QbD in developing semisolid formulations

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Outline

- Drug Product Specification - definition
- In Process Control specification
- Consideration for Drug Product Specification
- Justification of specifications
- Mandatory requirements for all dosage forms
- Topical dosage forms - specific requirements
- Topical dosage forms - periodic/one time requirements
Definitions, considerations, justification and mandatory requirements

• ICH guideline Q6A - SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS CHEMICAL SUBSTANCES

Topical dosage form specific requirements

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Definition of Drug Product Specification

- A list of tests with references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described.
- It establishes the set of criteria to which a drug product should conform to be considered acceptable for its intended use.
- Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.
- Specifications are only one part of a total control strategy for the drug product quality and consistency.
Definition of Drug Product Specification

• Other parts of control strategy include: product characterization during development, Good Manufacturing Practices (e.g. facilities, validated manufacturing process, validated test procedure, in-process testing, stability testing, etc.)

• Specifications are chosen to confirm the quality of the drug product rather than to establish full characterization, and should focus on those characteristics **found to be useful** in ensuring the **safety and efficacy** of the drug product.
Definition of In-Process Speciation

• In-process tests, are tests which performed during the manufacture of drug product for the purpose of:
  • Adjusting process parameters within an operating range - will not included in the Drug Product Specification.
  • Ensuring quality of the drug product - where the acceptance criterion is identical to or tighter than the release requirement the test [but not necessarily the results] should be included in the release specification.

The results obtained during manufacture may used and report in the Drug Product Specification…
Other specifications

- Intermediate specification
- Bulk specification
- In-house/release specification
  - The concept of different acceptance criteria for release vs. shelf-life specifications pertains to the establishment of more restrictive criteria for the release than are applied to the shelf-life.
  - Examples where this may be applicable include assay and impurity (degradation product) levels.
  - In the United States, this concept may only be applicable to in-house criteria, and not to the regulatory release criteria.
Considerations - on going development

Periodic or skip testing

- This concept may be applicable to, for example, residual solvents and microbiological testing, for solid oral dosage forms.
- It is recognized that only limited data may be available at the time of submission of an application therefore, this concept should therefore generally be implemented post-approval.

Limited data available

- It is recognized that only a limited amount of data may be available at the time of filing, which can influence the process of setting acceptance criteria. As a result it may be necessary to propose revised acceptance criteria as additional experience is gained with the manufacture. The basis for the acceptance criteria at the time of filing should necessarily focus on safety and efficacy.
Considerations - Parametric release

Parametric release

• Parametric release can be used as an operational alternative to routine release testing for the based on satisfactory results from monitoring specific parameters, e.g., temperature, pressure, and time during the terminal sterilization phase(s) of drug product manufacturing.

• It is important to note that the process should be adequately validated before parametric release is proposed.

• The attribute which is indirectly controlled (e.g., sterility), together with a reference to the associated test procedure, still should be included in the specifications.
Consideration - Compendial vs. in-house testing

Compendial testing

- Wherever they are appropriate, pharmacopoeial procedures (testing and acceptance criteria) should be utilized.
- Differences between regions should be considered.

Alternative procedure

- Alternative procedures are those which may be used to measure an attribute when such procedures control the quality of the drug substance or drug product to an extent that is comparable or superior to the official procedure.
Justification of specifications

- Justification should be presented for each procedure and each acceptance criterion included.
- The justification should refer to: relevant development data, pharmacopoeial standards, test data for drug substances and drug products used in toxicology and clinical studies, and results from accelerated and long term stability studies, as appropriate.
- A reasonable range of expected analytical and manufacturing variability should be considered.
- Other approaches may be acceptable subject to appropriate justification based on data generated during drug product development.
Mandatory testing for all dosage forms (1)

- **Description:** A qualitative description of the dosage form should be provided (e.g., size, shape, and color). If any of these characteristics change during manufacture or storage, this change should be investigated and appropriate action taken. The acceptance criteria should include the final acceptable appearance. If color changes during storage, a quantitative procedure may be appropriate.
Mandatory testing for all dosage forms (2)

• **Identification**: Identification testing should establish the identity of the drug substance(s) in the new drug product and should be able to discriminate between compounds of closely related structure which are likely to be present. Identity tests should be specific for the drug substance, e.g., infrared spectroscopy. Identification solely by a single chromatographic retention time is not acceptable. The use of two chromatographic procedures, such as HPLC/UV diode-array, HPLC/MS, or GC/MS, is generally acceptable.

