# Excipient risk analysis: A new ERA?

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*He who knows not and knows not that he knows not is a fool; avoid him.*
*He who knows not and knows that he knows not is a student; teach him.*
*He who knows and knows not that he knows is asleep; wake him.*
*He who knows and knows that he knows is a wise man; follow him.*

The above ancient proverb is very relevant to categorization of excipient-related risks. Those who supply raw materials as excipients without knowledge of pharmaceutical requirements and those who use excipients pharmaceutically without understanding them, are to be avoided, especially in tandem.

The International Pharmaceutical Council (IPEC) (1) and others seek to teach and reawaken understanding of the role of excipients in Pharmaceutical products. The IPEC approach of Total Excipient Control (2) should be followed.

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Excipient risk management must address the three sources of excipient-related risk:

- Safety
- Supply Chain Integrity
- Technological Risk

The intrinsic safety of an excipient relates to the level of human exposure via a specified route of administration. A regulatory safety assessment as part of a finished product marketing application is a prerequisite to pharmacopoeial listing. The absence of a separate regulatory approval mechanism for excipients has long been a barrier to the introduction of new-chemical-entity excipients. This is being addressed by IPEC Americas and the IQ Consortium, a Biopharma association, who are collaborating to encourage the development of

an improved regulatory pathway for novel excipients in the US.

The source of the excipient, and the integrity of the supply chain, is also safety critical. If not subject to Good Manufacturing & Distribution Practices (IPEC GMP/GDP Guides (3-4)) and change control (IPEC Significant Change Guide for Bulk Pharmaceutical Excipients (5)) there is the potential for contamination, adulteration, substitution, undeclared additives, and/or degradation. Compliance with a Pharmacopoeial specification is not in itself an adequate guarantee of quality for human use. It should always be remembered that compliance with a Pharmacopoeial specification is to be expected with the more sophisticated attempts at economically motivated adulteration.

*An important consideration when assessing excipients and API is that, due to the global nature of our business, third party sourcing has become routine and accepted. Therefore, it is crucial to understand the supply chain in each and every case. Complexities in the supply chain can cause a minimization or loss of information and thus loss of control if the intention is to become more educated to design better. We must understand and fully know the supply chain for excipients and API to ensure we understand where weaknesses exist so that we can plan to implement better controls* (6).

Excipients are generally more complex than simple synthetic chemical entities. They may be multicomponent, polymeric, and polydisperse. Composition, physical properties, and performance in specific applications, may be dependent on the source, manufacturing history, processes and raw materials. Compositional complexity may not be adequately defined in the supplier or pharmacopoeial specifications. IPEC has therefore developed an Excipient Composition guide (7). For simple solution chemistry reagents (e.g. buffers) the specification (essentially purity standards) may be relied upon. For more complex excipients, especially when relying on solid properties, it is essential to think beyond the Certificate of Analysis (CoA). For APIs in Europe it is forbidden to rely solely on compliance with the Ph Eur monograph without a source-specific Certificate of Suitability (CoS). This is not mandatory for excipients (and not all excipients have a Ph Eur monograph) but the concept does address overreliance on compliance with specification alone.

Excipient supply chain integrity is increasingly challenged by globalization and outsourcing. Diethylene Glycol (DEG) poisoning was the impetus for the US Food, Drug, and Cosmetic Act of 1938. Continuing adulteration of glycerol with DEG over the intervening seven decades prompted an FDA guidance in 2007 requiring a specific mandatory identity test that includes a limit test for DEG (and ethylene glycol (EG)) on all containers of all lots of glycerol. This has been extended to the monographs of several similar at risk materials, which now include limits (0.1%) for DEG and EG in their mandatory identification section. An FDA/USP Monograph Modernization Initiative is also underway to upgrade monographs for a dozen excipients which lack specific assays or ID tests (8). There is increasing regulatory interest in adding spectral methods to excipient monographs. Additional monograph tests cannot anticipate all future adulterants but will make it more difficult for economically motivated adulteration.

Excipient supply chain security has been tightened with the US FDA Safety & Innovation Act 2012 (9), which requires registration globally of all excipient manufacturers with traceability via the ANDA/NDA. Excipient supply chain security has also been tightened in the European Union through the provisions of the Falsified Medicines Directive (10).

