Quantisweb Formulaware APPLICATION NOTE

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Quanstisweb

"the one step, conclusive, optimization methodology ensuring easy Six Sigma Deployment"

Optimize your Complex Processes

Continuous process improvement is an essential building block of modern manufacturing.

This aims at improving the overall efficiency by optimizing complex processes and eliminating wasted efforts in production.

With pharmaceutical manufacturing costing an estimated 25 percent of revenues, even a one percent improvement in efficiency produces significant financial benefits.

Complex Processes

Complex process is synonymous to pharmaceutical manufacturing. From the development of the perfect drug formulation to its final dosage form, scientists and process engineering face a myriad of decisions and potential difficulties.

To define a complex problem we will use the example illustrated in Figure 1 – Compression Problem.

The problem consists of directly compressing a blend into solid oral dosage forms (tablets).

The blend (input) is loaded into the tablet press hopper where it is gravitically fed to the feed frame. Paddles move the blend from the base of the hopper and forces into the dies. The dies, punches and press cams enable the compression (process) of the blend into tablets (output).

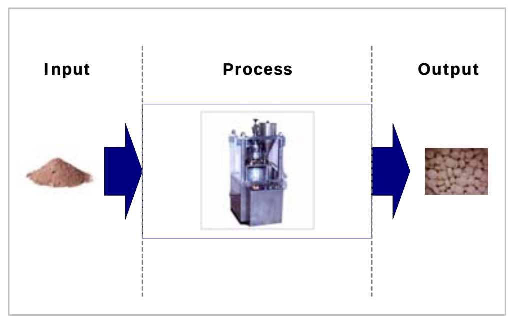

Figure 1 – Compression Problem

Traditional Approach

Engineers and scientists often perform (OFAT) one-factor-at-a-time experiments, which vary only one factor or variable at a time while keeping others fixed. This methodology assumes improving "critical" process variables but often fails to be conclusive.

However, statistically designed experiments that vary several factors simultaneously are more efficient when studying two or more factors.

The pharmaceutical industry has been investing more money and energy towards systematic improvement methodology.

Six Sigma Methodologies

The core of the Six Sigma methodology is a data-driven, systematic approach to problem solving, with a focus on customer impact. Statistical tools and analysis are often useful in the process. However, it is a mistake to view the core of the Six Sigma methodology as statistics.

The basic "DMAIC" methodology consists of the following five steps: define, measure, analyze, improve and control.

Its limitations are in the number and type of critical variables that can be treated at the same time and the large number of experiments required to generate conclusive output.

Quantisweb Methodology

Quantisweb combines three areas of Applied Mathematics: Decision Theory (AHP approach, Analytical Hierarchical Process), Statistic Modeling and Optimization Techniques.

The combination of these mathematical fields in the pharmaceutical manufacturing of new drug products stemming from mixtures of ingredients and process variables achieves a simultaneous twofold benefit. It allows minimizing the number of required experiments regardless of their levels, while at the same time eliminating the added parameters induced exponential effect, and arriving to a solution of optimum products endowed with global optimality since the entire product attributes (outputs) are simultaneously optimal.

This optimality results from a reduced number of combinations, and is due to the notions of interaction of parameters and each of the response functions according to their importance in the global objective. These interactions are estimated either by parametric and/or nonparametric methods.

(1) Identifying the Objectives

A scientist/engineer using the Quanstiweb methodology starts by defining the desired properties or objectives (output). This process is illustrated in Figure 2 - Quantisweb Approach.

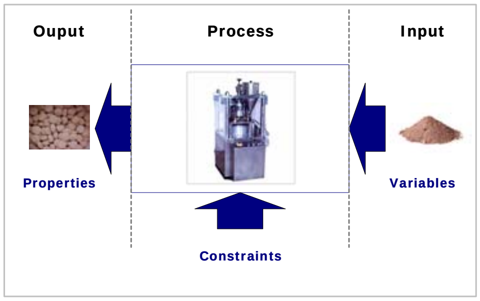

Figure 2 - Quantisweb Approach

The scientist/engineer introduces the value of the analyses to be achieved corresponding to the objectives (pre-defining the *goal*).

These values must be measurable and quantifiable, and they constitute the mathematical definition of the *goal*. The objectives are the results of the analyses that will be performed using the combinations proposed by the Dynamic Design of Experiment (DDOE) and tested under real conditions.

(2) Properties Importance

The mathematical process of Quantisweb takes into account the sensitivity of the objectives in determining the relative weight for each of those objectives. The utilization of decision theory, at this stage in the process, allows the architecture of the mathematical signature relative to the targeted objectives to be influenced.

In order to facilitate the weighing of the objectives by the scientist/engineer, Quantisweb displays comparison tables of these objectives, two by two, by group. The two by two comparisons of the objectives assures a direct evaluation of each of the objectives.

Based on the Analytical Hierarchical Process (AHP) method, Quantisweb then provides the leaf plot of the factors together with their local weights and possible global weights. The global evaluation of the objectives is monitored by the consistency index. This index measures the level of cohesion in the weighing of the objectives and is only an indication of the state of this consistency.

AHP is used for this process because it is the only multi-criteria method that formulates the attributes weights by a simple and effective pair comparison method.

(3) Variables Selection

Quantisweb can capture the academic and empirical know-how of the scientist/engineer through variables selection. The values of these process variables can be continuous and discrete in nature.

For more flexibility and in order to introduce the maximum of the scientist/engineer's intuition in the process, the number of parameters treated at the same time can be up to 25 different parameters and each parameter may have up to 25 different levels.

