Quality Risk Management of Compliant Excipients.

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ABSTRACT

Raw material compliance and GMP do not eliminate variability. Quality by Design should minimize the risk that raw material variability will adversely affect the finished product Critical Quality Attributes. The sources of technological risk from excipients are reviewed and approaches to excipient risk management are discussed. Supplier involvement throughout the product life-cycle is recommended to minimize excipient-related risk.

KEY WORDS: QbD, Quality Risk Management, Excipients, ICH Q9, Performance

INTRODUCTION

ICH Q9 recognizes that the manufacturing of a drug product, including its components, necessarily entails some degree of risk, including risk to the drug product quality throughout the product lifecycle. Quality risk management (QRM) ensures patient safety by providing a proactive means to identify and control potential quality issues during development and manufacturing. QRM facilitates better and more informed decisions if quality problems arise, provides regulators with greater assurance of a company's ability to deal with potential risks, and can beneficially affect the extent and level of direct regulatory oversight(1). The title 'Quality Risk Manage-ment of Compliant Excipients' assumes that the user is sourcing compliant GMP materials from pharmaceutically aligned suppliers. Doing otherwise assumes risks beyond the scope of this article.

Raw material compliance with specification and manufacture to GMP do not eliminate variability. Quality by Design (QbD) should minimize the risk that raw material variability will adversely affect the finished product Critical Quality Attributes (CQAs). Formulation & process design must accommodate the raw material variability (robustness). The API typically gets most attention. Excipients are often divided into critical and non-critical categories, the latter receiving less attention. Such arbitrary classification runs the risk of surprises if subsequent experience invalidates the assumption of non-criticality.

Excipient supply chain security is necessary but insufficient to guarantee quality and patient safety. Section 711 of the recent Food and Drug Administration Safety and Innovation Act (2)

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('Enhancing the safety and quality of the drug supply') extends cGMP to include 'managing the risk of and establishing the safety of raw materials.'

Reliance solely on pharmacopeial compliance is a major risk for three reasons:-

i) Compliance to specification provides no insight into the supplier quality systems or GMP. The definition of adulterated substance in USP <1078> (3) includes material not manufactured using good manufacturing practices. Although USP <1078> is a General Information Chapter, the evolving NSF/ANSI 363 (4) consensus standard (GMP for Pharmaceutical Excipients) will be enforceable by FDA.

ii) Reliance on pharmacopeial specification alone has driven commoditization of many excipients. True commodities lack qualitative differentiation and are fungible (capable of mutual substitution). Given the general lack of understanding of excipient composition and functionality, the assumption of interchangeability of sources is a risk in many applications. The term 'commodity excipients' has also been used for those excipients where the majority usage is non-Pharma/industrial. This is a supply-chain risk (diversion) versus the more insidious risk due to pharmacopeial commoditization (assumption of interchangeability). Downward cost pressures increase the risk of non-compliance to GMP and Economically Motivated Adulteration (EMA).

iii) Pharmacopeial standards define minimum purity and safety requirements but do NOT define Fitness for Purpose in an application. NSF/ANSI 363 (4) defines quality as 'the suitability of an excipient for its intended use' in addition to attributes such as identity, strength, and purity.

ICH Q9 (1) defines Quality as 'the degree to which a set of inherent properties of a product … fulfils requirements.' The risk of equating quality with compliance is illustrated by the melamine in milk scandal. Under the ICH definition melamine could be described as a quality enhancing additive, the intent being to improve compliance to specification. Inappropriate reliance on compliance actually makes compliant materials riskier than non-compliant materials. The latter should be prevented from entering the chain by the quality system, the detectability of known but non-compliant attributes eliminating the risk.

Taleb describes in his book 'The Black Swan: The Impact of the Highly Improbable' (5) the extreme impact of rare and unpredictable events ('Black Swans'), the risk being accentuated by the tendency to place too much reliance on what we know and ignore or underestimate what we don't know. Pharmaceutically, there tends to be over- reliance on the Certificate of Analysis, focused on pharmacopeial parameters, of limited relevance to determining excipient fitness for purpose in an application. Other unspecified excipient attributes may vary uncontrolled in the background, but will be unknown to the user unless discussed with the excipient supplier. This must be addressed during development, either by designing the formulation and/or process to be robust enough to cope with the variability of such previously unknown attributes, or by appropriately specifying the excipient to limit the impact on finished product CQAs.

