Deutered Drug Molecules: Focus on FDA-Approved Deutetrabenazine

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Deutetrabenazine (an involuntary movement disorder) associated with Huntington’s disease and tardive dyskinesia. This key limitation will be less likely for stereomutation at a C–H stereocenter because bond breaking in this case will likely be the rate-determining step.

The power of the technique of deuterating a stereogenic center to stabilize enantiomerization was soundly illustrated with analogues of the notorious drug thalidomide. Normally, the two enantiomers of racemic compounds exist as a 50:50 ratio, which can be separated to permit the independent examination of each entity. However, in certain situations, such as for some thalidomide analogues, each enantiomer cannot be studied pharmacologically because of fairly rapid interconversion of them in solution and in vivo. For analogue CC-122, deuterium substitution at the stereocenter slowed the interconversion rate and allowed each enantiomer to be studied independently, such that the antiinflammatory and antitumor pharmacology was expressed by the (−)-enantiomer of CC-122, as opposed to the corresponding (+)-enantiomer.

Through history, the introduction of deuterium into drug molecules has come in and out of favor, time and again, with numerous dead ends having been encountered. Nevertheless, chemists maintained an interest in replacing C–H with C–D to extend the lifetime of active drugs in vivo, while improving their pharmacokinetics and toxicological properties. Basically, the goal has been to obtain better efficacy with a reduction in both clinical dosage and the number of adverse events. Currently, there is considerable clinical activity surrounding deuterated compounds as drugs, with the following known drugs or agents being D-modified: dextromethorphan (Phase 2/3; AVP-786), ruxolitinib (Phase 2; CTP-543), ivacaftor (Phase 2; CTP-656), pioglitazone (Phase 1; DRX-065), linoleic acid (Phase 2; RT001), and apremilast (Phase 1; CT-730). It is evident from this assemblage of advancing drug candidates that the idea of deuterium-substituted drugs is finally gaining a lot of traction.

Development of a deuterated analogue of an approved drug may be derisked and expedited via a 505(b)(2) regulatory pathway. By using this approach, an applicant relies on studies completed for approval of the parent nondeuterated drug, even though the studies for it “were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted”, according to FDA document 21 U.S.C. 355(b)(2). When deuterium is incorporated to
stabilize stereoisomer interconversion, an expedited regulatory pathway is also anticipated by FDA guidance for the development of stereoisomeric drugs. Deutetrabenazine (1) was developed by a 505(b)(2) approach, and all of the deuterated drug candidates mentioned above are being developed in that manner (or by a very related approach).

Tetrabenazine (2) has been known as a chemical entity since the 1950s. Over the years, it became useful in several countries as a neurological drug for the treatment of involuntary movement disorders, such as Huntington’s disease-associated chorea and tardive dyskinesia. In 2008, this molecule (as a racemic mixture) was approved for the treatment of chorea in the United States by the FDA. While its precise mechanism of action is unknown, tetrabenazine is known to inhibit vesicular monoamine transporter 2 (VMAT2), a transmembrane protein on presynaptic neurons that is responsible for reducing the levels of monoamine neurotransmitters (e.g., norepinephrine, dopamine, and serotonin) in the synaptic regions. This mechanism is thought to contribute to the drug’s clinical efficacy. Deutetrabenazine is cast in the same mold, but with a special advantage of prolonged in vivo half-life due to stabilization of metabolic conversion and thus slower depletion. This new drug version has a twice-a-day dosing regimen, instead of thrice-a-day, and also permits a smaller quantity to be dosed, which mitigates some undesirable side effects.4

The approval of Austedo (deutetrabenazine) as a new chemical entity (NCE) via the 505(b)(2) regulatory pathway established an important milestone for the development and marketing of deuterated drugs. Its notable introduction into clinical medicine could well be the harbinger of a new era for the utility of deuterium-substituted drug molecules. This point of view is further supported by the sizable collection of other deuterated molecules that are currently in clinical trials (several mentioned above); we are hopeful some of them will emerge successfully for the benefit of patients.

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Notes
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■ REFERENCES


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