• **Assay**: A specific, stability-indicating assay to determine strength (content) should be included for all drug products.

• **Impurities**: Organic and inorganic impurities (degradation products) and residual solvents are included in this category.
Topical dosage forms - specific requirements (1)

- **Description/appearance**: a qualitative description, organoleptic qualities, and consistency of the drug product should be provided as a test specification. If the drug product is prone to change in color during storage, it is prudent to include the color test in the drug product release and stability specifications. The acceptance criteria for the color of the drug product should be consistent with the description of the drug product and should include a numerical specification and a validated quantitative color test method.

- **Visual test** for homogeneity of drug product may be useful, to ensure no separation of phases, no syneresis (extrusion of water from a gel), and no foreign matter. In addition, if test drug product contains a dispersion of drug substance, number of crystals per ten fields of microscopic view is useful to ensure product quality.
Topical dosage forms - specific requirements (2)

- **pH** potentially affects the stability of the drug substance and physicochemical properties of semisolid products (e.g., emulsion stability, rheological behavior). In such a case, pH limits need to be tightened to minimize the degradation of the drug substance or justified by stability data of the drug product at different pH limits. pH also may affect effectiveness of the preservatives and viscosity of the drug product.

- **Product consistency** (i.e., thickness, firmness, elasticity, plasticity, and tackiness) needs to be appropriate for the application. Viscometers with different geometries are most frequently used to monitor product consistency in the pharmaceutical industry. The shear history of the semisolid sample being tested has a significant impact on the actual viscosity observed, which may explain considerable variability and many out-of-specification results in viscosity testing.
Topical dosage forms - specific requirements (3)

- **Tube/pump uniformity**: It is required to set an appropriate acceptance criteria for the homogeneity test, for example a maximum RSD of 5% from assay results of ten aliquots of an appropriate amount of the product and all assay values falling between 90.0% and 110.0% of the label claim. Phase separation of the drug product is one possible reason for a high variation of assay results from content uniformity test. The risks, such as content non-uniformity and phase separation, need to be minimized via QbD development paradigm.

- **Specific gravity**: The variation of specific gravity of semisolid drug product may be caused by the entrapment of air during the manufacturing process, which may indicate a need of a de-aeration process to remove the entrapped air. The variation of specific gravity may also cause a variation of assay value for the drug product in some cases.
Topical dosage forms - specific requirements (4)

• **Weight loss/gain:** is used to determine the amount of evaporation or absorption of a product in a particular container. Weight loss tests, particularly for plastic containers and formulations containing volatile materials, are required for the stability program. On the other hand, sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers. General principles on packaging materials used for human drugs and biologics can be found in Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics.

• **Particle size:** If drug product contains a dispersion of drug substance, particle size and the crystal habit of API in drug product needs to be monitored in the stability program. For emulsion-type drug products, globule size should be considered as a specification for drug product release and stability specifications.
Topical dosage forms - specific requirements (5)

- **Antioxidant content** measurement should be performed for the drug product release testing. Shelf-life testing of antioxidant content may be unnecessary where justified by appropriate stability data generated in the development stage. If including an antioxidant assay in the stability testing, a wider acceptance limit can be justified by generating the satisfactory stability data at accelerated conditions for 3 months using a test product containing a lower level of antioxidant, e.g., 60% target amount.

  **The a.m relevant as well for preservative content**

- **Package visual test**: a visual test for package and label evaluation may be included in the drug product release and stability specification to ensure no fading of lettering on label, no change in container interior, and no container/product interaction.
- Package functionality should be demonstrated as well
Topical dosage forms - specific requirements (6)

- **In vitro drug release** tests are conducted to characterize performance characteristics of a finished topical dosage form as a quality control procedure and justification for scale-up and post approval changes. Diffusion cells, such as Franz cells are used. The most discriminant test conditions are recommendable in a drug release testing for semi-solid drug products. The amount of drug released from the sample at different time intervals is quantified and the slope of the straight line obtained by plotting cumulative amount of drug release across 1 cm² membrane vs. the square root of time represents the release rate (most commonly used release kinetics) or other appropriate release kinetics.
Topical dosage forms - specific requirements (7)

