methods for the testing. The FDA (61 FR 20103) implied the need for blend uniformity testing of all routine manufacturing batches to make certain that a high level of quality was maintained throughout a process, and not just upon completion of the final product

The content uniformity of a Pharmaceutical product is proportional to its blend uniformity. If during blending of raw materials, the blend uniformity is not achieved, the final product is liable to fail in its content uniformity. Product A is more problematic in achieving blend uniformity than most other pharmaceutical products because of various factors chiefly the difference in the particle sizes of API and excipient. But why does most of the Product A, production meet the specifications of content uniformity while only some of total production has failed content uniformity? There are various factors, which are not the same on every batch. These factors are the risk factors causing failed content uniformity of Product A, the risk factors that contribute to failed content uniformity are given below:

- Particle size differential between API and Dextrates: for API, the largest particle size is of 90 microns while the largest particle size of Dextrates is of 1100 microns
- The percentage of API in Product A formulation is very high as compared to the percentage of API in the formulations of other Pharmaceutical products
- The correlations between the particle size of API and excipients are not accounted for
- The interactions among other parameters of raw materials like moisture content, assay of API are not accounted for
- The formulations of Product A is not adjusted as per the interactions among the parameters of raw materials
- The process parameters are not adjusted as per the differences in the particle sizes of API and Dextrates

In the Pharmaceutical Industry, drug product quality has largely been based on a combination of locking down “in-process” controls to assure the same things are done for each commercial batch, locking down product specifications to assure the same tests are passed for the commercial batches as were passed for the development batches, and GMP to assure the facility is under control. Through the process of creating the PAT policy, this system is challenged by the approach used by industries where the product quality is more directly evident to the consumer. It is apparent that controlling manufacturing variability by controlling a manufacturing process, in real time, is a more reliable approach to assuring product quality when compared to testing the finished product and disposing of the batch if it fails the specification.

In a dynamic approach to process control, the important process attributes are measured during the process to control it and determine its endpoint. Adjustments can be made to the control variables in order to accommodate any variability in the material entering the operation. This approach of using the manufacturing operation as a lens to focus the materials into the most desired range of properties, greatly reduces product variability.

### 3 EXPERIMENTAL DATA

We collected data of five batches of Product A for its content uniformity and the parameters of the raw materials used in those batches. The data for raw materials used to get content uniformity is given in Table 1 below.

Table 1: Data of Raw Materials Used to Manufacture Product A

Tablet Batch #	Content Uniformity (%)	Emedex Particle Size (Average)(um)	API Moisture Content (%)	API Assay (%)	API Particle Size (Average) (um)
1	96.00	461	15.8	97.5	8.8
2	95.10	446	15.3	100.7	7.0
3	94.50	446	15.3	100.7	7.0
4	96.50	446	14.9	100.6	11.0
5	98.00	446	14.9	100.6	11.0

We are focusing on content uniformity of Product A and the content uniformity is affected by particle sizes of API and the excipients. To do the risk analysis, we will build a DOE model based upon the variability of Particle Size of API and Particle Size of excipient to get relationship between content uniformity and the input variables. We will run Monte Carlo simulation on the derived equation to do the forecasting of content uniformity. The Monte Carlo simulation model will also help us to find the impact of each variable, i.e. particle size of API and particle size of excipient on content uniformity. The building of mathematical models is described in the next section..

### 4 BUILDING OF DOE MODEL

We built a Screening model of DOE by taking Particle Sizes of excipients (PS\_1) and Particle Sizes of API (PS\_2) as Factors and Content Uniformity (CU) as a Response. Upon fitting the model with the experimental data set, we found that the DOE model is not only affected by particle size of API and excipient but there are interactions between the particle Sizes of API and that of the Particle Sizes of excipients that has a large impact on DOE model.

The reliability of impact is observed by adjusted  $R^2$  value of the model. These interactions are captured to get the true relationship between the Content Uniformity and Particle Sizes of API and excipients. In our Screening DOE Model, the value of adjusted  $R^2$  is 0.643 as shown in Figure 1, indicating that this is a viable model. In Table 2, the values of coefficients of Particle Sizes of API, Particle Sizes of excipients helps to build an empirical relationship between Content Uniformity and input variables.

Investigation: Overview graph of Content Uniformity2.3mip (PLS, comp.=2)

