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Locke Lord QuickStudy: Congress Forces FDA to Evaluate Some ??505(b)(2) Products for Therapeutic Equivalence ?Listing in ?Orange Book

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For nearly forty years, the Food and Drug Administration ("FDA") has required applicants seeking approval of "generic" or "branded generic" drugs under section 505(b)(2) of the Federal Food, Drug and Cosmetics Act ("FDCA") to file a Citizen Petition if they sought FDA to assign those drugs a therapeutic equivalence code in FDA's Orange Book that would trigger state automatic substitution laws. Congress recently removed this onerous hurdle for some drugs seeking approval under section 505(b)(2) in section 3222 of the Food and Drug Omnibus Reform Act of 2022 ("FDORA").

What Drugs Can Obtain a Therapeutic Equivalence Review?

Section 3222 of FDORA amends section 505(j)(7)(A) of FDCA to require that FDA determine whether certain drugs approved under section 505(b)(2) may be entitled to a therapeutic equivalence code, *i.e.* "A" rating, in FDA's Orange Book that would permit automatic substitution for a branded drug at pharmacies. Section 3222 restricts these mandatory evaluations to **parenteral**, **ophthalmic**, and **otic solutions** or **suspensions** that:

- are a "pharmaceutical equivalent" to the reference listed drug; and
- differ from the reference listed drug only in identity and concentration of preservative, buffer, antioxidant, tonicity adjusting agent, or thickener.

Section 3222 explicitly defines "pharmaceutical equivalent" by incorporating the definition of that term set forth in 21 C.F.R. § 314.3:

drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, *i.e.*, the same salt or ester of the same therapeutic moiety…that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency…

Section 3222, however, does not eliminate the FDA's previous Citizen Petition requirements for seeking a therapeutic equivalence evaluation of other types of drugs submitted under section 505(b)(2), including oral tablets and capsules, oral liquids and suspensions, topical preparations, and suppositories.

How Will Review of an Eligible Drug Work?

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Section 3222 sets forth a system for applicants to request that FDA review their parenteral, ophthalmic, or otic drugs for therapeutic equivalence based on the date of application and approval.

- For eligible 505(b)(2) applications submitted after the enactment of FDORA (January 1, 2023), the applicant may make a request either in the original application or in a resubmission in response to a complete response letter before approval.
- For eligible 505(b)(2) applications pending but not approved as of the enactment of FDORA, the applicant may make a request as part of an amendment or supplement filed at any time within 180 days of the drug's approval.
- For eligible 505(b)(2) applications approved before the enactment of FDORA, the applicant may make a request as part of an amendment or supplement at any time.

Should an applicant not file a request through these specified channels, FDA will not be under any requirement to conduct a therapeutic equivalence evaluation.

After the request is filed, FDA will evaluate the applicant's submissions to determine whether the approved drug meets the requirements for a therapeutic equivalence code: (1) proof of bioequivalence to the reference listed drug; and (2) evidence that the "generic" drug will have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling as the reference listed drug. Section 3222 requires FDA to complete and issue its evaluation no later than: (1) 180 days after the drug's approval for pre-approval requests; or (2) 180 days after the request if made post-approval.

The Ultimate Effect on Drug Makers and Patients

Section 3222 provides a streamlined process that eases the burden on applicants when seeking a therapeutic equivalence code for drugs approved under section 505(b)(2) that would otherwise be eligible for automatic substitution under state pharmacy laws if filed as an Abbreviated New Drug Application ("ANDA"). In particular, the amendment likely will increase the number of 505(b)(2) applications and approvals of "generic" drugs in the specific classes that otherwise would not have been eligible for automatic substitution because of differences in inactive ingredients from the reference listed drug that would preclude them from being filed as ANDAs.

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