FDA recently awarded new chemical entity (NCE) exclusivity to Austedo™ (deutetrabenazine). The Austedo approval is notable for two reasons: One, it is the first deuterated drug (i.e., a drug containing the stable isotope - deuterium - in place of a hydrogen atom) to be approved by FDA; and two, it was awarded NCE exclusivity despite earlier approval of the non-deuterated form of the drug. This NCE designation is another example of FDA's expansive statutory interpretation of NCE, which we outlined in our article “FDA is Evolving on Qualifications for ‘New Chemical Entity.’” (available at http://www.pepperlaw.com/publications/fda-is-evolving-on-qualifications-for-new-chemical-entity-2016-09-07/) NCE exclusivity benefits many innovators, but may also stimulate greater competition for innovators. These innovators should take note of the following:
A deuterated version of a previously approved drug is an NCE.

NCE exclusivity may incentivize development of deuterated drugs.

In April 2017, FDA approved Teva Pharmaceuticals’ Austedo (deutetrabenazine) for the treatment of chorea associated with Huntington’s disease in adults. Austedo is a deuterated version of tetrabenazine, which was first approved by FDA in 2008 under the tradename Xenazine® for the same indication. Xenazine went generic in 2015. In Austedo, certain hydrogen atoms of tetrabenazine were replaced with deuterium atoms - also referred to as “heavy hydrogen” atoms.

An NCE is a drug that contains “no active moiety that has been approved by FDA in any other” new drug application. An active moiety is defined as “the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.”

NCE status is important to commercialization because it affects the timing of generic company challenges and provides commercial exclusivity from generic competition. If a drug is granted NCE exclusivity, an abbreviated new drug application (ANDA) or 505(b)(2) application cannot be approved by FDA during the five-year exclusivity period. In addition, absent a paragraph IV certification that the Orange Book listed patents for the reference drug are invalid, not infringed and/or unenforceable, FDA cannot accept a generic drug manufacturer’s ANDA/505(b)(2) application until the five-year NCE exclusivity period has expired. Furthermore, if a drug has Orange Book-listed patents, a 30-month stay will be awarded, and no ANDA or 505(b)(2) application may be approved until the end of the 7.5-year period from the approval date of the NCE drug.

For deuterated versions of previously approved drugs, such as Austedo, the only difference in the molecule’s structure is at least one hydrogen atom has been replaced with a deuterium - a stable isotope of hydrogen that differs from the more abundant stable isotope of hydrogen, protium, by the presence of one additional neutron in the nucleus of the atom. Differences in efficacy and safety between a drug and a deuterated version of the same drug are not always clear or substantial. For Austedo, the approved doses are lower than the approved doses of tetrabenazine because Austedo is metabolized more slowly. In contrast, other deuterated versions of drugs have not demonstrated significant differences from their original counterparts in clinical trials.
While efficacy and safety differences may exist, the inquiry pertinent to NCE exclusivity appears to rest on the **structure** of the active moiety. In the case of a deuterated drug, it follows that so long as the active moiety of the drug contains at least one deuterium - or heavy hydrogen - it will be awarded NCE exclusivity. This award may provide incentives for developing deuterated drugs, which are made more attractive by a relatively favorable risk profile and possible shorter clinical development time.

Drug developers may want to consider deuteration as a strategy if NCE exclusivity is an important component of drug development. By granting NCE exclusivity to a deuterated version of a previously approved drug, FDA has signaled that it will expansively use data and marketing exclusivity to encourage drug development.

Deuteration may become a more widely used strategy; however, the NCE exclusivity award does not impact the patentability or freedom to operate for deuterated drugs. Drug developers should more fully integrate the possibility of deuteration into their own strategies from both an offensive and defensive perspective with a fulsome understanding of the potential benefits and risks.

**Endnotes**

1. 21 C.F.R. § 314.108.

2. 21 C.F.R. § 314.103.

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