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Draft – Not for Implementation

Draft Guidance on Mitomycin

November 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Mitomycin

Dosage Form: Powder

Route: Pyelocalyceal

Strength: 40 mg/vial

Recommended Studies: One in vitro bioequivalence study and other characterization tests

To demonstrate bioequivalence for mitomycin powder for pyelocalyceal solution, 40 mg/vial using in vitro studies, the following criteria should be met:

1. The test product should contain no difference in inactive ingredients or in other aspects of the formulation relative to the reference standard (RS) that may significantly affect the local or systemic availability of the active ingredient. For example, if the test product and RS are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the most recent version of the FDA guidance for industry on *ANDA Submissions –Refuse-to-Receive Standards*[a], and the criteria below are also satisfied, the bioequivalence of the test product may be established using a characterization-based bioequivalence approach.

2. The test product and RS should have the same physicochemical and structural (Q3) attributes, based upon acceptable comparative Q3 characterization of a minimum of three batches of the test product and three batches (as available) of the RS. The test product and RS batches should ideally represent the product at different ages throughout its shelf-life. The comparative Q3 characterization should be conducted with (1) the reconstituted mitomycin powder in the hydrogel (referred to as the "admixture") of the test product and RS and (2) the blank sterile hydrogel for reconstitution (referred to as "sterile hydrogel")

of the test product and RS. Sample preparation of the admixture for all product characterization tests should be consistent between the test product and RS, as per the reference listed drug (RLD) labeling.

The comparison of the test product admixture and RS admixture should include characterization of the following Q3 attributes:

a. Characterization of visual appearance and texture
b. Characterization of phase states and structural organization of matter
    - Microscopic examination with representative high-resolution microscopic images at multiple magnifications at 5°C and 37°C
    - Analysis of particle size distribution, crystal habit, and polymorphic form of mitomycin in the admixture drug product, if any, at 5°C and 37°C. If particles are observed, the quantitative comparison of fraction of undissolved mitomycin at 5°C and 37°C, and changes in such fractions after samples are held at 37°C for 6 hours, should be evaluated.
c. Characterization of rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. Rheological behavior of the test product and RS should be assessed at 5°C, a temperature near the gelation temperature of the drug product, and 37°C. The following evaluations are recommended:
    - Characterization of viscosity vs. shear rate and shear stress vs. shear rate. At a minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
    - Complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified (when possible).
    - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
d. Characterization of gelation temperature based on an evaluation of viscosity as a function of temperature by heating and cooling samples between 4 to 40°C for several cycles using an appropriate method that can closely reflect the true gel-sol transition temperature.
e. Characterization of gelation time based on an evaluation of the time for 15 mL of the admixture at 5°C to form a gel in an environment of 37°C, using sample holders made of materials with appropriate thermal conductivity, taking into consideration of thermal environment after the instillation of the product to the pyelocalyceal cavity for gel formation and retention at the site
f. Characterization of pH
g. Characterization of any other potentially relevant Q3 attributes

The comparison of the test product sterile hydrogel and RS sterile hydrogel should include characterizations of the following Q3 attributes:

a. Characterization of phase states and structural organization of matter
    - Microscopic examination with representative high-resolution microscopic images at multiple magnifications at 37°C
b. Characterization of rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. Rheological behavior of the test product and RS should be assessed at 5°C, a temperature near the gelation temperature of the drug product, and 37°C. The following evaluations are recommended:
    - Characterization of viscosity vs. shear rate and shear stress vs. shear rate. At a minimum, this should consist of numerical viscosity data at three shear rates (low, medium, and high).
    - Complete flow curve across the range of attainable shear rates, until low or high shear plateaus are identified (when possible).
    - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
b. Characterization of gelation temperature based on an evaluation of viscosity as a function of temperature by heating and cooling samples between 4 to 40°C for several cycles.

3. The test product and RS should have an equivalent mitomycin release based upon an acceptable in vitro dissolution bioequivalence study comparing a minimum of one batch each of the test product and RS using an appropriately validated method. The study should be conducted at 37°C based on the route of administration of this drug product. Applicants should consider developing a controlled and optimized sample preparation procedure to mimic semisolid gel formation in vivo. Sample preparation of the admixture should be consistent between the test product and RS. The batches of test product and RS evaluated in the study should be included among those for which the Q3 attributes are characterized.

Applicants intending to propose an alternative approach by which to demonstrate bioequivalence should refer to the most recent version of the FDA guidance for industry on *Controlled Correspondence Related to Generic Drug Development*[a] and the most recent version of the FDA guidance for industry on *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*[a] for additional information describing the procedures on how to clarify regulatory expectations regarding the applicants' individual drug development program.

Additional information:

Characterization of gelation temperature:

As the comparative gelation temperature test results will guide some routine quality tests such as viscosity test of the product at temperatures around the true gel-sol transition temperature, the proposed test method including the temperature sweeping program, if applicable, should ideally be able to measure the true gel-sol transition temperature or closely reflect the true gel-sol transition temperature.

Drug product and comparative in-use study:

The RLD is prepared and administered using a number of ancillary supplies that are provided by the end-use facility per the RLD labeling. However, these ancillary supplies are not device constituent parts, and the RLD product is not considered to be a drug-device combination product.

Due to the drug product complexity and the potential for complications during administration (e.g., premature gelling, clogging due to gelling and/or presence of excess amount of undissolved particles in the drug product, pressure build-up in the delivery system, and subsequent risks posed to the patients and care givers, etc.), applicants should conduct in-use studies using the test product and RLD, per the RLD labeling. The comparative studies should include various ancillary supplies required and specified for drug product administration per the current RLD labeling to demonstrate comparable performance of the test product and RLD, and compatibility of the test product with those ancillary supplies. The in-use study design should demonstrate the comparability of the test product and RLD in preparation robustness, dosing accuracy, dosing safety, and other performance (e.g., instillation force, leakage, clogging, among others) and quality characteristics, at controlled temperatures (mimicking in-use thermal environment) and a series of injection speeds based on the admixture preparation and instillation in-use conditions per the RLD labeling. In general, the study design should consider using multiple catheters and nephrostomy tubes with various materials of construction that are in accordance to the current RLD labeling. Thermal conductivity of the materials of construction of the catheters and nephrostomy tubes may impact heat transfer/exchange thus the clogging potential, therefore may be considered as a criterion in the study design. The in-use study design should also consider the sizes, lengths, and thermal environment of catheters and nephrostomy tubes portions that will be inserted into the body during administration and the impacts toward clogging potential, in addition to the portions that will be at the ambient temperature.

Applicants may consider performing in-use studies in the worst-case scenarios first related to clogging potentials. If clogging is not observed in the test product and the RLD product in a worst-case scenario (e.g., the 5 Fr catheter made with material of the highest thermal conductivity among the multiple materials of construction, along with other factors that lead to highest clogging potential for the 5 Fr catheter) of a series of comparative in-use studies, further clogging evaluation may not be needed for that series of studies (e.g., other materials of construction for the 5 Fr catheter). Bracketing study design may be considered using extremes of

a factor (such as thermal conductivity, size, dosing volume, dosing speed, etc.) if it can be properly justified with adequate supporting information.

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.