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Impact of Quality by Design on Topical Product Excipient Suppliers, Part I: A Drug Manufacturer's Perspective

Part I. The Pharmaceutical Manufacturer's Perspective
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Abstract

Quality by design (QbD) is a scientific and risk-based approach to product development that begins at the product concept stage. This article will equip the excipient vendor with an understanding of QbD from the perspective of the topical pharmaceutical product manufacturer.

The US Food and Drug Administration (FDA) began an initiative in 2002 entitled *Pharmaceutical Current Good Manufacturing Practices for the 21st Century—a Risk-Based Approach*, which encouraged the pharmaceutical industry to adopt modern quality management techniques (1). As a participant in the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals of Human Use (ICH), FDA contributed to a number of guidelines such as *ICH* Q4B (2), *ICH* Q8 (3), *ICH* Q9 (4), and *ICH* Q10 (5). These modern quality management techniques framed in terms of pharmaceutical regulatory concepts have been collectively called quality by design (QbD). QbD can be defined as a scientific, risk-based, holistic, and proactive approach to pharmaceutical product development. It begins at the product concept stage and is applied throughout development and into commercialization.

The QbD paradigm performs a risk assessment during the product concept stage to identify active and excipient attributes having a high likelihood to affect critical quality attributes (CQAs) of the pharmaceutical product. Experimentation is then performed to determine impact of formulation (active and excipient) attributes and processing parameters on pharmaceutical product attributes, and a control strategy is adopted to mitigate risk of CQA failure. By understanding variation of excipient properties as they relate to critical process parameters (CPPs) and CQAs, the pharmaceutical product manufacturer can build robustness and flexibility into their manufacturing processes. Excipients and excipient vendors are of vital importance to QbD, and pharmaceutical product manufacturers are highly motivated to adopt the QbD paradigm. QbD is here to stay and will be embraced by the developers of new drug applications (NDAs) and abbreviated NDAs (ANDAs) for topical products.

From the perspective of a pharmaceutical topical product development scientist, understanding and adopting QbD can be time consuming. It is hard to break the decades-old habit of limiting variability of the excipients so that an “optimized” product conforms to the narrowest specifications possible. The adoption of QbD for topical products prior to 2013 was further hindered by guidance documents often limiting their examples to oral solid-dosage forms. Fortunately for topical product developers, two papers have been published on the topic of generic development of topical dermatologic products (6, 7). These publications have made dramatic progress in clearing up misunderstandings about QbD as related to topical products. A third publication (8) describing the performance matrix for a topical cream provides a useful perspective on topical products being qualitatively equivalent (Q1), quantitatively equivalent (Q2), and structurally/functionally similar (Q3). Because QbD is a holistic approach that begins at the product concept stage and never really ends, product development scientists, process engineers, and technical support personnel require a broad understanding of QbD. While familiarity with the full spectrum of QbD is always useful, the excipient supplier can initially focus on QbD concepts specific to pharmaceutical excipients.

The goal of Part I of this two-part series is to equip the excipient vendor with an understanding of QbD from the perspective of the topical pharmaceutical product manufacturer. The topical product scientist will apply these modern quality management techniques not only to products in development, but also to products that have been on the market for years. For excipient vendors to meet the needs of their pharmaceutical customers, it is important that they understand the broader QbD framework used by development scientists. This article will focus on aspects of QbD that are specific to excipients in topical dermatological preparations (both NDA and ANDA) that are meant to be locally active. Part II will discuss what specific information the excipient supplier should provide the development scientist to satisfy a QbD

approach for topical product development.

Risk criticality and the quality target product profile

The starting point for QbD is the quality target product profile (QTPP). The QTPP is a prospective summary of the quality characteristics of a drug product that will ideally be achieved to ensure the desired quality, taking into account the safety and efficacy of the drug product (9). According to *ICH* Q8*,* it (10):

"Could include the intended use in a clinical setting, route of administration, dosage form, delivery systems, dosage strength(s), container-closure system, therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form being developed, and drug product quality criteria (e.g., sterility, purity, stability, and drug release) appropriate for the intended marketed product."

