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Impact of Quality by Design on Topical Product Excipient Suppliers, Part II: Reasonable Expectations

This article will clarify reasonable expectations for the responsibilities of topical product formulation developers and for excipient suppliers regarding the information and samples for experiments needed for QbD.

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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 clarify reasonable expectations for the responsibilities of topical product formulation developers and for excipient suppliers regarding the information and samples for experiments needed for QbD.


Billion Photos/Shutterstock.comAs noted in Part I of this series (1), 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 pharmaceutical industry is embracing QbD for topical products for both new drug application (NDA) and abbreviated NDA (ANDA) products. Recent publications (2–4) specific to topical dermatological products have been useful in providing guidance to development scientists that manufacture topical pharmaceutical products. QbD is truly the new paradigm in topical product development and is also being applied to topical products that have been on the market for many years.

The goal of Part II of this two-part series is to review reasonable customer expectations regarding excipient information and sample requests. When the product development scientist implements the QbD approach, significant excipient questions are raised that seldom were considered during the old “quality-by-testing” paradigm. Excipient suppliers are being asked to more extensively characterize their materials and to supply material that is at the edge of the vendor specification. Just as in Part I, this discussion will be limited to topical dermatological preparations (both NDA and ANDA) that are meant to be locally active.

Defining equivalence

Terms commonly used to classify product similarity when discussing design for equivalence are defined as follows:

> Q1 means that test and reference products have the same components.
> Q2 means that test and reference products have the same components in the same concentration.
> Q3 means that test and reference have the same components in the same concentration with the same arrangement of matter (microstructure). Structural similarity is established by comparisons between test and reference product of physicochemical characteristics, such as drug particle size, spreadability, viscosity, pH, and drug concentration in aqueous phase. Functional similarity is established by comparisons between test and reference product using in-vitro drug release testing (4).

The meaning of being “the same” as defined in Q1 and Q2 is discussed as follows. A difficulty for the topical semisolid formulator is that some of the excipients used for pharmaceutical products are not compendial but are commonly used in cosmetic products. Thus, dozens of different grades of certain excipients are available for use that will have the same name. Molecular purity of an excipient, such as stearic acid, may range from 50% for food grade to over 98% for a high-purity grade used as a lubricant in pharmaceutical tableting. Verification of the molecular purity of the “same” excipient from different suppliers will, therefore, need to be documented by the topical product developer. The excipient vendor will be asked for both test results and test methods to establish that their excipient is qualitatively (Q1) the same as the excipient supplied by a competitor. This verification is easier for compendia excipients, but some of the National Formulary (NF) and United States Pharmacopeia (USP) monographs are sufficiently outdated such that even raw materials passing all the tests are not assured to be equivalent. For ANDA products, reverse engineering is used to select excipients that are the same as the excipients used in the reference listed drug (RLD).

For innovator companies developing topical products, understanding the FDA concepts of Q1/Q2/Q3 is useful when they want to qualify a second source or when it becomes necessary to change from one excipient supplier to another during development. In both of these cases, the finished product produced before the excipient change needs to be shown equivalent to the finished product produced after the excipient change. For NDA submissions, the "test" product is the product manufactured later in development (i.e., second supplier or replacement vendor), and the "reference product" is the earlier product manufactured in development. For generics, the "test" product is the generic formulation and the "reference" product is the RLD. As stated by Chang et al. (2), "For semi-solid preparations, Q1/Q2 is not a must for generic products to be acceptable by the agency. However, the generic firm will face more regulatory scrutiny for a non-Q1/Q2 formula and need to demonstrate that the physicochemical characteristics, critical quality attributes, and in-vitro flux rate of its drug products are in line with the RLD, especially considering the insensitivity of clinical endpoint bioequivalence studies."

