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The role of Statistics in Quality by Design initiatives

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Recently, the Food and Drug Administration (FDA) and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use launched a **Quality by Design** initiative (ICH, 2005). It encourages new drug applications to include a **Design Space** and risk based control strategies. The basic idea is that drug product developers should study the behavior of **Critical Quality Attributes** in their proposed new products, under variations in the raw material and process control parameters. This area of application is beyond the traditional role of Biostatisticians in clinical trials (see Nasr, 2007 and 2009, Kenett and Kenett, 2008 and Peterson et al, 2009). Moreover, the application of simulation experiments, Bayesian adaptive designs and data mining techniques in the critical path of research investigating efficacy and safety of new drug products is also encouraged by the FDA. These recent developments have created new opportunities for Statisticians who can now play a key role throughout the life cycle of drug development and contribute actively to the discovery process, for the benefit of society in general. In this paper we review the essential elements of Quality by Design and map out several opportunities for Statisticians to contribute actively in this framework.

The aim of pharmaceutical development is to design a quality, safe and effective product with consistent and economical manufacturing processes. The information and knowledge gained from pharmaceutical development studies, and manufacturing experience, provide scientific understanding to support the establishment of the Design Space, specifications, and manufacturing controls.

The regulatory agencies (ICH, FDA, EMEA) recognize that quality cannot be tested into products; i.e., quality should be built in by design and that information from pharmaceutical development studies is the basis for quality risk management. Changes in formulation and manufacturing processes during development and lifecycle management are considered opportunities to gain additional knowledge. Similarly, inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful.

A Design Space of a drug product is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Including a Design Space in a new drug application is a key element of the Quality by Design initiative. Working within the Design Space is not considered a change

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requiring regulatory approval. Movement out of the Design Space is considered to be a change, and requires a regulatory post approval change process.

A sample Design Space indicating the effect of temperature, blending time and cooling time on 9 Critical Quality Attributes of a foam drug product is presented in Figure 1. The Design space is also indicating various reliability levels for the overall product attributes meeting the product specifications.

A Bayesian approach to setting up a Design Space was proposed by Peterson (2004, 2008, 2009). His approach accounts for model parameter uncertainty and correlation among the Critical Quality Attributes. Stockdale and Cheng (2009) provide examples where this approach is applied to identify a reliable operating range. In Peterson et al (2009), there is a general discussion on applications of Statistics to development and manufacturing in the pharmaceutical industry. Fuchs and Kenett (1998, 2007) describe multivariate methods for achieving process control and determining process capability. Kenett and Kenett (2008) present Bayesian methods for combining information from simulation and physical experiments with expert opinions, in order to derive a comprehensive Design Space. Advanced risk analysis, including considerations for "Black Swans" is also required in a Quality by Design initiative (Kenett and Tapiero, 2009).

Some of the statistical areas addressed by organizations implementing Quality by Design include:
– Design of Experiments (Factorial, Fractional Factorials, Response Surfaces)
– Statistical Process Control (X-bar S charts, CUSUM, Shyryayev Roberts)
– Simulation experiments (Latin Hybercubes, Metamodels such as DACE)
– Multi-objective optimization (Desirability Functions)
– Multivariate methods (Multivariate Control Charts)
– Risk management (Risk assessment, Mitigation strategies)
– Control strategies (Risk based control)
– Quality and risk economic models
– Extreme events modeling (Taleb's quadrant)
– Bayesian methods (Design Space, Bayesian Estimates of the Current mean)

Modern industrial organizations are meeting increased competition, cost reduction pressures and rising customer expectations. Management teams, on all five continents, are striving to satisfy and delight their customers while simultaneously improving efficiencies and cutting costs. In tackling this complex management challenge, an increasing number of organisations have shown that the apparent conflict between high productivity and high quality can be resolved through improvements in work processes and quality of designs.

Kenett et al (2008) formulate a **Statistical Efficiency Conjecture** that links management maturity with the impact level of problem solving and improvements driven by statistical methods. The different approaches to the management of industrial organisations can be summarized and classified using a four step **Quality Ladder** (See Figure 2). The four approaches are 1) Fire Fighting, 2) Inspection, 3) Process Control and 4) Quality by

Design and Strategic management. To each management approach, corresponds a particular set of statistical methods and the Quality Ladder maps each management approach with appropriate statistical methods (Kenett and Zacks, 1998).