Black Swan logic makes what you do not know far more relevant than what you do know. Any risk assessment based solely on pharmacopeial parameters may not be valid due to the unknowns. Risk assessment must also take into account that absence of raw material impact during development is not evidence of no problem (it is difficult to prove a negative). Gaps in excipient knowledge devalue risk assessment. It is easier to construct a (poor) design based on known attributes (especially of limited functional relevance), than to accommodate unknowns.

The man who knows he knows nothing knows more than the man who does not know he knows nothing, or, according to Donald Rumsfeld (6):

'[T]here are known knowns; there are things we know that we know.

There are known unknowns; that is to say there are things that, we now know we don't know.

But there are also unknown unknowns – there are things we do not know we don't know.'

Excipient unknowns fall into several categories and may be further categorized as being unknown to the user, unknown to the supplier and perhaps even

unknown to both. Risk assessment requires that unknowns (not unknowable) be addressed with all stakeholders, including the excipient suppliers. Unknowns add to system complexity, undermine risk assessment and make it difficult to develop meaningful models. It has been said that all models are wrong and some are useful, but how wrong do they have to be to not be useful (5)?

Excipient Unknowns

- Composition
- Functionality/Performance
- Limited Utility of Pharmacopeial Attributes
- Non-pharmacopeial attributes
- Variability
- Criticalities

Composition

Excipients are more complex than well-characterized active pharmaceutical ingredients ('APIs'). Non-biologic APIs are predominantly single synthetic small molecule chemical entities, manufactured in batches with well characterized impurity profiles (unintended or unavoidable constituents which differ from the labeled chemical entity). This is the exception for excipients, which are often polymeric or multicomponent with ill-defined compositional profiles. Excipients are also often manufactured using continuous production on much larger scales than APIs or drug products. Unlike APIs, the sum of the labeled entity and defined impurities will not add up to 100% for excipients due to other concomitant components. The functionality of some excipients may actually depend on so-called impurities, e.g. DiCalcium Phosphate and Non-crystallizing Sorbitol Solution.

NSF/ANSI 363 (GMP for Pharmaceutical Excipients) (4) specifies consistent excipient composition, and, where possible, limits for excipient composition, including known impurities. NSF/ANSI 363 also states that manufacturing processes shall be adequately controlled so the excipient composition falls within established limits. It will be difficult for users to agree on meaningful (application- specific?) compositional limits with their suppliers unless they understand in some detail the manufacturing processes and raw materials used to manufacture their excipients. A more realistic definition of an excipient 'impurity' is any component, other than the labeled entity, that needs to be controlled. Again, greater understanding of the excipient manufacturing history is required for such an 'impurity' specification.

Often, it is the multi-component nature of the excipient that drives many chemical incompatibilities with APIs. For example, although one might theoretically avoid the classic amine incompatibility with reducing sugars, by using non-reducing sugar excipients, trace levels of reducing sugar 'impurities' may thwart the avoidance strategy. Even for the most commonly used excipients, it is necessary to understand the context of their manufacture in order to identify potential API interactions with trace components.

It is common practice to approve specific excipient sources but it is better to identify the mechanism of reaction and specify the excipient with respect to the level of reactive components. Risks associated with changes in excipient-induced API degradation are particularly insidious if only detectable by long-term stability studies, when at-risk product will already be in the market. Change control and notification are less effective if impact cannot be immediately assessed. An API incompatibility specific to a particular excipient source is evidence that the reactant is something other than the labeled excipient entity.

Functionality/Performance

Excipient functionalities are qualitative classifications describing the purposes or roles of an excipient in a drug product, and are the rationale for inclusion in the formulation (7). Excipient performance is a more holistic term embodying the actual expression of the excipient properties, including functionalities, in a specific drug product. The current regulatory environment and the paradigm of QbD go beyond simply identifying excipient function and emphasize performance through the identification, evaluation, and control of Critical Material Attributes (CMAs) that assure consistent performance throughout a product's life-cycle (7).

