QbD: The cost of doing business.

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Editorial

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The objective of multivariate Design of Experiments (DoE) is to yield statistically significant (not necessarily equivalent to scientifically correct) answers, only in situations where those multiple questions (factors) are stochastic and function independently of each other. In addition, the sparsity of effects principle is implicit in DoE, it being assumed that higher order (≥ 3) factor interactions are insignificant in affecting the response variable(s). However, most unforeseen interactions involving excipients in pharmaceutical processes proceed via insidious cascading mechanisms with the response variable affected only when all these factors are sequentially or simultaneously present and/or activated. Furthermore, even non-sequential multifactorial events, i.e., those that ordinarily would not cause undesirable reactions under Markovian conditions, can affect the response variable(s) due to the equilibrium nature of chemical processes; even when reactions can be driven far to the product side. Some examples of such equilibrium conditions that can occur in pharmaceutical processes are:

1. The ratio of non-ionized to ionized, deprotonated to protonated, non-micellized to micellized, API/excipient/buffer species.
2. The ratio of ionized to non-ionized, ionizable substituent/functional groups on polymeric backbones.
3. The ratio of solvated to non-solvated polymer chains.
4. The ratio of glassy (amorphous) to crystalline regions in (freeze dried) or processed API or excipient polymers.
5. The ratio of multiple protein and/or peptide quaternary structures.

These ratios are determined by Le-Chatelier's principle, including the common ion effect, and equilibrium constants, which are in turn dependent on temperature, pressure, pH, chemical interactions and known and unknown raw material attributes. The ratios affect ion-pair and hydrophobic interactions, buffer capacity, solubility and precipitation, emulsification or micellization capacity, degradation kinetics/pathways, adsorption to and extraction of (plasticizers, antioxidants, lubricants etc.) from manufacturing materials and/or other excipients/APIs/primary

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packaging containers, propensity and magnitude of re-dox reactions, sub-micellar association, and a variety of other factors that can affect CQAs. In the absence of a knowledge of the reaction mechanisms, a mere probabilistic absence of DoE response, even on multiple occasions, does not constitute evidence that such a response will never occur.

Ironically, process optimization to minimize a 'known' risk may 'activate' other factors that may exacerbate or precipitate other 'unknown' risks. Borrowing jargon from the biochemical field, factor(s) may be sufficient, but not necessary, to affect the response variable(s); or, factor(s) may be necessary, but not sufficient, to affect the response variable(s). The (manifestations of those) factors themselves may behave non-linearly or discontinuously even within the design space (critical micelle concentrations, cloud points, association constants, ion-pair interactions, equilibrium constants, solubility product, adsorption kinetics etc.) which makes the definition of a design space much more challenging than that portrayed by DoE responses alone.

Complex macromolecular excipients may possess sub-populations whose chemical attributes differ significantly from the averages (and also between lots and suppliers) on which compliance to compendial specifications is based. Furthermore, 'non-compendial' material attributes may manifest in erratic fashion depending on their interaction with other known or unknown excipient or API material attributes or process parameters. Due to the complexity of excipients, and attribute dependence on manufacturing history/ processes, many users may not be aware of true variability or non-compendial attributes. The intermolecular weight between cross-links, the positional randomness of glyceride poly(ethoxylation) or that of multiple residual functional groups on a polymer backbone, the length of a 'block' in a block co-polymer, the ratio of different sugars in a polymer backbone or the degree of branching, the molar substitution, polydispersity, differing ratios of hydrophobic or hydrophilic species subpopulations in hydrophilic or hydrophobic amphiphilic molecules represent a small sampling of such attributes. Identification of CMAs and CPPs' from a DoE performed on the upper and lower specification limits of nominal compendial specifications of macromolecular excipients is inherently probabilistic because each experimental design point itself embeds a bell curve of unknown standard deviation of undefined chemical attributes. What may be "non-critical" today may suddenly become critical tomorrow even with the same excipient specifications in the same design space.

Finally, the adage of 'correlation not being equivalent to causation' is eminently germane to the current practice of using DoE responses alone as measures of criticality with little or no mechanism based understanding. Furthermore, those responses are generated from subjectively chosen attributes regardless of or without sufficient knowledge as to whether there exist chemical and/or mechanical mechanism(s) (of failure, reaction, interaction) associated with those attributes.