Using only approved excipients from pharmaceutically aligned manufacturers and distributors is essential to finished product quality and patient safety. However this does not preclude other excipient-related problems

in production. Pharmaceutical quality is generally high (6σ) but this is due to inspection and rejection rather than manufacturing efficiency: 2-3σ compares unfavorably with other regulated industries. Excipients are a potential source of risk to manufacturing quality. The complexity of both the excipients and the finished drug product, and the potential for interactions, are often underestimated. Even in the hands of those skilled in the art, residual technological risk from excipients can arise from:

- Unknown interactions
- Unknown (unspecified) attributes
- Unknown excipient variability
- Unknown finished product criticalities or latent conditions

A good design will address the knowns but cannot cover unknowns. Performance will be satisfactory until impacted by an unknown, a so-called Black Swan event (11). Past satisfactory performance is no predictor of future performance. Or, to put it another way, absence of evidence of a problem is not evidence of absence of the problem!

Excipient unknowns, including unknown attributes and variability, have been reviewed in detail (12). It is not possible to assess the robustness of a design with respect to excipient impact if the design is subject to unknown factors beyond the CoA and the limited excipient batch/source experience at the time of marketing authorization. These unknowns, which represent potential failure modes, are not unknowable, but require early discussion with the excipient manufacturers and their authorized distributors. The FMC QbD Express® program is an example of an excipient supplier's educational/QbD support initiative on unknowns, covering both unspecified attributes and variability. Unknown excipient attributes and variability are "known unknowns" in the sense that the excipient manufacturer may know, and what was unknown to the user becomes known on discussion. These unknowns are knowable, preferably before they cause problems.

A more insidious technological risk comes from criticalities or latent conditions within the drug product. These are "unknown unknowns", in that neither the excipient manufacturers, nor the manufacturer of the drug product, are aware of the presence of such potential weaknesses or susceptibilities within the product. They are artefacts of the design analogous to the bugs in software systems. They are not there by design but arise out of the complexities of the subsystems and how they interact. Excipients are complex materials which are used in complex systems, giving rise to myriad interactions. A specific "unknown unknown" is by definition unknowable before it impacts product quality but pharmaceutically aligned suppliers of excipients should be able to provide general guidance to make designs more robust with respect to potential excipient-correlated failure modes.

The International Conference on Harmonization (ICH) defines criticality in terms of severity, probability and detectability, but omits the common physics/mathematics definition of criticality as a transition between two states. If the finished drug product undergoes a critical transition out of specification you may have a severe impact with little warning (low probability, low detectability). What is less understood is that a critical transition is analogous to moving into a parallel universe, where the rules are different. It is not a case of too much noise taking the existing model beyond a specified limit but rather a new model. It is difficult to demonstrate being a state of control if the model and the understanding underpinning the design have unexpectedly changed. An analogy might be the impact of the tide going out on a body of navigable water. If the design space was unknowingly based on high tide then movement within the design space might suddenly be curtailed if low water levels had not been factored into the design. Criticalities may

also be scale-dependent but detectability drops with the decreasing number of experimental batches as the process is scaled up.

Percolation effects are a good example of criticalities, or critical transitions, in pharmaceutical systems, especially in powder mixes and compaction. The term "explosive percolation" refers to the characteristic binary step function where the system goes from one state to another with little or no warning. Analogies relevant to movement within the design space would be like falling off a cliff, or stepping on a landmine. These are latent conditions if you are unaware of the topography or location of the mines.

Conflicting technological objectives are another source of criticalities. The closer the formulation is to a performance margin the greater the impact of excipient variability. Ranging studies during development are useful: if you can vary the level of an excipient by ± 50% and maintain product performance then the impact of variability of that excipient is generally going to be less than that associated with a more impactful ± 5% titration. However if you are trying to balance too many multiple competing objectives then you will have a very narrow operating margin with much greater susceptibility to excipient variabilities and unknowns. Good examples can be found with design-critical rate-controlling polymers in modified release. The higher the level of gelling-matrix-former the less impact from variability in the excipient attributes. If faster release is required it might be better to maintain a high level of a "weaker" polymer rather than reduce the original polymer to a level where the impact of excipient variability is greater. Similarly, maintaining a high loading of a rate-controlling controlled release coating is preferable to reducing to a level where it is subject to the impact of both the coating precision and variability of the excipient attributes.

Excipients are often arbitrarily categorized into critical versus non-critical during the design phase. This actually heightens the risk from the so-called non-critical excipients, especially if there are no specific contingencies in the Control Strategy. A better approach is to focus on the design-critical excipients during late stage Design of Experiments (DOE). Design-critical means that there is some reason to expect an impact on finished product performance; e.g. the choice and level of a modified release polymer.