Managers mainly involved in reactive Fire Fighting need to be exposed to basic statistical thinking. Their challenge is to evolve their organization from typical data accumulation to data analysis so that numbers are turned into information and knowledge (See Kenett, 2008). Managers who attempt to contain quality and inefficiency problems through inspection and 100% control, can alleviate their tasks by using sampling techniques. More proactive managers, who invest in process control and process improvement are well aware of the advantages of control chart and process control procedures. At the top of the Quality Ladder is the Quality by Design approach where up front investments are secured to run experiments designed to optimize product and process specifications. At that maturity level, robust designs are run on simulation platforms or otherwise, risk analysis and reliability engineering is performed routinely and reliability estimates are compared with field returns data to monitor the actual performance of products and improve the organisation's predictive capability.

Efficient implementation of statistical methods requires a proper match between management approach and statistical tools. The Statistical Efficiency Conjecture states that organisations that increase the maturity of their management system, moving from Fire Fighting to Quality by Design, enjoy increased benefits and significant improvements in their competitive positions. Kenett et al (2008) validate this conjecture with 21 case studies in a variety of organizations from different geographical locations. In addition to the Quality Ladder, linking management maturity level with statistical methods, one also observes a convergence between the Quality and Risk disciplines (see Kenett and Tapiero, 2009).

The FDA and ICH Quality by Design initiative is therefore implicitly acknowledging the Statistical Efficiency Conjecture. In brief, the goal is to move organizations up the Quality Ladder, from Fire Fighting to Quality by Design. In this process new opportunities arise for the application and development of statistical methods as outlined above.

Going up the Quality Ladder is a challenge faced by many industries, besides the Pharmaceutical industry. As an example, consider the aircraft industry that develops, produces and maintains airplanes (Lintelman, 2009). New systems involve complex e-enabled aerospace systems and network-centric operations for effective safety, maintenance and traffic management. The challenge consists of meeting high variability in infrastructures of airports and traffic management systems across the globe. In addition, new materials are deployed in a variety of roles and extensive experimentation, both with simulators and physical experiments is required to build enough confidence in these new technologies. Here again, moving up the Quality Ladder to Quality by Design will allow organizations including aircraft and airline companies to achieve higher quality, higher safety and higher efficacy and efficiencies. In this domain the Federal Aviation Authority (FAA) might follow the initiative of the FDA.

This paper presents new opportunities for the application and development of statistical methods in the Pharmaceutical industry and beyond. The achievement of Quality by Design requires an increase in management maturity and a comprehensive integrated view where R&D groups collaborate with operations, quality assurance and quality control, purchasing and regulatory affairs. Without such a collaborative culture proper Design Spaces and control strategies cannot be properly determined.

In sum, the main points of this opinion paper are:
1. The FDA Quality by Design initiative offers new opportunities for developing and implementing advanced statistical methods in the pharmaceutical industry.
2. In order to reap the benefits of Quality by Design, one has to also work on increasing the management maturity level.
3. Quality by Design is applicable in many industrial areas, especially those dealing with safety and life critical applications.

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Figure 1: A Sample Design Space