These immensely complex considerations often make DoE (the most widely accepted surrogate for QbD), or any risk analysis and mitigation efforts based on misguided or the common-denominator compliance application of DoE alone, irrelevant to a vast array of multifactorial pharmaceutical processes, which are neither stochastic (even across a single unit operation) nor single (or even multiple) factor cause-effect isolable. The compliance driven, algorithmic compression of QbD leads to a flawed model that is hard pressed to improve, build in quality, or minimize rejection rates in pharmaceutical processes.

These caveats are lost on the legions of technicians who labor in designing and performing experiments and in proclaiming the problem to be solved or the risk to be mitigated

based on software generated Pareto values and interaction coefficients, until the same problem surfaces again in another batch. The fascination with DoE as a surrogate QbD panacea rests on the non-necessity of possessing any prior chemical, physical or engineering knowledge, the almost certain 'identification' of the 'contributory factor(s)' affecting the response variable(s) and last, but not the least, having mathematically verifiable and reviewable content to fill out the QbD modules of regulatory submissions, and satisfy regulatory compliance requirements.

One of the more indiscriminate uses (and there are many) of factorial design is to include almost every variable in the process and run a DoE representing the culmination of a process where a 'compliance convenient' disconnect exists between the 'why' and the 'how to'; between mechanisms and statistical probability. A list of purported 'mechanisms' that appear in regulatory submissions would probably not be worthy even of inclusion in 'Mechanisms for dummies', encompassing such verbiage as 'decrease in solubility', 'change in pH', 'increase in number of particulates' etc. These scenarios occur with significantly more (alarming) regularity than erudition would lead one to believe. In an example typical of (say) a polymeric excipient, the *modus operendi* would be to run a DoE on a 'catch all' list of 'critical process parameters' and 'critical material attributes' that 'affect' one or several release and shelf life specifications of the product that the polymer is a constituent of. Some of these attributes would include the following, in part, because they are macro-visible steps of the process and therefore easily intuitively envisaged as having 'something to do' with process criticality:

- Viscosity of polymer (per the certificate of analysis from the excipient manufacturer)
- pH of polymer (fixed concentration in water, per the certificate of analysis from the excipient manufacturer)
- Temperature of water used to disperse/dissolve the polymer
- Time of dispersion/dissolution of polymer
- Concentration of polymer
- Filtration speed
- Pore size, surface/volume ratio of filter/ filter train
- Temperature/volume of rinse water
- Bulk sterilization F_0
- Bulk sterilization time to reach 121°C
- Bulk sterilization time to cool down from 121°C to room temperature (RT) (chilled water or RT water in jacket)
- Mixing speed

The 'design space' would then be constructed, usually from a fractional factorial design of experiments, based on the software calculated 'critical process parameters', associated software generated numbers and the magnitude to which each CPP affects the response variable(s).

Implementation of such simplistic models is perhaps implicitly encouraged by regulatory submission requirements which prefer the presentation of data in a statistically quantifiable 'clean' format , place the onus of process knowledge and understanding on the manufacturer and assume that the manufacturer *is desirous of* improving process capability and product quality. Akin to aviation parlance, where 'any landing which you can walk away from is a good landing', in pharmaceutical processes, any process which consistently produces a product that meets release specifications is a good process and is generally embraced as such by a risk-averse pharmaceutical industry. The question then is why a pharmaceutical manufacturer would want to improve product/process quality *for its own sake* in the absence of a history of batch failures (although not in the frequency of deviation reports) and (in the presence of) exclusivity of excipient/API supply agreements (more on this below).

What is needed is a *mechanism based* approach to identify and minimize risk, on an *ongoing basis*, that addresses the following questions:

1. Why is this a risk?

2. What is/are the chemical, physical and engineering mechanism(s) by which this risk is manifested?
3. Are these mechanisms only able to be altered or mitigated by adjusting the CMAs' or CPPs', or do these and other attributes that are not listed on the certificate of analysis and/or the USP/NF monographs change these risk/chemical, physical and engineering mechanisms as well? Can these attributes or their interactions change *within* the confines of the design space (see point 5)
4. What is the probability and magnitude of this risk being exacerbated or mitigated by other risk factors; in other words, can different individual low risk mechanisms interact to form a significantly larger risk or *vice-versa*? (detectability)
5. Can this risk be adequately modeled by a stochastic DoE? Will the magnitude of the effect of the CPPs' on the response variable(s) (severity) remain the same no matter where the process operates within the design space?
6. Can this risk be intentionally precipitated / activated by deliberate application of one or a combination of simultaneous, sequential or non-sequential; monograph or non-monograph attributes within the confines of the design space thus validating the risk mechanism(s)?

