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# Enantiomer Exclusivity Revisited

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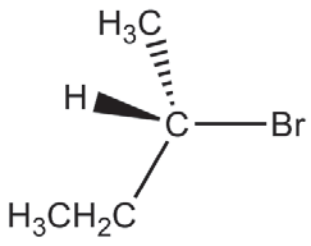
**The Food and Drug Administration Amendments Act of 2007**

Tucked away at the end of the Food and Drug Administration Amendments Act of 2007 (FDAAA) is a provision that modifies FDA's long-standing refusal to award five-year new chemical entity (NCE) exclusivity to enantiomers of previously-approved racemic mixtures. Pub. L. No. 110-85, __ Stat. __ (2007); FDAAA § 1113

The Food and Drug Administration (FDA) has the authority under the Hatch Waxman Act to grant 5 years of exclusivity to drugs that contain new chemical entities, referred to as NCE exclusivity in the Orange Book, but up until this legislation the FDA had declined to grant NCE exclusivity to enantiomers that were part of previously-approved racemic mixtures. See Federal Food Drug and Cosmetic Act (FDCA) §§ 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii). According to FDA, exclusivity was not justified because the enantiomer had been previously approved – albeit as part of a racemic mixture. See 54 Fed. Reg. 28872 at 28898 (July 10, 1989).

In an effort to encourage the continued development of these important chemical species, the FDAAA has modified FDA's policy with the addition of a new subsection (u) to section 505 of the FDCA, so that FDA can award NCE exclusivity to enantiomers under limited circumstances. However, to ensure that the exclusivity fosters significant medical innovation and does not become simply another tool for life cycle management, the legislation limits the award of exclusivity to particular circumstances.




Enantiomers are compounds that have the same ordering of atoms as each other, but that differ from one another when viewed in three dimensions. The compound drawn to the left is an enantiomer because it has the H3C group projecting up from the page toward the reader. The corresponding enantiomer would have the H3C group projecting below the page away from the reader. A racemic mixture refers to a 50:50 mixture of two corresponding enantiomers.

Two significant events occurred during the 1980s and 1990s that elevated enantiomer chemistry to its current prominence. The first was a growing


recognition among biochemists of the importance of three dimensional structure in biological systems, including the three dimensional structure of many drugs. The second was the development of techniques to synthesize and isolate enantiomers, and to test for the purity of isolated enantiomers. These techniques have led to the development of many important new drugs over the last two decades, and improved the safety of many others.

FDA has historically refused to grant NCE exclusivity to enantiomers of previously-approved racemic mixtures because the enantiomer is not technically new. As FDA stated in its first formal statement on the issue, "a single enantiomer of a previously approved racemate contains a previously approved active moiety and is therefore not considered a new chemical entity." 54 Fed. Reg. 28872 at 28898 (July 10, 1989). In a 1997 Federal Register notice, FDA considered a revision of its policy to encourage medically significant innovation, but it never completed the rulemaking. 62 Fed. Reg. 2167 (Jan 15, 1997).

Congress's decision to grant five years of exclusivity to enantiomers coincides with the declining patentability of enantiomers under the U.S. patent laws. While innovators have defended their enantiomer patents successfully of late, including successful outcomes for Forest Laboratories and Sanofi Aventis in generic challenges to their Lexapro® and Plavix® patents, they were successful because the technology for making purified enantiomers was not adequately developed when their applications for patent were originally filed. As the sophistication and predictability of enantiomer chemistry continues to progress, the patentability of enantiomers will continue to decline.

Life cycle management was clearly a concern to Congress in granting this exclusivity, and the legislation contains several limitations that ensure that exclusivity is only awarded in cases of significant medical innovation. For example, exclusivity is only available for new drug applications that that do not rely on studies for a previously-approved racemic mixture. FDCA § 505(u)(1)(A), as amended by FDAAA 1113. Exclusivity is also only available if the enantiomer is approved in a different therapeutic category than the racemic mixture. FDCA § 505(u)(1)(B), as amended by FDAAA 1113. Conversely, FDA will not approve the enantiomer for use in the same therapeutic category as the racemic mixture for ten years from the enantiomer's approval date. FDCA § 505(u)(2)(A), as amended by FDAAA 1113.

Unless the legislation is reauthorized, the exclusivity is only available for new drug applications filed before October 1, 2012. FDCA § 505(u)(4), as amended by FDAAA 1113.