Excipient CMAs may not be identifiable or evaluable using the specific tests and specifications listed in compendial monographs. To minimize the risk of inappropriate over-reliance solely on compendial specifications, the USP Excipient Performance General Chapter <1059> (8) is

designed to provide an overview of material attributes and tests for many functional categories of excipients. These additional tests are not typically included in excipient monographs, and are not exclusive. The appropriate tests and specifications to ensure consistent and reliable excipient performance, in terms of finished product quality, may also come from neither the monograph nor the chapter <1059>. A thorough understanding of the formulation and manufacturing processes, the dosage form performance requirements, and the physicochemical properties of each ingredient (including the manufacturing history of each ingredient) is essential for a meaningful risk assessment. Pharmacopeial guidance on excipient performance or functionality- related-characteristics will not of itself eliminate the risk of performance/functionality-related surprises. Finished-product CQAs may be dependent on ill defined physical, multi-particulate properties of excipients, and such CMAs may themselves be dependent on the method of excipient manufacture and complex precursor materials.

Limited Utility of Pharmacopeial Attributes

Most pharmacopeial attributes are derived from measures of the original sponsor's consistency of production, using the sponsor's methods. Subsequent suppliers will comply with the monograph but their raw material feed stocks and production processes may differ, affecting other excipient properties. Adding to the risk, the majority of pharmaceutical excipients have been adapted from other industrial markets, the pharmaceutical market often being a relatively small proportion.

A method developed to measure the consistency of one supplier's output may not be relevant in determining the interchangeability of multiple sources, let alone fitness for purpose. A good example is viscosity. A medium viscosity grade of polymer could be provided by one supplier as a true medium molecular weight distribution and by another as an average of high and low molecular weight distributions. If the molecular weight distribution, not viscosity, is the true CMA, expect surprises on finished product quality when changing sources. The difficulty of characterizing macromolecular excipients has been reviewed by Apte (9).

Reliance on pharmacopeial viscosity methods is also risky given that most are dilute solution apparent viscosities, measured using simple viscometers. Viscosity is often the least relevant rheological parameter in many applications (especially suspensions) and the dilute concentration may not reflect the effective concentration in-use. For example polymer matrix CR tablets will have effective in-use concentrations at least an order of magnitude higher than the pharmacopeial viscosity methods. Not only may the rank order of viscosities differ but other rheological effects, such as gelation, may intervene as well.

Pharmacopeial compliance ensures neither fitness for purpose in a specific application, nor equivalence between sources. Pharmacopeial compliance should be regarded as a minimum standard, not a guarantee of interchangeability between multiple sources. Pharmaceutically aligned suppliers will often provide additional data to demonstrate functional equivalence in support of change control, but cannot warrant interchangeability in a specific application.

A PQRI survey (10) found that more than 70% of all respondents performed additional functionality or processability testing on excipient from a new supplier. About 25% of the time, excipient suitability testing involved laboratory or pilot scale manufacturing batches. Although reported as 'higher than expected', such findings are not surprising given the limited understanding of excipient composition and performance in complex systems.

Reliance solely on pharmacopeial attributes runs the risk of failing to identify CMAs, introduction of non-interchangeable material, and consequent risk to finished product quality.

Non-pharmacopeial attributes

Focus only on pharmacopeial attributes is the pharmaceutical industry example of blindness to uncertainty associated with Black Swan theory (5). If other unknown attributes of an excipient vary uncontrolled in the background there is risk to finished product quality, especially for fixed processes and formulations. This risk is commonly magnified by the tendency to arbitrarily tighten ranges of pharmacopeial attributes in response to finished product quality problems. Controlling the

wrong attributes gives a false sense of security, adds compliance burden and predisposes to future failures. Rearranging the deckchairs on the Titanic does not impart resistance to icebergs. It is better to be roughly accurate than precisely wrong. Detectability of risk from unknown CMAs is low as the leading indicators (pharmacopeial attributes) will give compliant results up to the point of product failure. As an example, microcrystalline cellulose is widely used as a 'water manager' in wet granulation and extrusion-spheronization, yet it is rarely specified with respect to water interactions.

Assessing the risk from unspecified attributes is made more difficult in that many unknown CMAs will be application specific. Some excipients will also have no pharmacopeial attributes as CMAs.