The QTPP is different from the product specification because the QTPP should include patient-relevant, product-performance elements such as clinical efficacy/bioequivalence or stability that are not carried out in batch-to-batch release. It provides an understanding of what will ensure the quality, safety, and efficacy of a specific product for the patient and is the starting point for identifying the CQAs, CPPs, and control strategy. The introduction of ICH Q9 (11) states that: "…the protection of the patient by managing the risk to quality should be considered of prime importance." The ICH *Quality Implementation Working Group Points to Consider* (12) states: "Risk includes severity of harm, probability of occurrence, and detectability, and therefore the level of risk can change as a result of risk management. Quality attribute criticality is primarily based upon severity of harm and does not change as a result of risk management. Process parameter criticality is linked to the parameter's effect on any critical quality attribute. It is based on the probability of occurrence and detectability and therefore can change as a result of risk management."

CQAs are product attributes that have the potential to be altered by changes to process parameters or formulation variables during pharmaceutical development. If a product attribute cannot change during the pharmaceutical development process, even though it is an essential element of a marketable product, then that product attribute should not be a CQA. In addition to having the potential to change during development, a CQA must also be directly related to the safety and efficacy of the topical product. Selection of appropriate, product-performance-focused CQAs represents the biggest QbD challenge for topical liquid and semisolid products. A CQA is usually an attribute of the final product, but it is also possible to indicate a CQA of a raw material.

Although it is possible for a raw material to be a CQA, it is much more likely that an excipient will be a critical material attribute (CMA). It is well recognized that excipients can be a major source of variability in topical products. CMAs such as pH, particle size distribution, particle aggregation, or appearance of a single excipient may dominate the analogous CQA of the final pharmaceutical product. Lionberger *et al.* states "Independent critical material attributes (CMAs) are the best way to provide a mechanistic link of the product quality to the critical process parameters in the manufacturing process" (13). This means that independent CMAs may better define product quality than CQAs. For example, *in-vitro* release testing (IVRT) using a Franz cell for a topical gel product containing suspended drug might seem like the best way to evaluate the manufacturing process. Thus, IVRT is designated as a CQA and is used to evaluate the impact of different mix times and mix speeds used to form the gel and suspend the drug. IVRT results are gathered for 6–10 gels to characterize mixing during manufacturing. This approach is a reasonable way to establish a design space for this product, but is it the best way? The quote from Lionberger *et al.* suggests that the product development scientist should consider defining API particle size and gel rheology as independent CMAs rather than defining *in-vitro* release as a CQA. A potential scenario in which these two CMAs would provide a mechanistic link is when the higher mix speed generates heat that alters particle size. At the same time, higher mix speeds reduce the gel viscosity by lowering the molecular weight of the shear-sensitive gelling agent. The IVRT response surface may be less sensitive to potentially "competing" changes in particle size and viscosity compared to the particle size response surface and viscosity response surface generated from the same 6–10 gel experimental design.

QbD concerns of topical product development scientists

When focusing on topical product risk and criticality as related to raw materials, typical CQA items are phase separation, rheology, precipitation of dissolved active/excipient or particle changes in suspended active, microbial contamination, pH, assay/impurities, heavy metals, and residual solvents.

Phase separation. Phase separation of a topical product in a multi-use container can result in super-potent dosing for some of the treatment applications and sub-potent dosing for the remaining treatment applications. In the example QTPP for fluorouracil cream (7), this element was labeled "homogeneity and tube uniformity." Phase separation can be most dramatic when the active is found primarily in the dispersed phase of a product that contains little of the dispersed phase (e.g., a hydrophobic drug that is almost completely dissolved in the oil phase of an oil-in-water emulsion that has more than 85% water). If this product is a cream that separates into a half milliliter of oil-rich phase that is at the orifice of the tube, then 90% of the drug may be applied in the first few applications. Alternatively, if the separated oil-rich phase of a lotion creams to the top of a bottle fitted with a pump that has a long dip tube, then 90% of the drug may remain inside the bottle and never be applied. Another example is when a gel containing uniformly dispersed solid-drug particles loses viscosity on storage and the previously dispersed drug falls to the bottom of the container. For topical products that are semisolids or fluid dispersions, assuring content uniformity (i.e., avoiding phase separation) tends to dominate the control strategy.

