*Contains Nonbinding Recommendations*

*Draft – Not for Implementation*

**Draft Guidance on Dexamethasone**

**November 2025**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

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| **Active Ingredient:** | Dexamethasone |
| **Dosage Form:** | Implant |
| **Route:** | Intravitreal |
| **Strength:** | 0.7 mg |
| **Recommended Studies:** | One in vitro bioequivalence study with comparative characterization studies |

To qualify for the study recommendations outlined in this guidance, a generic dexamethasone intravitreal implant should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD).[3]

**One in vitro bioequivalence study:**

1. Type of study: In vitro drug release testing (IVRT)
   Design: IVRT should be performed on three batches of both test product and reference standard (RS) using at least 12 units from each batch
   Strength: 0.7 mg/implant

[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] Refer to 21 CFR 314.94(a)(9)(iii).

Additional comments:

- Provide a properly developed and validated IVRT method that captures the complete release profile of dexamethasone from the implants.[4]
- Provide a full method development and validation report to demonstrate that the selected IVRT parameters have been sufficiently optimized with reproducibility and discriminatory ability. To support discriminatory ability of the IVRT method, provide drug release data comparing the target test drug product and test products intentionally manufactured with meaningful differences in formulation and/or process variables[5] (e.g., polymer characteristics[6], dexamethasone loading and/or particle size).
- Equivalence in dexamethasone release from test product and RS should be established using a proper statistical method. One suggested approach is a model independent similarity (f2) factor. For more information on calculation of f2 factor, refer to the most recent version of the FDA guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.[a]

**Comparative characterization studies:**

The comparative physicochemical characterization of the test product and the RS should be performed on at least three batches each of the test product[7] and the RS, and should include:

- Physical characterization of finished implants, including:
    a. Appearance
    b. Physical dimensions
    c. Weight
- Microstructural characterization, including:
    a. Implant internal and outer surface structure
    b. Porosity
- Mechanical characterization, including implant breaking force
- Dexamethasone physical properties in the finished implant, including:
    a. Particle size and particle size distribution
    b. Polymorphic form/crystallinity
- Implant in vitro degradation profiles

[4] Costello M, et al., Drug release mechanisms of high-drug-load, melt-extruded dexamethasone intravitreal implants. European Journal of Pharmaceutics and Biopharmaceutics. 2023 June;187: 46-56. https://doi.org/10.1016/j.ejpb.2023.04.003

[5] Costello M, et al., Manufacturing dexamethasone intravitreal implants: process control and critical quality attributes. 2023 Nov 25; 647:123515. https://doi.org/10.1016/j.ijpharm.2023.123515

[6] Costello M, et al., Role of PLGA variability in controlled drug release from dexamethasone intravitreal implants. Molecular Pharmaceutics. 2023 Nov 23; 20 (12). https://doi.org/10.1021/acs.molpharmaceut.3c00742

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

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative release testing on 12 dosage units of the test product and RLD[8]. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

**Additional information:**

Formulation:
To support Q1 sameness of poly(lactic-co-glycolic) acid (PLGA), provide comparative characterization data including polymer composition (molar ratio between glycolide and lactide), molecular weight and weight distribution, and PLGA architecture (e.g., linear or branched) on the PLGA polymer extracted from the test product and the RLD.[9,10] Branch frequency should be provided if it is a branched polymer.[11] In addition, to support quality assessment of the test product, provide characterization on the extracted PLGA including but not limited to polymer end cap analysis, inherent viscosity, and glass transition temperature. Sufficient validation data for the methods used for comparative characterization of PLGA should be provided in the ANDA submission.

Device:
The RLD is presented as a preloaded, biodegradable, single-dose implant in a sterile, single-use applicator. The implant and the applicator are the device constituent parts. 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 of biodegradable implant
- Single-use, single-dose
- Preloaded, sterile, single-use applicator

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 most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

[8] If the RLD is not available, refer to the most recent version of the guidance for industry *Referencing Approved Drug Products in ANDA Submissions*.
[9] Garner J, et al., A protocol for assay of poly (lactide-co-glycolide) in clinical products. International Journal of pharmaceutics. 2015 Nov 10;495(1):87-92. https://doi.org/10.1016/j.ijpharm.2015.08.063
[10] Castello M, et al., Reverse engineering the Ozurdex dexamethasone intravitreal implant. International Journal of Pharmaceutics. 2023 March 5;634:122625. https://doi.org/10.1016/j.ijpharm.2023.122625
[11] Hadar J, et al., Characterization of branched poly (lactide-co-glycolide) polymers used in injectable, long-acting formulations. Journal of Controlled Release. 2019 Jun 28;304:75-89. https://doi.org/10.1016/j.jconrel.2019.04.039

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**Unique Agency Identifier:** PSG_022315

[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.