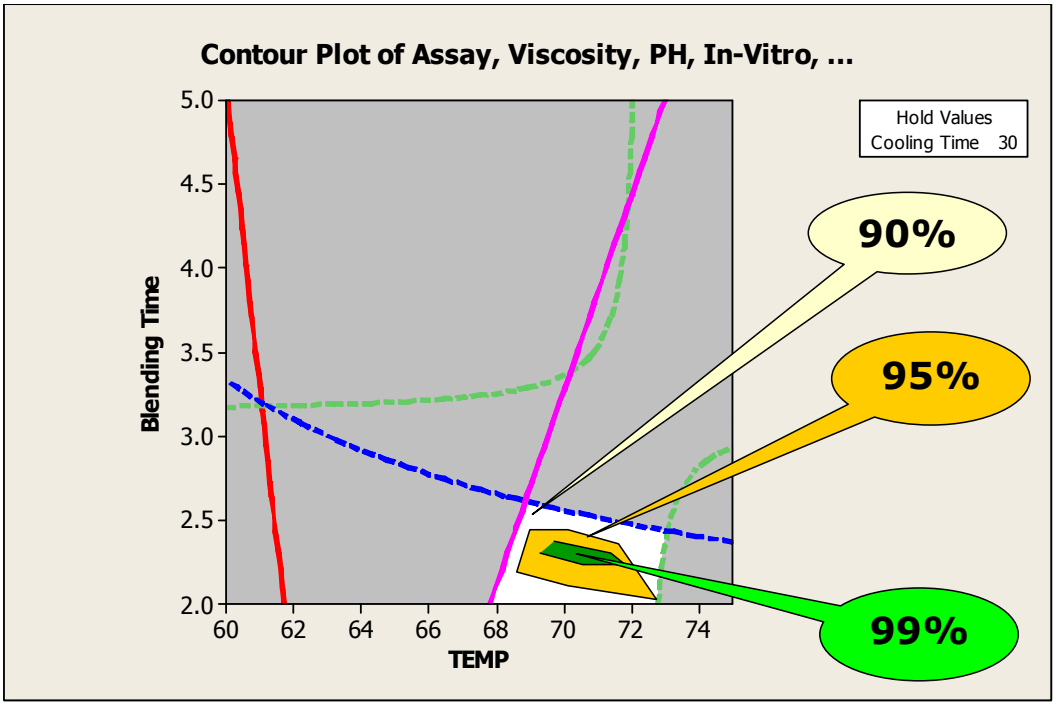
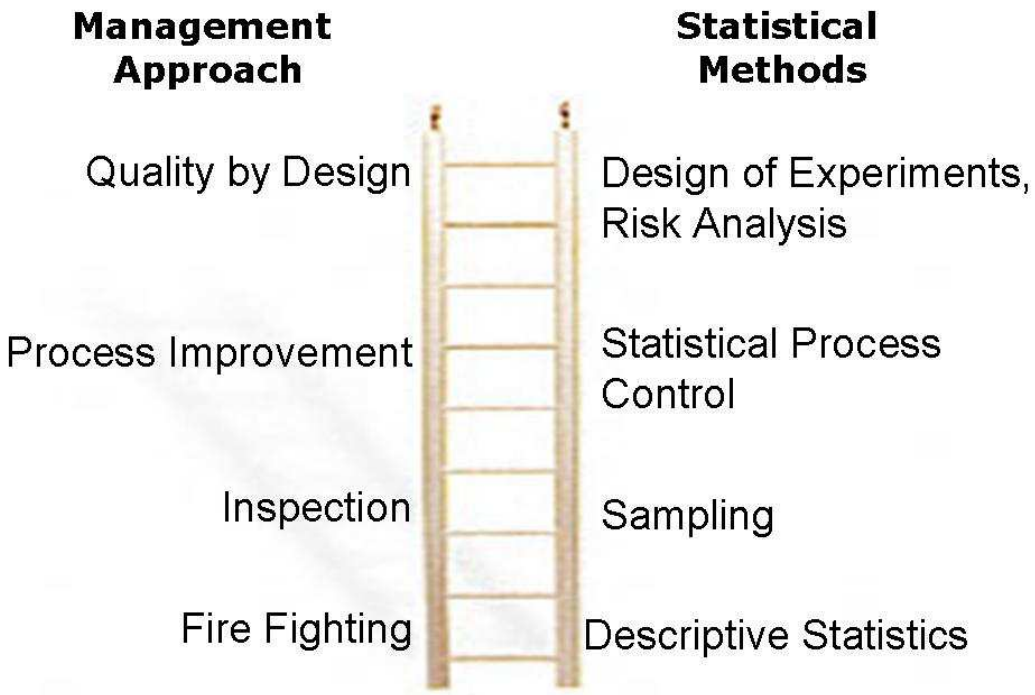


Figure 2: The Quality Ladder



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