A common logic trap is to assume that utilization of non-critical excipients during development without incident confirms that they are not critical. If there is no reason to expect impact then absence of impact does not prove absence of potential impact: just that it hasn't hit you yet. Even if not design-critical, all excipients in the product are potentially performance critical: appropriate contingencies should be built into the Control Strategy. Early discussion with the excipient suppliers will bolster the Control Strategy with respect to excipient risk management.

Regulators are paying increasing attention to discussion of excipient impact in applications. If no information beyond the formula level and pharmacopoeial compliance is provided then an assessor cannot judge the significance of excipient impact. PQRI defines reliance on pharmacopoeial or supplier specification with no further justification as the highest risk category of applicant (13).

Given the limited data in most applications reviewers may request tightening of excipient specifications if they look too wide relative to submitted data. Tightening of an excipient specification should never be agreed without discussion with the excipient supplier to ensure that the tighter specification is within process capability. Another disadvantage of arbitrary tightening of an excipient specification is that it may not improve finished product quality but will add to the compliance burden.

Users often request excipients at the extremes of specifications. This may not be feasible for

continuously produced excipients where Production is targeted at centre specification. IPEC is developing a QbD Sampling guideline (14) where better alternative approaches are discussed.

A further problem for the reviewer is that the quality of the design is not predictive of failure. Titanic shared the same design as its earlier sister ship Olympic, nicknamed "Old Reliable", which was retired after 25 years service. Quality by inspection is no more appropriate to marketing applications than to pharmaceutical production. An alternative approach would be to look at the quality of the manufacturing, such as the FDA quality metrics initiative to support risk-based inspection as per FDASIA sections 704 to 706 (9). If an applicant has an excessive reject rate then they fall into a higher risk category. Those who aspire to 6σ manufacturing require less scrutiny and oversight. 6σ will not be achieved without increased excipient understanding and closer collaboration with excipient suppliers will be required. The cost of poor quality will increase significantly if the users risk categorization is adversely affected.

## IMPLICATIONS FOR THE FUTURE OF EXCIPIENTS

Future trends in pharmaceutical excipients have been reviewed. Moreton (15) highlighted the double jeopardy of new excipient development: a new chemical entity excipient incurs the cost of safety studies, in the same way as a new drug entity, but afterwards there is no regulatory mechanism for review and approval as a pharmaceutical excipient. The developer of the new excipient must then persuade a pharmaceutical company to incorporate the new excipient into their new product so that the excipient is reviewed as part of the drug product marketing application. Because pharmaceutical companies seek to minimize regulatory risk, few will be willing to incur the added risk of incorporating a new excipient. Whatever the many shortcomings of current excipients, pharmaceutical companies will stick with them rather than risk delay to their regulatory filings. Consequently the regulatory environment continues to be very inhibitory to new excipient development. Only three new chemical entity excipients have been launched in the last two decades:

1. Sulfobutylether β-cyclodextrin enabled a pharmaceutical product, so development costs and inclusion in the marketing application were supported by the pharmaceutical company.
2. Hydroxystearic acid PEG ester (Solutol® HS15) was included in a marketing application but the regulatory risk was reduced by use of the IPEC Novel Excipient Safety Evaluation Procedure (16, 17). This allows review by an independent panel of toxicologists which can be shared with FDA. This is not a regulatory approval but highlights at an early stage any safety issues, reducing the risk that the novel excipient will delay the finished product approval.
3. A novel polyvinyl caprolactam, polyvinyl acetate, polyethylene glycol graft copolymer (Soluplus®), developed for Hot Melt Extrusion, was launched in 2009.

The alternative to new chemical entity excipients is to develop new physical combinations, co-processed excipients, where the components are physically combined using processes, such as co-spray-drying, to give functionalities or attributes not achievable by simply blending the components. Because there is no new chemistry (to be verified by provision of a suitable analytical bridging argument) there is no real regulatory barrier to utilization. However the pharmaceutical industry is risk averse to the point where some companies forbid the use of new co-processed excipients.
Traditionally a new coprocessed excipient had to offer a compelling synergy or benefit, not achievable from the separate components, to justify the launch of a new coprocessed excipient. In practice the rate of adoption will be governed by limited use on marginal

products. Only after precedence of use is established and subsequent monography, will the coprocessed excipient enter mainstream use. This could easily add five to ten years on top of the excipient development timeline, which greatly shortens the effective patent life. Unlike the additional patent exclusivity for drug products under Hatch-Waxman (to compensate for long development and approval times) excipients have no such mechanism for patent extension.