Rheology. Rheology is the science that characterizes the flow of materials. For topical products, rheology considers the impact of shear on the apparent viscosity of a non-Newtonian liquid. Rheological behavior is directly correlated to microstructure of a topical product formulation. For two products that have the same composition (qualitatively [Q1] and quantitatively [Q2] the same), if they have the same microstructure (Q3), then these two products will have the same bioavailability. The manufacturing process can have a significant impact on the formulation microstructure (6). This means that characterizing rheological behavior as a function of excipient variability, processing parameters, and even active purity or particle size distribution may provide valuable insight with regards to the microstructure of the product. Dramatic change in rheological properties may affect the bioavailability. This impact applies to rheological changes over the shelf-life of the product, lot-to-lot changes in

the rheology of the product, and differences in rheological properties between a generic formulation and the reference listed drug.

Precipitation. If the API is completely dissolved in the topical product, then it must remain completely dissolved over the shelf life of the product. Because only dissolved drug penetrates the stratum corneum of intact skin (14), the precipitation of drug is expected to change bioavailability. Formulations that are prone to supersaturation, followed by unpredictable timing for precipitation, are rarely viable commercial products. Likewise, topical products formulated near API saturation that precipitate with relatively small drops in temperature need to rapidly redissolve upon storage at their labeled temperature range to be viable commercial products. Concerns about precipitation midway through stability of a material completely dissolved at product release are not limited to API. A good illustration of the preservative methylparaben precipitating out of a topical gel is provided in the specification and examples of US patent 8,053,427 (15).

Particle changes. If the drug substance is dispersed in the formulation as solid particles, particle size and content uniformity throughout the entire container/closure system will be two critical attributes for the topical drug product. Characterization of segregation and/or aggregation of particles will be necessary, in addition to demonstrating that no changes in the drug substance polymorph occur throughout the stability studies. Particle size of the drug substance throughout the shelf life of the topical product must be determined and may need to be controlled. For particles less than 10 microns, changes in particle size and/or morphology of suspended drugs in topical products are presumed to change bioavailability (14, 16).

Microbial contamination. It is important that products applied to the skin are not contaminated by bacteria or fungi and for this reason, topical products, especially products packaged in multiple-use containers, are usually preserved. Healthy skin provides a reasonably effective barrier against microbes, but this barrier is often compromised in skin conditions that are treated with topical products. Products applied to the face will eventually find their way into a patient's eyes, which is another reason that even vehicle controls must be adequately preserved to assure patient safety. For topical products, passing *United States Pharmacopeia (USP)* <51> Antimicrobial Effectiveness Testing (AET) over the entire product shelf life is sufficient to assure that if contaminated, the product will not support growth and be a risk to the patient (17). AET testing assumes that incoming raw materials will not have significant lot-to-lot differences in the level of bacteria/fungi contaminating the API or excipients that are used to make the product.

pH. Most topical formulations will be adjusted to a specified pH at some point during processing. If the pH remains stable over the shelf-life of the product, then an appropriate control strategy can be put into place to keep pH as a very low risk, non-critical quality attribute. However, some actives degrade into weak acids (e.g., benzoyl peroxide degrading into benzoic acid) and if the product is not buffered (or insufficiently buffered), then the pH steadily drops over the shelf life of the product. If the active has pH-dependent solubility or a dissociation constant near the product pH, then it is likely that bioavailability may change with changing pH (8). The acid/base properties of some excipients can significantly impact the initial pH of the formulation. Lot-to-lot variability of excipients that can shift pH should be a risk mitigation focus for APIs that carry charge.

Assay and impurity tests. Assay tests that are specific, accurate, and precise are mandatory to quantify the amount of API present (per unit weight or volume) in the topical drug product. Likewise, impurity tests are required for specified impurities as justified by ICH Q3B (18) qualification threshold and unspecified impurities as justified by the identification threshold based on the maximum daily dose for the drug product (7). Excipients must be compatible with the API, and drug–excipient incompatibility is usually noted early in development and the formulation modified to assure an adequate shelf-life. A much more difficult problem is when trace level substances (e.g., catalysts, heavy metals, unreacted reagents) contained within an excipient are incompatible with the API. Degradation of the API may be rapid and limited by complete consumption of the trace levels of the excipient impurity. Usually this degradation of the activewill be viewed as a processing loss and be ignored (if less than 1%) or corrected by use of an overage. However, if this reactive trace excipient impurity has significant lot-to-lot variability or is not uniform throughout the excipient batch, then the drug product may risk occasional lots failing on stability.