Reasonable expectations for sampling

In broadest terms, the excipients responsible for preventing phase separation and providing microstructure to the product are the structure-forming excipients described in FDA's scale-up and post-approval changes guidance for semisolids (SUPAC-SS) (5). For emulsions (creams and lotions), the emulsifiers provide this function. For gels, the gelling agent, such as carbomer or cellulose, will be the structure-forming excipient. Some products, such as ointments, will primarily contain an excipient that thickens upon cooling (e.g., petrolatum) to provide microstructure to the product. It is reasonable for the product developer to request samples of excipients that fall at the extremes of the raw-material specification range, especially for structure-forming excipients. For example, Carbopol 934 polymer (Lubrizol) has a specification range of 30,500 mPa-s to 39,400 mPa-s for a Lubrizol viscosity test (i.e., Brookfield viscosity for a 0.5% neutralized solution). Carbopol 934 polymer is known to be shear sensitive, so any design of experiment to characterize how mixing speed/mixing time influences finished product viscosity will require carbomer spanning the Carbopol 934 specification range for Brookfield viscosity. What may not be reasonable is to expect that the low-viscosity carbomer sample and the high-viscosity carbomer sample will be sourced from commercial-scale batches of Carbopol 934 polymer. Often times, it will be years between commercial batches falling near either extreme of the specification range. It is also unreasonable to expect a vendor to purposefully alter their commercial process from historically optimal settings to generate "tons" of material in an attempt to satisfy one company's need for a few kilograms of unexpired raw material at the edge of a specification range. It should be expected by excipient vendors, product developers, and FDA that samples of raw materials manufactured at the edges of the vendor's specification range will be laboratory-scale material.

Variability in critical properties

API crystallization (precipitation) and suspended API particle changes. It is the product development scientist's responsibility to assure that their topical product is not formulated on a solubility boundary that will cause the API to crystallize due to minor changes in temperature, normal lot-to-lot variability in excipients, or end of shelf-life evaporation (weight loss) of a volatile solvent such as alcohol. It is also the product development scientist's responsibility to identify potential excipient impurities, such as multivalent ions, that might react with the API and trigger precipitation.

It is the excipient vendor's responsibility to identify highly reactive species, such as residual catalyst, that might occur at trace levels in the excipient. Because excipient vendors typically already test for heavy metals, according to *USP* <232> (6), and residual solvents, according to *USP* <467> (7), it is unlikely that embracing QbD will require significant additional effort from excipient vendors to assure that the raw material they provide does not precipitate the API or cause a change in API form during storage.

Excipient dissolution and precipitation. For many years, topical product formulators would write in batch records "mix until dissolved" and leave an area for "start time," "finish time," and "mix speed" to be entered. This practice was common as related to dissolving methyl paraben into the water phase or propyl paraben into the oil phase. In recent years, regulatory investigators have required that a specific mixing speed and duration be specified in the batch record. Formulators know that for some solute/solvent combination of excipients, the time required for complete dissolution can vary by hours. It is expected that the excipient vendor will know how best to add their raw material into a commercial-scale batch. Does heating help? Should the excipient be dissolved in a separate vessel and added as a concentrated solution? Does a wand or inductor need to be used to evenly distribute the excipient without clumping? This information is usually available in the technical package that describes the excipient. It is reasonable for an excipient vendor to be sufficiently aware of QbD terminology to use phrases such as "critical material attribute (CMA)" and "critical process parameter (CPP)" in their technical literature. An example would be describing a typical CPP for forming a smooth gel with the excipient supplier's gelling agent.

Microbial contamination. Water is the excipient associated with the greatest risk of microbial contamination of a topical product. Fortunately, pharmaceutical water quality is well understood, and standardized testing assures that this risk is minimized in a compliant pharmaceutical product manufacturing facility. The inactive ingredients database (IID) lists ingredients (8) contained in approved topical products that cover the full range of risk for being the source of microbial contamination in the finished product. At one end of the spectrum are natural excipients, such as lecithin and tallow glycerides, that may be prone to microbial contamination. At the other end of the spectrum is isopropyl alcohol, which is a potent antiseptic that has no risk of microbial contamination during storage as a neat liquid.