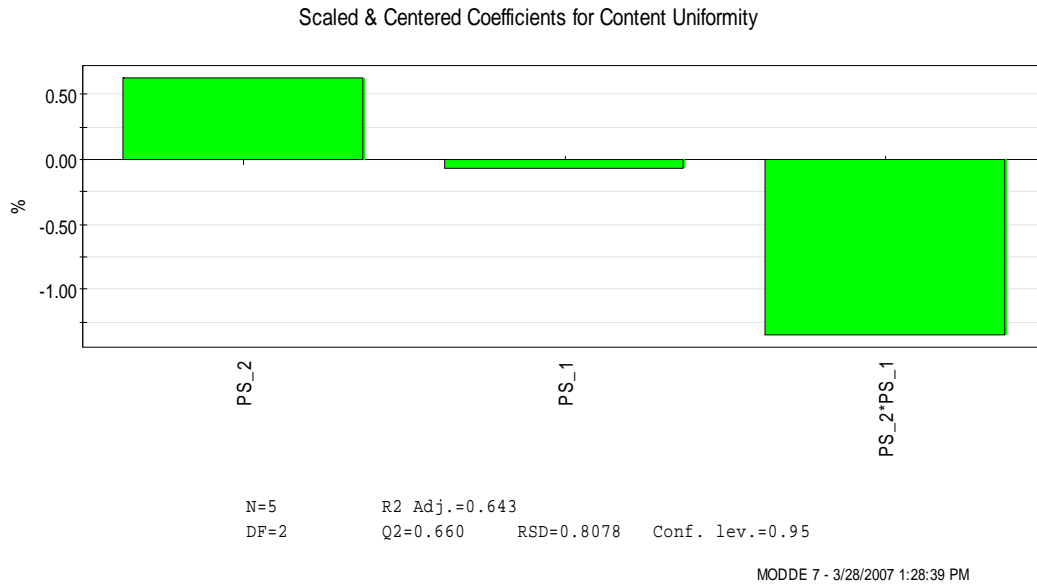


Figure 1: Coefficients of Inputs for Content Uniformity as Shown in DOE Model

Table 2: The Values for the Coefficients of Inputs for Content Uniformity Derived from DOE Model

Content Uniformity	Coeff.	Std. Err.	P	Conf. int(±)
Constant	-306.159	--	--	--
PS_2	45.3593	--	--	--
PS_1	0.889397	--	--	--
PS_2*PS_1	-0.100329	--	--	--

N = 5                      Q2 =      0.660  
 DF = 2                    R2 =      --  
 Comp. = 2                R2 Adj. =   0.643

The derived Equation from DOE model is:

$$CU = 0.889397 * PS_1 + 45.3593 * PS_2 - 0.100329 * PS_1 * PS_2 - 306.159$$

## 5 RISK ANALYSIS

Risk Analysis is a concept that is applied to deal with uncertainty. In this concept, a probability distribution function is assigned to the unknown variables and then the Monte Carlo simulations are run to determine the combined effect of multiple variables. The seed value of the individual variables is calculated by the probability density definition of each variable. A standard sensitivity study shows us the sensitivity of the resulting improvements from the range of outputs from a single variable.

The risk analysis approach selects values for independent variables as a function of a probability distribution function for each variable. The independent variable that we have in our case study are the particle size of API and the particle size of excipient. The value of content uniformity is viewed as a probability function rather than a single-valued answer.

Thus, for a given data the variability in effectiveness can be viewed as a probability distribution. For a given set of data the simulation model gives maximum and minimum values of content uniformity as 101.71 and 87.37 with a most probable value as 95.59 as per the results shown in the table in Figure 2. If the company specifications for content uniformity are between 80 and 120, then there is 100-percent certainty to get content uniformity within specifications as per the given data for input variables.