In this context, the ICH definition of criticality can recommend a 'mechanisms based' categorization into the 'detectable', 'severe' and 'probable'. The more explicit mechanisms that can be listed for an unfavorable event, the less is the subjectivity in assigning risk. 'Unknown-unknowns' arise in part due to an inadequate understanding of the mechanisms, nature and magnitude of chemical, physical and/or engineering interactions and/or due to their, deliberate, chance or benighted, decoupling or obfuscation from the (already pharmaceutically inapplicable) DoE statistical model in pursuit of regulatory approval. To state that there will always be 'unknowns' in a pharmaceutical process that no good statistical design can foresee may be true to a certain extent but must not serve as an excuse not to fully and thoroughly understand the chemistry, physics and engineering of the process. The 'black swan' unforeseen event rationalized by hindsight *has a greater probability of being predicted beforehand* by a mechanism based process understanding that accounts for more relevant data during risk assessment with the consequent identification of the design sub-space where these event may occur.

In this brute-algorithmic-force world, where the number of mathematical operations is not rate-limiting, it has become anathema to suggest that not all processes/problems are algorithmically compressible. Manuscripts in this journal have addressed the concern that innovation and/or quality control is being increasingly driven to compliance satisfying ends and not toward an increased understanding of nature or pharmaceutical processes. Nobody wants CQAs' to fail specifications and batches to be dumped in bulk. However, the necessity of achieving 6σ process capability, especially when the historical rate of batch failure is low enough to be financially manageable, is (understandably) lost on manufacturing facilities where understanding how and why a process works the way it does or tightening process or product specifications seldom affects product *in vivo* efficacy and does not proportionately increase the elasticity of demand. When dealing with a clinical trial stage new product or process that has no or little historical precedent, a significantly greater rejection rate can be tolerated by the CMO and/or innovator because of access to, and ability to raise capital from speculative financial markets. By the time an NDA or BLA is ready for filing, enough 'trial and error' data has been generated on batches to enable writing of QbD modules in regulatory dossiers. A concerted, focused and intentional strategy of process risk minimization, by chance or design, may hence fall by the wayside with little or no impetus for

resurrection. A regulatory approach that allows for an ongoing post market assessment and mitigation of risk may be of much utility in getting pharmaceutical manufacturers to understand their processes better. This concept of continuous verification has been espoused in the most recent FDA process validation guideline. The conceptualization of risk, not as a temporal static entity, but of something that evolves over time can do much to eliminate the 'one shot and done' mentality of NDA or BLA filers of QbD modules. But more than that, the visualization of risk as a time dependent concept changes the thought paradigm from a futile mismatching exercise of unsuitable mathematical algorithms with a smorgasbord of subjectively chosen process parameters or material attributes, to one of a mechanism based scientifically relevant sound approach. A mechanism based assignment of effect(s) to cause(s) is likely to be an inherently greater incentivizer of process understanding than an unsuited algorithmic statistical one.

All statistical models are probabilistic. Much more so is a statistical, stochastic, higher order interaction and mechanism invariant model that is made even more irrelevant as a predictor of CQAs' when only the more obvious 'compliance convenient' factors are used to interrogate the chemical process. The probability of unfavorable effects on CQAs' and/or the response variable occurring in such a 'design space' is consequently significantly greater than is observed. Small wonder then that the need for 'deviation reports' has continued to proliferate for pharmaceutical processes even in the presence of the purported advantages of a 'flexible' design space that supposedly has the ability to produce a product that consistently meets design/release specifications. The identification of molecular mechanisms does not necessarily require empirical experimentation but does require a considerable degree of expertise in chemistry, physics and engineering. For a given mechanism, CPPs' or CMAs' (compendial or non-compendial for API, excipients and primary packaging components) or their specific combinations (whether within or outside the design space) where the undesirable effect on the CQA will occur can be predicted significantly more precisely and accurately than can with DoE. Mechanism based risk prediction is manufacturer, manufacturing lot and supply chain invariant i.e. the identification of the (non-detrimental to CQAs') design sub-space only requires a knowledge of the CMAs' and the CPPs' (illustrated in Figure 1).