At least three of the significant product contamination situations in the author's experience were similar because they occurred with: 1) high-volume products, 2) that had been successfully manufactured for over a decade without any indication that the product could be susceptible to microbial contamination, and 3) the source of contamination was unambiguously traced to an excipient that had recently experienced a change in process or source. In one of these situations, the raw material was a powder contaminated with Bacillus spores. The product was biocidal to the spores, but it took a few days for the formulated product to kill the spores. Thus, only product samples that were neutralized (prepared for microbial limit testing) within hours of completing the batch revealed contamination. Resampling and retesting of the product a few days later never confirmed that the product was contaminated.

It is reasonable for the excipient vendor to provide excipients that do not have significant lot-to-lot variability in the amount of microbial content. It is also reasonable that the excipient vendor knows (and clearly communicates to the product developer) the identity of all microbes that are known to be contained in the raw material. If the specific microbes contained in a raw material are dependent upon a specific manufacturing site or source of a starting material, the vendor is responsible to know their excipient well enough to set meaningful specifications and clearly communicate details to the product developer.

pH. If the API can be ionized, then pH of the finished product will be a critical quality attribute and the pH of the bulk should be adjusted to a target value. In this scenario, lot-to-lot variability in the acid-base properties of an individual excipient is unlikely to significantly influence the ability to reach the target pH value. If the pH of an excipient trends up or down with storage, then that could be vital information for the product development scientist. A raw material re-assay date of less than a year may be required. For products that do not have a pH adjustment step during processing, such as ointments or other non-aqueous topical products, the acid-base properties of each individual excipient may become important. It is the responsibility of the formulator to determine the influence of different excipients on finished product pH. However, it is the responsibility of the excipient vendor to communicate (e.g., through technical product brochures) raw material pH variability for different lots at the time of release and how (and why) raw material pH changes upon storage.

Assay and impurities. It has been shown that by reducing moisture, residual catalyst, peroxide levels, and aldehyde levels from excipients commonly used in topical products (e.g., PEG 400, Polysorbate 80, Dimethyl Isosorbide), significant improvements in API chemical stability and/or physical stability of topical product can be obtained (9). Although it is the formulator's responsibility to determine compatibility between excipients and the API, it is the responsibility of the excipient supplier to produce a consistent raw material that clearly states the levels of reactive impurities in their raw material. The excipient vendor should know if (and to what extent) these impurities are likely to change over time and have a shelf-life or re-assay date for the raw materials that they supply. Reactive impurities should have an actual value reported in the certificate of analysis (COA) even though the specification is "less than" a limit value. Few things are worse than a formulator developing a product with multiple lots of surprisingly good raw material, only to be faced with a recall during the first year of commercial production due to out-of-specification stability results. A hypothetical example would be a residual catalyst that happened to vary between 0.1 and 0.3 ppm for the three lot numbers that were used during development. The specification for residual catalyst on the COA is less than 50 ppm with the specific result being listed as "meets test." The formulator has no way of knowing that this value typically ranges between 0.5 ppm and 5 ppm with the occasional spike up to 30 ppm unless the vendor provides the numerical test result for each lot of excipient. For

product development companies that embrace QbD, the excipient supplier must be as transparent as possible concerning variability in their dermatology product excipients.s

Conclusion

The goal of Part I of this two-part series was to familiarize the excipient supplier with some of the QbD concepts and terminology specifically related to topical pharmaceutical products. With this understanding of QbD, it should be possible to build more effective partnerships between topical product development scientists and topical excipient vendors. Part II of this series focused on an important aspect of this partnership—what are reasonable customer expectations regarding excipient information and sample requests? In general, the excipient vendor should thoroughly characterize the qualitative (Q1) aspects of their material, provide laboratory-scale samples of excipient at the edge of the vendor specifications, and closely monitor and report lot-to-lot variability of critical properties/impurities of the excipient.

The pharmaceutical industry is embracing QbD for topical products for both NDA and ANDA products. QbD is truly the new paradigm in topical pharmaceutical product quality for the 21st century both for products currently in development and for products that have been on the market for many years. Excipients and excipient vendors are of vital importance to QbD and, therefore, need both an understanding of QbD principles and consensus regarding reasonable expectations for excipient information and sample requests.

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