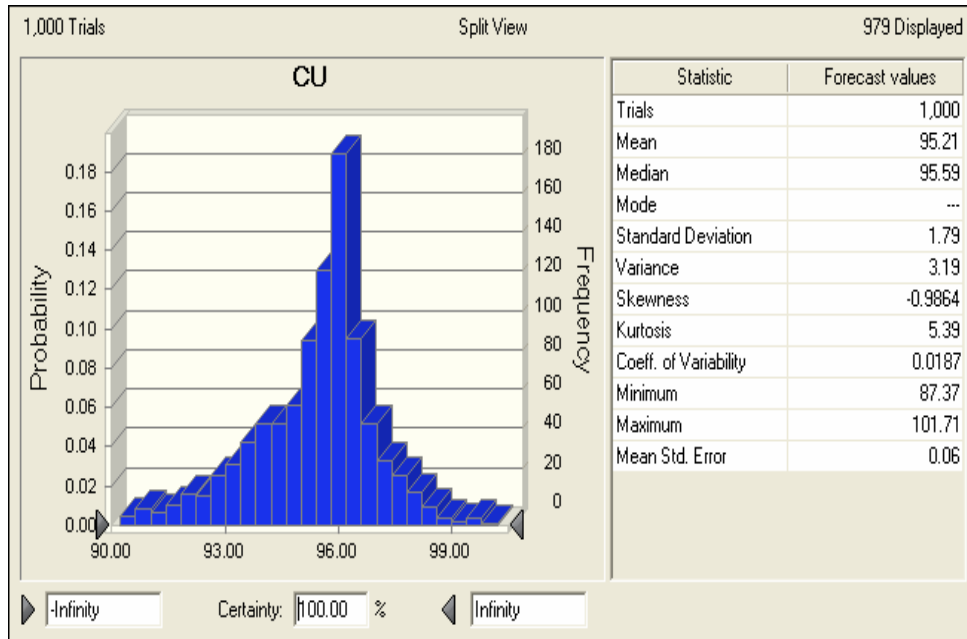


Figure 2: Forecasting for Content Uniformity

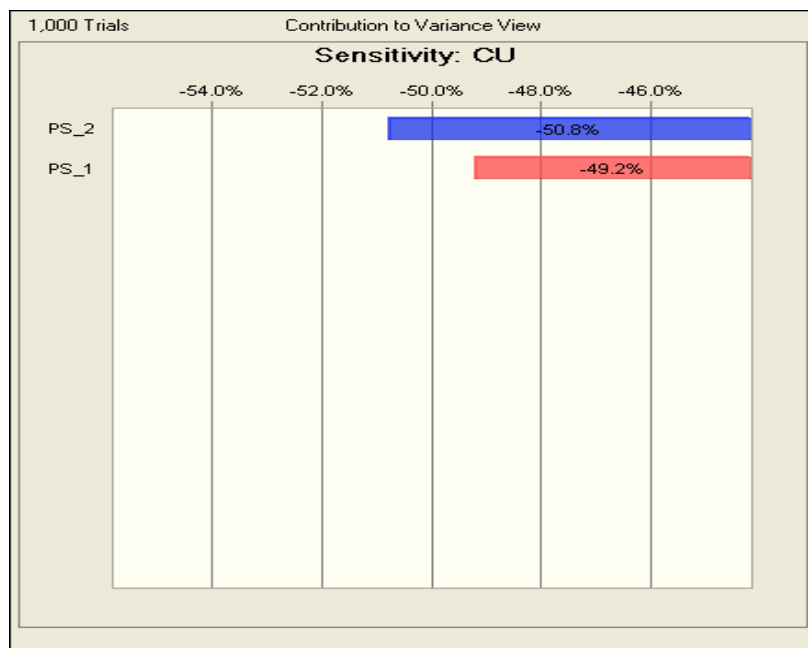


Figure 3: Sensitivity Analysis of Forecasting of Content Uniformity

## 6 CONCLUSION

The application of risk analysis in Pharmaceutical product design requires the setting of the problem definition, constraints and objectives in the proper format to apply the tool. The FDA stresses on building quality into products as per the guidance of its PAT initiative. The quality is designed by two mathematical modeling techniques before it is built during manufacturing. The value of content uniformity is optimized for the Particle Size of API and Particle Size of excipients during Monte Carlo simulations after getting an empirical relationship by building a DOE model. The sensitivity report helps to find out which variable has more impact on output. In our model, both the variables have almost equal impact on the value of content uniformity. To build this model, we had only a limited set of data. A large data set for each variable would improve the mathematical model.

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## BIOGRAPHIES

Dr. Barry Gujral is a Process Analytical Technology (PAT) coordinator and is working to implement PAT at DSM Pharmaceuticals Inc Greenville, NC. He has worked in different fields including Analytical Development, Quality Control, Open Chain Management and Operations. Dr Gujral has obtained his MBA from Duke University, Master of Chemical Engineering from Illinois Institute of Technology, Chicago and Doctorate from Meerut University. His special interests includes: Use of Monte Carlo Simulations to do forecasting and risk analysis in financial value-added indicators and in Pharmaceutical Product Design. Dr. Gujral has a US Patent on Cation-exchangers, has published 44 research papers and is co-author of three books in Chemistry. Dr Gujral is also a co-author of paper, "Applications of Process Analytical Technology," published in the November 2006 issue of *Current Pharmaceutical Analysis*. He has participated in IFPAC-07 and presented a poster on "Use of Monte Carl Simulations to account for the Variability in Product Design" with his colleague Dr Freeman Stanfield. Barry Gujral can be reached at [bir.gujral@dsm.com](mailto:bir.gujral@dsm.com), Tel # 252-707-7220

Dr. Stanfield holds a Ph.D. in Organic Chemistry from the University of Arizona. He has worked in the Pharmaceutical and Biotech industries since 1988, starting as a post-doctoral at Hoffmann-La Roche in Nutley, NJ. His last 3 positions have been at DSM Pharmaceuticals (Greenville, NC), MedImmune, Inc.(Gaithersburg, MD), and Sigma Genosys Biotechnologies. (The Woodlands, TX). Dr. Stanfield has held postions of increasing responsiblity at DSM Pharmaceuticals over the past seven years. He is now the Manager of Analytical Development, with three Chemistry groups reporting to him. He is married with one daughter. In his spare time Dr. Stanfield enjoys tournament chess, writing poetry, playing guitar, and archery.

Doug Rufino is the Sr. Director of QC and Analytical Development at DSM Pharmaceuticals Inc, in Greenville, NC. He has 23 years of experience in the Pharmaceutical Industry covering R&D, QC, Pilot Plant Manufacturing, and QA. He has worked for various organizations such as Warner-Lambert, Bristol-Myers Squibb, and Johnson & Johnson before joining DSM in 2001. He has been utilizing the Lean Six Sigma operational platform for 7 years and is a certified Greenbelt. He heads up the PAT and Lean Six Sigma Programs at DSM. His background is in Microbiology and is a graduate of Rutgers University in New Brunswick, NJ. He is married with four children and enjoys woodworking and recreational scuba diving.