Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Dexamethasone

May 2026

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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:	Dexamethasone
Dosage Form:	Insert
Route:	Ophthalmic
Strength:	0.4 mg
Reference Listed Drug:	NDA 208742
Recommended Studies:	One in vitro bioequivalence study and comparative characterization studies

Eligibility: In accordance with 21 CFR 314.94(a)(9)(iv), a generic dexamethasone ophthalmic insert must contain the same inactive ingredients[1] and in the same concentration[2] as the reference listed drug (RLD).[3] If there are compositional differences between the proposed generic product and the RLD that extend beyond those permissible under 21 CFR 314.94(a)(9)(iv), the applicant may submit a waiver request under 21 CFR 314.99(b). This request should be included with the abbreviated new drug application (ANDA) and be supported by data and justification demonstrating that the differences do not impact the safety and efficacy of the proposed product.

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[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD.

[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ± 5% of those used in the RLD.

[3] An applicant may seek approval of a drug product that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

Meeting recommendations: Prospective applicants are advised to request a pre-ANDA product development meeting to discuss the justification for any such deviations and the intended approach for ANDA filing and bioequivalence demonstration.

1. Class of study: Bioequivalence
   Type of study: In vitro drug release (IVR)
   Design: Real-time IVR study
   Strength: 0.4 mg
   Analyte to measure: Dexamethasone
   Acceptance criteria: Comparative analysis of release profiles should be established using an appropriate statistical method (e.g., model independent approach using similarity factor (f_2)). For more information on calculation of f_2 factor, refer to the guidance for industry *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.[a]
   Study design recommendations:
   - A properly developed and validated method that can detect potential formulation differences and capture the complete release profile of dexamethasone should be provided.
   - The applicant should identify relevant critical quality attributes of the drug product that can impact product performance in terms of drug release, and develop the IVR methodology to discriminate meaningful differences in these attributes (e.g., particle size distribution of dexamethasone, molecular weight of polymeric excipients[4]).
   - A complete IVR method development and validation report should be provided.
   - The study should include at least three batches of test product, and three batches of the Reference Standard (RS) product if available, using at least 12 units from each batch
   - The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches

2. Class of study: Characterization
   Type of study: Microstructure imaging
   Design: Comparative
   Parameters to measure: porosity, pore size distribution, drug particle size and size distribution, spatial distribution of pores and drug particles
   Strength: 0.4 mg

3. Class of study: Characterization
   Type of study: Thermophysical Profiling
   Design: Comparative
   Parameters to measure: Assessment of thermal transitions
   Strength: 0.4 mg

[4] Michael A. VandenBerg, Rokon Uz Zaman, Christine L. Plavchak, William C. Smith, Hossein Birjandi Nejad, Andre O'Reilly Beringhs, Yan Wang, Xiaoming Xu. Impact of Polymer Source Variations on Hydrogel Structure and Product Performance in Dexamethasone-Loaded Ophthalmic Inserts. Int J Pharm. 2025 September 15; 682: 125959. doi:10.1016/j.ijpharm.2025.125959.

Study design recommendations:

- Establish a comparative thermophysical profile between the test product and the RS. This should include identifying critical thermal transitions and stability profiles via thermogravimetric analyses.

4. Class of study: Characterization
Type of study: Visual appearance and dimensions
Design: Comparative
Strength: 0.4 mg
Parameters to measure: shape, color, physical dimensions (diameter and length), weight, and density. Visual characterization should be conducted on both the finished product in its dry state and its fully hydrated/swollen state.

5. Class of study: Characterization
Type of study: Surface morphology characterization
Design: Comparative
Parameters to measure: surface roughness, absence of surface defect
Strength: 0.4 mg
Study design recommendations:

- Surface morphology and absence of defects should be qualitatively evaluated using electron microscopy.
- Surface roughness should be quantitatively measured using Atomic Force Microscopy, 3D Optical Profilometry, or another suitable technique.

6. Class of study: Characterization
Type of study: Mechanical properties
Design: Comparative
Strength: 0.4 mg
Parameters to measure: comparative stress relaxation and strain-to-yield

7. Class of study: Characterization
Type of study: Swelling kinetics of the inserts in simulated tear fluid
Design: Comparative 24 hour study
Strength: 0.4 mg
Test system: Simulated tear fluid
Parameter to measure: physical dimensions and weight of hydrated insert
Study design recommendations:

- Suggested time points: Hours 0, 1, 12, and 24
- Express the data as: Percent change in diameter versus time, Percent change in length versus time, Percent change in weight versus time
- Provide images of wet inserts at each time point as supportive information.
- Because the inserts may lose physical integrity at later stages of degradation, measurement at Day 60 may not be feasible. In such cases, applicants may select an alternative later time point to demonstrate the advanced stage of insert degradation. In addition, applicants should provide adequate data or scientific

justification to support that the inserts are expected to be fully degraded within a comparable timeframe under the test conditions compared to the RS.

8. Class of study: Characterization
Type of study: Degradation kinetics of the inserts in simulated tear fluid
Design: Comparative 60 day study
Strength: 0.4 mg
Test system: Simulated tear fluid
Parameter to measure: weight of dried residual insert
Study design recommendations:
    - Suggested time points: Days 0, 5, 15, 30, and 60.
    - Express the data as percentage of initial inert mass versus time.
    - Provide images of wet inserts at each time point as supportive information.
    - Because the inserts may lose physical integrity at later stages of degradation, measurement at Day 60 may not be feasible. In such cases, applicants may select an alternative later time point to demonstrate the advanced stage of insert degradation. In addition, applicants should provide adequate data or scientific justification to support that the inserts will be fully degraded within a comparable timeframe under the test conditions compared to the RS.

Batch selection: The comparative studies should be performed on a minimum of three exhibit batches of the test product,[5] and three batches of the RS, if available.

Device: The RLD is presented as a single-dose ophthalmic insert. The insert is the device constituent. FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the test device including:

- Size and shape of the resorbable insert
- Visibility under blue light

User interface assessment: An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the guidance for industry *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

Document History: Recommended May 2026

[a] We update guidances periodically. For the most recent version of a guidance, refer to the FDA guidance webpage at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[5] The manufacturing process for the exhibit batches should be reflective of the manufacturing process to be utilized for commercial batches.