At that level, Quantisweb is handling a matrix of 25x25 with only Np+1 combination of tests or 26 experiments instead of running an astonishing number of tests for classical methodology.

(4) Constraints

In all cases, the expertise and the knowledge of the scientist/engineer can influence the experimental design with different constraints corresponding to the influences and/or limits of these parameters between themselves. The application of such constraints in the parametric window influences the composite hypotheses (knowledge-based) of the architecture of the mathematical signature established in the final stage of the optimization.

Constraints are driven from compliance activities (SUPAC), marketing requirements, financial goals, and production requirements such as: technology, process parameters, cycle-time, and formulation.

(5) Dynamic Design of Experiments (DDOE)

Quantisweb dynamically and automatically establishes the choice of statistical models for the global representation and the interrelationship of the variables.

The variables are analyzed by Quantisweb to identify their number, type, number of levels, and associated constraints to select the appropriate design of experiment.

For simple problems (i.e., number of continuous variables ≤ 25, two levels each and no constraints), the mathematical algorithm allows for a systematic selection of classical experimental design calling upon common statistical libraries to construct the DOE. In this case, a crossover of Plackett and Burman method may be applied.

For more complex problems (i.e. number variables levels > 2 and no constraints), a full factorial design is considered. When constraints are applied to variables not only the constraints are fully respected but a reduced factorial design is selected and the use of systematic mathematical randomization techniques is introduced.

Furthermore, Quantisweb's innovative integrated mathematical algorithm enables the optimization of complex problems as mixture design or of composite problem (i.e., ingredients and process variables).

In any case, Quantisweb generates its own set of experiments based on a set of criteria, as well as systematic approach, addressing the extremes of each problem to achieve Np +1 design of experiment in all cases.

The results of experiments (ROE) are fed back to Quantisweb to be used in the next step optimization.

(6) Optimization Process

The strength of Quantisweb is its capacity to integrate the set of information provided by the scientist/engineer and the concrete results generated by the design of experiments.

Quantisweb translates the following information in mathematical language:

- The knowledge and the expertise (DDOE-proposed tests to be run);
- The results of experiments from each test (ROE);
- The weighing of the objectives (AHP test);
- The statistical analyses generated by mathematical patterns (Behavioral Laws);
- The description of the ideal values of each objective (IFV) describing the targeted *goal*.

The above information is integrated into a *Goal* function that generates the mathematical signature; this is the simultaneous synthesis of the synergy of the whole of this information.

This *Goal* function leads to the finality (*goal*) by proposing the optimal combination of variables

(OCV), it being the combination of the parameters to be tested to confirm or deny the initial hypotheses (Validation Process).

The two main characteristics of this *Goal* function are: first, the simultaneous integration of all global weights of the objectives unlike the usual individual processing of each of the objective in a sequential nature; and, second, the use of stochastic models representing the tendency of each of the objectives known as behavioral laws which play the role of deterministic laws normally used in the optimization methods.

Trying to minimize the *Goal* function actually amounts to minimizing the deviation that separates the tendency of each characteristic from its ideal value in a simultaneous fashion for all characteristics. This optimization is carried out by prioritizing the characteristics according to their weights.

(7) Validation

Once the optimization step is completed, the user is in possession of the optimal combination of variables (OCV).

The OCV is tested in a real situation to demonstrate the perfect harmony between the Mathematical language of the studied phenomenon, generated by Quantisweb and the reality of the complex multidimensional world where this phenomenon evolves.

The efficiency will then be proved by realizing that ALL the objectives (Outputs) values are in the neighborhood of the specified ideal values in case all these objectives are regular.

In the case that at least one of the characteristics has a large variability, the produced OCV is situated in the optimality region and the scientist/engineer will have to conduct a limited number of experiments to refine the OCV.

ADDENDUM – Quantisweb Process Flowchart

Define and Prioritize the Properties (OUTPUTS)	The experimenter defines the output specifying the required quality attributes for each of its properties. values express the ideal/desired values which can be continuous or discrete in nature. The properties are prioritized by assigning a ratio of importance on a scale of 1 to 7, using the Pair wise Comparison method, where two properties at any given time is compared.
Quantisweb Verify Consistency	Quantisweb validates the consistency of the ratio of importance assigned to each property using Analytical Hierarchical Process (AHP) method by converting the pair wise comparison matrices into criteria weights, thereby ensuring the uniqueness of the weights.
Identify, Select and define Process Variables (VARIABLES)	Experimenters define critical and non-critical process variables. Up to 25 variables are selected and intervals are set for each variable, spanning from 2 to 25 levels, based on the desired design space.
Apply Constraints to the Variables (CONSTRAINTS)	Constraints are limitations applied to variables. They might be financial, technology, formulation, process parameters and/or compliance related.
Quanstiweb Selects and Generates the Best DOE (DDOE)	Quantisweb dynamically and automatically establishes the choice of statistical models for the global representation for the interrelationship of the variables to combined and tested in the laboratory, whose result of experiments (ROE) are fed back to Quantisweb to be used in the next step- optimization.
Quanstiweb Generates Optimum Combination of Variables OCV (DOPT)	The optimization process automatically and dynamically generates a goal function, integrating the ideal specifications, the weight provided by the experimenter as calculated by AHP, the DDOE, and the ROE, behavioral laws generated automatically and representative of the interrelationships existing between the input variables and the output properties, to generate an optimal combination of variables (OCV).
Experimenter Validate the OCV (VALIDATION)	The (OCV) defines the optimum operating domain, an experiment necessary to validate the combination of variables.