Variability

PQRI (11) defines robustness as the ability of a manufacturing process to tolerate the expected variability of raw materials, operating conditions, process equipment, environmental conditions and human factors. Moreton (12) similarly describes a robust formulation as 'able to accommodate the typical variability seen in the API, excipients, and process without the manufacture, stability, or performance of the product being compromised'. In addition to uncertainty as to composition or performance, excipient risk also arises if the true variability is underestimated. Assessment of what variability is to be expected or is typical will be confounded without detailed knowledge of the excipient manufacturing history or supplier process capability.

The risk of underestimating excipient variability is mainly attributable to four main causes:

- Equating excipients with reagents
- Unilateral assessment
- Limited excipient experience
- Continuous manufacture of excipients

Some excipients are simple reagents such as buffers. Add the right amount of the right purity and performance (chemistry) is guaranteed. This is also referred to as the API mindset, where composition and performance (efficacy) are understood. Process-dependent excipient composition, performance and variabilities are less understood. This risk of underestimating excipient complexity is reinforced if the users do not discuss the use of excipients in their products with the excipient suppliers.

During development and scale-up the number of excipient batches (and suppliers) will be insufficient to meaningfully characterize the impact of excipient variability on that product. The risk can be mitigated by reference to other products in commercial production using those excipients. The excipient supplier can also supply data additional to that on the limited number of purchased batches. This could be CoA data or summary statistics for their Production. With trust (or CDA) the excipient supplier can also provide in-process data or data on attributes beyond the CoA.

Many common excipients are manufactured in much larger volumes (>10,000 tons pa) than pharmaceutical products, often by continuous production. In continuous production, the 'batch' is the production campaign, extending over variable periods up to several months. In practice the continuous production is usually time-sliced into discrete batches but even days or weeks of production can still be many tons. Of necessity, the data for some parameters on the CoA will be a composite or an average. Reliance on CoA data alone runs the risk of underestimating the true variability if the in-process data is noisier than the CoA data. Access to the most relevant in-process data also requires traceability back from the individual packed unit, the need being dependent on how noisy the in-process data is relative to CoA data. Supplier process capability should always be determined from supplier in-process data, never by user estimates from CoA data. User testing is much less statistically relevant in the assessment of excipient variability compared to the much larger supplier databases.

According to Tim Cabelka, Dow Polymers, 'Since excipient users usually do not know the manufacturing process and raw material variation for any given excipient, the extent of product variability cannot be known or even estimated by users.'

An inadequate assessment of true excipient variability also incurs Regulatory risk. A reviewer may reasonably query excipient specification limits which are much wider than the narrow range of excipient data typically presented. The applicant

runs the risk of delay, either justifying their supplier limits, or being asked to explain the potential impact of operating in specification regions beyond their experience space, if not explained in the control strategy. Reviewers have been known to demand that excipient specification limits be narrowed, which is risky as they do not know the supplier process capability. Even greater risk ensues if the applicant agrees to the narrower limits without supplier agreement, as the routine supply of material meeting such specification may not be feasible, technically and/or commercially.

Criticalities

'Critical' is a much used term in QbD relating to anything which affects the safety or efficacy of the finished product. Critical process para-meters (CPPs) and critical material attributes (CMAs) must be controlled to ensure the finished product CQAs, the surrogates for safety and efficacy, remain within the Design Space.

MIL-STD-1629A uses the word 'critical' as a severity classification (II) one stop short of catastrophic (I), and defines a criticality as a relative measure of the consequences of a failure mode and its frequency of occurrences (13). However, another definition of criticality relates to being in a state, or at a point, where some quality, property, or phenomenon under-goes a definite change (14). This latter defini-tion is rarely used in QbD but is equally impor-tant because a criticality, a point of transition from one state to another, can be critical, if encountered during Production. Other relevant descriptors include, but are not restricted to, thresholds, non-linearities, discontinuities, tipping points and edges. Critical transitions have been described as catastrophic bifurcations, where a minor trigger can invoke a self propagating shift to a contrasting state. (15,16)

A literal pharmaceutical example is the critical micelle concentration (CMC), commonly encountered in dissolution testing, where concentrations of surfactant in the dissolution medium above CMC are used to maintain sink conditions. Dissolution of API (or lack thereof) in media where the surfactant is present below CMC is not predictive of the behavior above CMC, where there is a disproportionate (with respect to surfactant concentration) increase in drug solubility, proportional to the number of surfactant micelles. The CMC is a criticality, the point of transition from a surfactant solution to a two phase solution/micellar system. Furthermore, the CMC itself may depend on a particular compositional profile in the case of (usually) multicomponent surfactant excipients.