- **In vitro drug release test** (con.): Currently, in vitro drug release test is rarely included in finished drug product release test and specification. This test appears to be a reasonable and practical procedure to ascertain batch-to-batch uniformity and to measure the quantities of drug reaching the dissolved state after topical application. QbD emphasizes the development of the meaningful drug product specifications that are based on clinical performance. In vitro release test is the first step toward that goal. **Hence, it has many reasons to be implemented as a required drug product release and stability test.**
Topical dosage forms - specific requirements (8)

- **Microbiology testing**: microbiological examination of non-sterile products, i.e., USP <61>, <62>, and <1111>, should be included in drug product release and stability specifications, based on USP monographs. Most topical preparations, especially those with emulsion formulations, have much higher chances of contamination by various bacteria. Generally, topical preparations containing an appropriate amount of ethyl alcohol (e.g., more than 10%) or inactive ingredients with low water activity do not support the growth of large numbers of microorganisms.
Topical dosage forms - specific requirements (9)

- **Impurity tests and maximum daily dose:** MDD calculation: the (MDD) calculation is not straightforward, compared to a solid oral dose or injection. The sponsor needs to come up with its calculation of MDD for the drug product. In general, the treatment duration is not specified. A finger tip amount of 0.5 g and how many fingertip units are required to cover the maximum affected area may be used to calculate the MDD. If the treatment duration is specified in the literature or packaging insert, the largest pack size in the market for the same drug product divided by the treatment duration may be used to calculate the MDD. In some cases, expert opinion from a qualified dermatologist was used to justify the calculation of MDD. The exposure levels from a topical dermatologic product can be considered much less than that from other routes of administration.
Topical dosage forms - specific requirements (10)

• **Assay tests**: because of formulation complexity, emulsion state and oleaginous materials used for semi-solid drug products, extra care must be taken in the sample preparation and laborious extraction procedure optimization to ensure adequate recovery of drug & Impurity tests.

• **Residual solvents**: drug product release specification is required to include residual solvent tests with test specification listed as “Complies with USP <467>”. Semi-solid preparations may include a significant amount of solvent(s), e.g., ethyl alcohol. In such cases, the solvent used is counted as an excipient, not a residual solvent.
Topical dosage forms - periodic/one time testing (1)

• **Antimicrobial effectiveness tests:** a demonstration batches with the preservative(s) at 100% label claim need to pass preservative effectiveness testing. Efficacy of antimicrobial preservation tests for a test product containing a lower level of preservatives are used to establish the lower limit of preservatives for the stability program. The acceptance criteria for category 2 products, according to USP <51> antimicrobial effectiveness testing are NLT 2.0 log reduction from the initial count at 14 days and no increase from the 14 days’ count and 28 days for bacteria and no increase from the initial calculated count at 14 days’ count and 28 days for yeast and molds. Ideally, an antimicrobial preservative effectiveness test is to be performed for the exhibit batch, first three commercial validation batches and one stability batch annually thereafter.
Topical dosage forms - periodic/one time testing (2)

- **Bulk hold study** - a hold time study should be performed to establish a static hold time for a bulk product when stored in a holding vessel at ambient temperature. Samples may be taken from the top, middle, and bottom of the vessel at day 0 and the end of reasonable hold time (e.g., day 5) and tested. Appropriate test items include assay and appearance to demonstrate no settlement of drug substance and no separation of ingredients within the hold time.

- **Release controlling agents** - The ability of Release controlling agents to provide their intended functionality, and to perform throughout the intended drug product shelf life, should be demonstrated (ICH – Q8(R2))
Retin-A-Micro - ANDA

- **Active ingredient:** Tretinoin (NDA 020475)
- **Form/Route:** Gel/Topical
- **Pharmaceutical Equivalence:** If a proposed generic drug product does not use microsphere technology, or if the formulation contains microspheres that are substantially different from that of the reference listed drug (RLD), then a drug stability test in presence of benzoyl peroxide (BPO) and UV light exposure and a comparative in vitro release test should be performed to support pharmaceutical equivalence. We recommend you conduct the in vitro release test using a diffusion cell system with excised human skin, a non-occlusive system in the donor cell, a finite dosing technique, and aqueous media at physiological pH in the receptor cell. The model should be adequately validated. We recommend…