The United States Pharmacopoeia has attempted to facilitate the monography of coprocessed excipients by publishing guidance on the development of monographs (18). They also allow the development of a "pending" monograph in parallel with industry adoption and FDA NDA/ANDA review. Once precedence of use is established the pending monograph becomes official, greatly reducing the overall time to pharmacopoeial listing, which encourages adoption. Unfortunately the European Pharmacopoeia does not permit monographs for excipients still covered by patent.

The USP position is prescient as the interplay of several drivers will encourage the development and use of new coprocessed excipients:

Co processing itself can be a Critical Process to counter variability of attributes and minimize their impact on finished product quality.

- Increased understanding of complex systems under QbD may require novel attribute combinations not achievable from the separate components
- Increasing Cost of Poor Quality (COPQ) where the applicant's history of manufacturing quality becomes a factor in assigning a risk category to their application.
- Increasing use of continuous manufacture where the complexity of metered dosing control becomes too high for a large number of excipients. Co-processing fixes the uniformity of several components (especially low dose additives) and reduces the number of metered inputs.

Hogan (19) predicted diversification of excipient industry into "two groups, one focusing on high-tech excipients with greater functionality and high prices - developed in partnership with drug companies and in a manner akin to an active pharmaceutical ingredient - and a commodity sector." Sulfobutylether β-cyclodextrin is an example of an excipient developed in partnership with a drug company. Excipient development in a manner (and cost) akin to an active pharmaceutical ingredient may explain why only one such example has emerged.

Biotech requires much more highly characterized raw materials but the role of excipients may be more intimately tied to the active moiety than in small molecule development. Small molecule discovery is independent of the excipients which subsequently enable development of the dosage forms. Biologics discovery is much more sensitive to the excipients used in research. Excipients have traditionally been regarded as pharmacologically inert but "active" excipients could be a future area for development. How many so-called "poorly permeable" drugs are in reality permeable but subject to efflux? A wide range of excipients have been suggested as P-glycoprotein inhibitors (20)

Hogan (19) described a commodity sector, the "pharmaceutical divisions of companies whose main business is outside of the pharmaceutical sector," with competition on price and service. Excipients have indeed been subject to pricing pressure and putting a commodity tag on excipients makes them an easy target for cost cutting. However lower prices has led to withdrawals from the Pharma market with 41 out of 103 drug product manufacturers reporting difficulty in finding a manufacturer of USP-NF grade excipient in a 2006 PQRI survey (21).

The term "commodity" implies fungibility or interchangeability regardless of source. The 2006 PQRI survey (21) demonstrated the lack of such interchangeability with 76% of drug product manufacturers performing additional tests to determine excipient suitability for their intended use. In addition to functionality and processability, concerns were related to stability and impurities. Surprise was expressed about the 25% frequency of drug product manufacturers testing excipient suitability for processing using experimental (laboratory) scale batches, or pilot scale manufacturing batches.

The commoditization of excipients based solely on pharmacopoeial compliance is problematical:

- Pharmacopoeial specifications do not determine fitness for purpose in a specific application
- GMP compliance (a pharmacopoeial requirement) is not easily specified.
- Reliance solely on pharmacopoeial specifications facilitates economically motivated adulteration.
- Inability to experimentally prove that "non-critical" excipients will not impact finished product quality.

This contributes to the 2-3σ Pharma manufacturing efficiency with a direct Cost of Poor Quality (COPQ) of 10-15%. The traditional threefold markup of indirect COPQ on top may increase substantially if regulatory authorities start to use quality metrics to categorize applicants in terms of risk.

"The fundamental problem we identify is the inability of the market to observe and reward quality. This lack of reward for quality can reinforce price competition and encourage manufacturers to keep costs down by minimizing quality investments" (22).

With greater recognition of their supply chain and technological risks the information value of excipients will increase. From a design point of Critical Process Parameters (CPPs) are preferred as they are in the hands of the drug product manufacturer. Critical Material Attributes (CMAs), if known, are in the hands of the excipient manufacturer. Greater excipient supplier involvement will be required to minimize dependency on CMAs initially, and to rescue products from unanticipated CMAs when inherent criticalities appear.

"Excipients originate from all around the world, in many different forms, and with many different attributes. Learning about an excipient as if it were your own product is critical to design" (6).

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