Criticalities are inherent to, but not intentionally incorporated, into the design. A poor design will cause quality problems, but a good design does not always guarantee absence of problems. RMS Titanic was the same design as her first-of-the-line sister ship RMS Olympic. The latter was retired after 25 years service, including 257 transatlantic crossings and 3 collisions, earning the nickname 'Old Reliable.' Criticalities and other unforeseen failure modes will always bedevil complex systems.

Most so-called 'simple' formulations (what can go wrong?) are quite complex when one considers:

- limited understanding of raw material complexity and performance
- no fundamental powder mixing rules or prediction of cooperative properties
- the black hole between the punches: inhomogeneity of force transmission and tablet density
- conflicting technological objectives
- fixed processes & formulations, which increase sensitivity to raw material variability
- compliance requirements beyond quality requirements
- submission data generated on small/pilot scale with limited excipient experience
- cumulative process tweaks and changing raw material sources

Excipients may disproportionately impact CQAs if minor excipient variability interacts with a criticality in the application, and the minor excipient variability is suddenly governing the transition from one state to another. A hitherto 'non-critical' excipient attribute has now become critical. The offending application-specific excipient CMA may be a known attribute and the variability may also be within normal limits and prior experience, but the drug product has become sensitized and no longer robust to variability in that particular excipient attribute.

Excipient unknowns compromise risk assessment but are not unknowable. Pharmaceutically aligned

suppliers can identify excipient aspects unknown to the user and pre-empt criticalities in the finished product by identifying potential failure modes (if they are aware of the application). NSF/ANSI 360-20 excipient GMP (4) requires suppliers to consider 'requirements not stated by the customer but necessary for the specified or intended use, where known', when determining excipient quality.

Managing excipient risk

The steps outlined below are iterative and not strictly sequential. Risk assessment is an ongoing process throughout the product lifecycle, not just during development. QbD often refers to continuous improvement but continual monitoring is essential to better understand the limitations of the product in commercial reality, with old assumptions, models and analyses under constant revision.(17)

- Communication with suppliers
- Quality of Design
- Build-in compensatory flexibility
- Risk Assessment
- DOE/Development
- Contingencies/Control Strategy

Communication with suppliers

Early discussion with excipient suppliers is recommended to ensure fitness for purpose, especially for new applications. Proceeding in the absence of, or contrary to supplier advice is risky. If the application raises safety issues the supplier should refuse to supply. If a supplier cannot provide application support, historical data or is unwilling to comply with pharmacopeial requirements, the option of selecting another supplier or an alternative material should be pursued. Even for conventional applications, supplier insight into failure modes will strengthen risk assessment. Many grades of excipients are incorporated into formulations off the shelf with no understanding, or specification, of attributes that govern performance in a specific application. If the supplier changes or stops supplying that specific grade there is risk to finished product quality and risk of shortage.

Development personnel should visit their suppliers for insight into the manufacturing background and properties of the excipients. Compliance audits do not count in this respect. Design Review Based on Failure Mode (DRBFM), states that good discussions during preliminary design can achieve the same result as validation testing in identifying design weaknesses (18). Communication with suppliers should continue throughout the product lifecycle.

Quality of Design

Poor designs should be self-limiting but, unfortunately, prototypes developed with limited pharmaceutics expertise can accrete sufficient stability and clinical data to inhibit redesign, running the risk of eventual regulatory or manufacturing failure. An oral solid dose form (OSDF) without disintegrant is an example of a weaker design, at greater risk of excipient-related effects at some stage in the product life-cycle. A similar but more subtle risk attaches to immediate release OSDFs not validated as non-rate-limiting on release.