A mechanism based approach to minimizing trivial or non-trivial undesirable effects on CQAs' and/or response variable(s) is what should drive the optimization of the 'design space'. A competent coach will assign players to their maximum positional capability (and advantage) in the soccer field (design space) that is not necessarily based only on historical position-specific statistics (a player may not be competent at the position he/she occupies not because of positional inadequacy but because other players are mismatched or incompetent at their positions).

"You must want it"; is my response to my first question of the year to students in my class, the question being: What is the most important characteristic of learning and/or of education? The premise of the current iteration of QbD focusing unduly on canned compliance using an unsuitable statistical model, of not adding anything to the bottom line, of not rewarding better processes and quality and not lending itself to the scientific building of quality into the product does not make it a particularly desirable

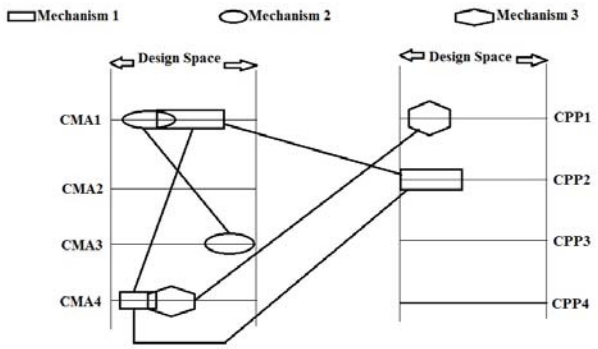

Figure 1 Schematic representation of challenges in using algorithmic DoE as a QbD heuristic

entity for adoption, is not entirely unjustified in this regard, and seems to be the proverbial case of good intentions gone awry. The current flawed model of QbD may actually incentivize the adoption of the folksy aphorism: 'if it ain't broke, don't fix it', because the model is unsuited for predicting non-trivial cause-effect relationships in multifactorial, non-stochastic, chemical reactions or physicochemical and engineering processes thereby significantly undermining its usefulness in consistently preventing undesirable effects on CQAs' and/or the response variable(s), its application involves the subjective choice of, and assignment of arbitrary criticality to, 'compliance convenient' obvious process parameters, its assessment in terms of regulatory rubric encourages over-simplification and reliance on mathematical algorithms disconnected with reaction mechanisms, kinetics, thermodynamics and equilibrium and it promotes complacence *via* its overtly optimistic probabilistic designation of a 'design space'.

The author has had the good fortune and opportunity to witness and solve many non-trivial chemical process related problems firsthand including some that required no less than three CMA and CPP related attributes, some non-compendial, to be simultaneously present/activated. *Not one* of those was predicted or solved (or could have been capable of being predicted or solved) using the current DoE iteration of QbD. *All* could have been predicted with a mechanism based approach. Nevertheless, the status-quo of paying lip service to QbD persists and countless man-hours are devoted to conjuring up CPPs', CMAs' and a 'design space' for regulatory submissions. It is ironical to note that pharmaceutical companies have to resort to 'outside' consultants on a regular basis to solve or predict process related problems on a not irregular basis. Has the pharmaceutical industry adopted QbD out of choice or because of regulatory coercion? So long as pressure on (already generous) profit margins (due to manufacturing defects or batch failures) can continue to be alleviated by either a value added or patent extensible product pipeline, there will be little or no financial incentive to genuinely adopt the current unsuitable iteration of QbD. So long as there is tacit realization that a DoE generated flexible 'design space' does not significantly improve quality, has little or no influence on the frequency of black-swan unfavorable events and is just as probabilistic as the earlier '3 batch' version of QbD, there will be little financial, scientific or innovation driven impetus to adopt the current unsuitable version.

There is a danger that QbD, as currently enforced, interpreted and practiced, will become another acronym associated with the cost of doing business.