Residual solvents and heavy metals. The drug product manufacturer will always be concerned about complying with *USP* General Chapter <467> Residual Solvents (19) and *USP* General Chapter <232> Elemental Impurities-Limits (20). The requirements include not exceeding limits for the finished drug product by controlling the elemental impurities and residual solvent of excipients. It should be noted that topical products may contain a significant amount of solvent (e.g., ethyl alcohol) and for these products, the solvent used is counted as an excipient, not a residual solvent (6).

Conclusion

The goal of Part I of this series is to familiarize the excipient supplier with some of the QbD concepts and terminology specifically related to topical pharmaceutical products. The pharmaceutical industry is embracing QbD for topical products for both NDA and ANDA products. With this understanding of QbD, it should be possible to build more effective partnerships between topical product development scientists and topical excipient vendors. QbD is truly the new paradigm in topical product development and is providing patients with more robust treatment options. Part II will propose reasonable customer expectations regarding excipient sample requests and specific information about excipients needed for the QbD approach.

References

1. FDA, *Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach, Final Report* [2] (Silver Spring, MD, September 2004).
2. ICH, *ICH Harmonised Tripartite Guideline: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions* Q4B [3], Step 4. (Geneva, Switzerland, Nov. 1, 2007)
3. ICH, *ICH Harmonised Tripartite Guideline: Pharmaceutical Development* Q8(R2) [4] (Geneva, Switzerland, August 2009).
4. ICH, *ICH Harmonised Tripartite Guideline: Quality Risk Management* Q9 [5](Geneva, Switzerland, Nov. 9, 2005).
5. ICH, *ICH Harmonised Tripartite Guideline: Pharmaceutical Quality System* Q10 [6] (Geneva, Switzerland, June 4, 2008).
6. R.K. Chang et al. *AAPS J.* 15 (1) 41-52 (2013).
7. R.K. Chang et al. *AAPS J* 15 (3) 674-683 (2013).

8. Y.S.R. Krishnaiah et al. *Int. J. Pharmaceutics* 475 (1-2) 110-122 (2014).
9. H. Winkle, et al. *Pharm. Tech.* 33 (10) [7] (2009).
10. FDA, *Guidance for Industry* Q8(R2) *Pharmaceutical Development* (Silver Spring, MD, November 2009).
11. FDA, *Guidance for Industry* Q9 Quality Risk Management. (Silver Spring, MD, June 2006).
12. ICH, *Quality Implementation Working Group Points to Consider (R2) ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation.* (Geneva, Switzerland, Dec. 6, 2011).
13. R.A. Lionberger et al. *AAPS J.* 10 (2) 268-276 (2008).
14. M.S. Roberts and K.A. Walters. *The Relationship Between Structure and Barrier Function of Skin. Chapter 1 Dermal Absorption and Toxicity Assessment,* M.S. Roberts and K.A. Walters, Eds. (Marcel Dekker, New York, 1998) pages 1-42.
15. J.C. Buge, K. Nadau-Fourcade, and C. Meunier. "Bromonidine gel composition," US Patent 8,053,427, Nov. 8, 2011.
16. A. Vogt et al., *JID Symposium Proceedings* 10 (3) 252-255 (2005).
17. USP, *USP* Chapter <51>, "Antimicrobial Effectiveness Testing," *USP29-NF24* (US Pharmacopeial Convention, Rockville, MD, 2005), p. 2499.
18. ICH, *ICH Harmonised Tripartite Guideline: Impurities in New Drug Products* Q3B(R2) (Geneva, Switzerland, June 2, 2006).
19. USP, *USP* Chapter <467>, "Residual Solvents," *USP37* (US Pharmacopeial Convention, Rockville, MD, 2011), https://hmc.usp.org/sites/default/files/documents/HMC/GCs-Pdfs/c467.pdf [8]
20. USP, *USP* Chapter <232>, "Elemental Impurities—Limits," (US Pharmacopeial Convention, Rockville, MD, Feb. 1, 2013), www.usp.org/sites/default/files/usp_pdf/EN/USPNF/key-issues/c232_final.pdf [9].

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