Pharmaceutical formulations have multiple competing technological objectives. Compromises or trade-offs increase the risk of susceptibility to raw material variability. Can competing priorities be uncoupled? Disintegrants uncouple release from tablet robustness. Structured vehicle formers uncouple viscosity from suspending power. Any product associated with the terms 'over' or 'under' needs only minor excipient variability to push it over the edge (e.g. overgranulation, underlubrication).

Good designs emphasise robust processes to cope with raw material variability, rather than be dependent on a particular CMA. However, not all CMAs can be avoided, such as particle size of poorly soluble API (dissolution), and excipient chemical compatibility with API. Surface area, particle size, morphology, composition and degree of hydration are all possible CMAs for magnesium stearate, the classic example of competing technological objectives, in a single excipient. Some CMAs will only surface in commercial production after scale-up and greater raw material experience.

Good designs will always take manufacturability into account, well before scale-up and commercialization. Reviewers are always concerned about the impact of scale-up if applications only contain data from small-scale or pilot batches. This

risk can be mitigated by involving Production and Quality groups early in the development program.

A certain number of good designs will eventually fail, the problem being that there is no way of predicting which ones or when. The Concorde crash in 2000 ended a 24 year perfect safety record. One designs for Olympic performance but the Control Strategy should be Titanic, covering as many potential failure modes as possible.

Build-in compensatory flexibility

Fixed processes together with fixed formulations are poor designs where excipient variability can feed forward to the detriment of finished product quality. If the excipient variability cannot be reduced the Control Strategy becomes meaningless. QbD requires that flexibility be built into the system to compensate for the variability inherent in the raw materials.

The overwhelming emphasis in QbD has been on process controls, with near complete retention of fixed formulations. Building flexibility into the formulation itself also provides compensation against the impact of raw material variability. Quantitative variation of an excipient level in accordance with a validated algorithm could counter the incoming variability of the API or other excipients. Excipients with functional concentration optima, such as glidants and lubricants, are obvious candidates to deliver fixed performance with variable composition versus the traditional fixed composition and variable performance.

Whether the formulation is fixed or not, excipient risk assessment also benefits from excipient ranging studies during development. If the prototype contains a certain level of excipient what happens to functionality and performance as the level is titrated downwards? If increased variability of the finished product (or failure) occurs close to the target level then there is a greater risk of a criticality within the formulation and/or susceptibility to variability of that excipient. On the other hand if the level has to be halved in order to see effects, it suggests that the excipient level is not near a criticality and that the target level offers a reserve of performance. Sensitivity to raw material variability is generally greater nearer the margin. Demonstrating understanding of the impact of such changes also facilitates quantitative formula changes during the product life cycle. If a fixed formula is not critical why maintain it at the expense of product consistency?

The traditional focus has been on excipient consistency (variable performance) but under QbD the logic inverts. How can excipient variability be turned to competitive advantage by pharmaceutical manufacturers in pursuit of consistent performance and finished product quality? Many excipients when used as food ingredients are specified by a functionality which is standardized by addition of varying amounts of agreed food-grade diluent, thus eliminating batch-to-batch performance differences. It is to be hoped that the pharmaceutical fixation on composition, at the expense of performance and finished product quality, is eliminated by QbD.

Risk Assessment

ICH Q9 (1) states that it is neither always appropriate, nor always necessary, to implement a formal risk management process. The use of informal risk management processes can also be considered acceptable. 'The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and the level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.' More importantly, the risk assessment ethos should apply throughout the product lifecycle, regardless of risk assessment method.

Excipient risk assessment starts with risk identification, defined in ICH Q9 as a 'systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders.' (1) Are excipient suppliers not stakeholders with informed opinions? They have the knowledge of variability and unspecified attributes without which excipient risk assessment is flawed. Their application knowledge can identify potential excipient-related modes of failure, which the user would not have unilaterally identified.

DOE/Development

Once a design, or prototype, is available, risk assessment guides what is to be done experimentally in development and what is NOT to be done in

development (Design of Experiments (DOE) vs. Control Strategy in QbD terms). What is seen as critical gets tested and what is thought to be non-critical does not, the risks being deemed insignificant, improbable, or detectable. There is some risk in choosing what is critical as omission means that the experimental design is less able to assess the potential criticality of the omitted item. Sighting studies cover more variables than a targeted experiment but have less power to identify subtle effects. It should be remembered that a null finding in an experiment is not evidence of no problem, negatives being difficult to prove.

With increasing insight and regulatory scrutiny on excipients, Orloff (19) highlights the 'potential for QRM to degenerate into a non-value added exercise of identifying noncritical, improbable, low risk scenarios indefinitely.' This is true if it triggers unnecessary experimentation for the sake of perceived regulatory compliance but arguably the designated non-critical, improbable, low risk scenarios are also important. If the applicant identifies something as critical, and institutes controls, that risk is mitigated. However, as many other potential failure modes as possible should be identified, and integrated into the control strategy if necessary. Regulatory authorities currently tend to focus on critical items but as they gain cumulative experience of originally non-critical items turning critical post-approval, the focus will shift. Including only critical items in a submission could also be counterproductive for similar reasons.

Ensuring a representative sampling of variability requires early discussion with suppliers. Continuous processes for many high volume excipients tend to be run at the center of specification, and material at or near the edge of specification may not be commercially available. To start up and target a new continuous process set-point could consume several hundred tons of material, at least half of which will be out of specification if running at a specification limit. If the supplier is aware of specific requirements it may be possible to reserve material from an excursion in a relevant direction, or drive the process through a specification limit as part of a campaign shutdown. Alternative approaches are also available to the user, such as grade bracketing, fractionation or blending.

Quality before quantity is important before deciding on the number of experiments. Simply running large numbers of experiments to cover potential failure modes is unscientific because null results (no evidence of problem) are not evidence of no problem. If multi-sourcing of an excipient is evaluated during development, any intersource differences mean either that the product design be changed to eliminate the sensitivity, or that the excipient be specified to distinguish between the acceptable and the unacceptable source.

Multivariate data analysis is better than the traditional 'change one variable at a time' to miminise the number of experiments and identify interactions. It should be noted that correlation does not prove causation so mechanistic understanding should be sought. Sugihara *et. al.* (20) demonstrate an example of ephemeral or mirage correlation, with a simple mathematical model where the variables spontaneously correlate, anti-correlate and decouple. Model development should be underpinned by mechanistic understanding. Empirical models can guide future experimentation but should not be used for GMP-critical decisions. Apte (21) lists common mistakes in application of DOE, particularly reliance on 'mix and match' experiments dictated by the DOE software and recording their effects on preselected CQAs.

Contingencies/Control Strategy

Contingencies for foreseeable events, such as scale-up and expansion of raw material experience space, should be included in the control strategy. Evaluating new excipient sources would be expected under conventional change control, but if the full variability of a single source was not evaluated during development, similar additional testing can be specified in the control strategy.

Unforeseen events also need to be anticipated by continual monitoring. Unexplained increases in variability or new correlations could be indicators of impending criticalities or transitions. A design which is too resistant to change could undergo a critical transition unless redesigned for more gradual adaptive response or to strengthen the preferred state (Scheffer 16).

Any models developed during development need to be continually updated to confirm ongoing relevance and validate their predictive power.

Excipient sourcing must be under control of R&D and/or Quality. Commodity buying is not QbD and is the highest risk sourcing strategy. Joint due diligence, between the users and their excipient suppliers, is the lowest risk sourcing strategy.

CONCLUSIONS

The greatest risks from excipients are the unknowns. QbD requires supplier collaboration to close the excipient knowledge gap. There are significant benefits to better understanding excipients and leveraging supplier expertise:

- Knowledge of the product itself
- Knowledge of how the product was created
- Knowledge of the how the product will behave in unexpected circumstances
- Knowledge of the how the product can be changed or improved
- Knowledge of how to specify the product
- Knowledge of the risks associated with the product

Mahboubian-Jones G (22)

Collaboration will allow adequate specification of excipients reflecting shared understanding and fitness for purpose in the application. Ideally, there should be regulatory recognition of supplier-user partnerships, jointly reducing excipient-related risks through mutual due diligence, as this provides the lowest risk basis for approval in terms of excipient QRM.

'Learning about an excipient as if it were your own product is critical to design' (23).

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