Protecting deuterated drugs

With companies paying substantial sums for marketing rights over deuterated drugs, **Michael Furrow** and **Erin Austin** examine critical patent strategies and considerations

Deuterium (^2H) is a nonradioactive isotope of hydrogen that contains a neutron in addition to hydrogen's proton and electron. Deuterium can covalently bind to other atoms in the same manner as hydrogen. Because deuterium and hydrogen are essentially the same size, a deuterated compound and its hydrogen-containing (proteo) counterpart may bind similarly to a biological target, such as a protein relevant to treating disease. However, deuterium is heavier than hydrogen and can form stronger bonds with carbon. These differences can give rise to differences in pharmacological properties.

For example, where a drug's primary route of metabolism involves the breaking of carbon-hydrogen bonds (eg, by the oxidative cytochrome P-450 enzymes of the liver), replacing the relevant hydrogen atom(s) with deuterium may slow metabolism. A longer half-life may permit a reduced dose amount or dosing frequency, or may help to decrease unwanted side effects caused by metabolites. As another example, replacing carbon-hydrogen bonds with carbon-deuterium bonds may also slow undesirable epimerisation (the interconversion of enantiomers of a chiral drug).

Whether deuteration has any meaningful beneficial effect, however, depends on the compound and its use. For example, reduction of one metabolic pathway may lead to a compensatory increase in metabolism at a different site (metabolic switching). Further, even where a compound's metabolism involves breaking a C-H bond, that cleavage may not be a rate-limiting step, and inhibiting it may not affect the compound's pharmacokinetic profile. Additionally, benefits in terms of half-life of the active ingredient may be counterbalanced by undesirable increases in the half-life of certain deuterated metabolites.

Industry investment in deuterated drugs

Scientists began incorporating deuterium into potential drugs over 50 years ago,[1] and enthusiasm about using deuterium to modify pharmacological properties waxed and waned over the subsequent decades. In the 1970s and 1980s, Merck advanced the deuterated antibiotic fludalanine into the clinic, but development ultimately stopped due to toxicity resulting from a metabolite.

More recently, several deuterated drugs have advanced clinically and companies have started paying substantial sums for marketing rights. In 2012, Celgene paid $42m for rights to Deuteria's deuterium-enriched analog of Celgene's anti-cancer drug Revlimid (lenalidomide). In 2015, Teva acquired Auspex and its then-clinical candidate Austedo (deutetrabenazine, discussed further below) for $3.5bn. Concert Pharmaceuticals, a company focused on deuterium chemistry, has partnered or sold several deuterated drugs, including Avanir's AVP-786 (d6-dextromethorphan), which is in Phase III clinical trials for the treatment of agitation in Alzheimer's disease, and VX-561 (a deuterated version of Vertex's Kalydeco (ivacaftor)), which is part of a combination treatment in Phase II trials for cystic fibrosis. Otsuka acquired Avanir for $3.5bn in 2014, and Vertex paid $160m for VX-561 in 2017, with an additional $90m in milestones possible. Another company focused on deuterium chemistry, DeuteRx is investigating DRX-065, a deuterium-stabilised version of the (R)-enantiomer of the diabetes drug Actos (pioglitazone), for the treatment of nonalcoholic steatohepatitis, a liver condition.

Pharmaceutical companies have shown interest not only in deuterated versions of approved drugs, but also in incorporating deuterium into their discovery programmes. In 2017, Merck KGaA paid Vertex $230m up front (with a promise of royalties on future sales) for M9831, a deuterated inhibitor of DNA-dependent protein kinase with the potential to enhance certain cancer treatments, that resulted from Vertex's efforts to improve the metabolism of a leading candidate in one of its R&D programmes.

The amount of recent investment in this area evidences the potential for deuterated drugs to provide new and improved treatments for patients, and to be an important consideration in drug life cycle management.

Proof of principle: Austedo

In April 2017, the US Food & Drug Administration (FDA) approved the first deuterated drug, Teva's Austedo (deutetrabenazine).[2] Deutetrabenazine is a selectively deuterated version of tetrabenazine, the active ingredient in Xenazine, a drug approved in 2008 for treating chorea associated with Huntington's disease. Compared to tetrabenazine, deutetrabenazine provides deuterated active metabolites with longer half-lives, and it may be dosed less frequently.

Austedo's approval is interesting for reasons beyond showing that a deuterated drug can receive FDA approval. It was based on a 505(b)(2) application, meaning that,

although Teva conducted clinical and other studies for Austedo, it relied in part on data for the reference listed drug Xenazine to gain approval. Austedo was also granted five-year new chemical entity (NCE) exclusivity and seven-year orphan drug exclusivity.[3] When deciding Austedo's entitlement to those exclusivities, the FDA determined that deutetrabenazine is not the same drug as tetrabenazine based on the agency's chemical structure-centric interpretation of the term "active moiety". Thus, Austedo's approval shows how a deuterated version of a previously approved drug can benefit from reliance on the proteo drug's data for approval yet also receive regulatory exclusivities for new drugs.

Patent strategies and considerations

Given the potential, and newly highlighted importance of deuterated compounds to drug R&D, patent practitioners should be aware of certain considerations when prosecuting patent applications for a discovery programme, evaluating a patent portfolio for potential acquisition or life-cycle management, or assessing the merits of post-grant or litigation challenges.

For those drafting patent applications for discovery programmes that are not already zeroed in on a particular deuterated compound or motif, consideration should be given to whether and how to support claims to deuterated compounds. In *Incyte Corp v Concert Pharmaceuticals, Inc,*[4] the Patent Trial and Appeal Board (PTAB) held that a disclosure of a genus encompassing ruxolitinib, the active ingredient in Incyte's Jakafi, and general language about "all isotopes of atoms occurring in the intermediates or final compounds" was not so limited that it could be treated as equivalent to a description of each embraced species. Although that case involved an unsuccessful anticipation challenge to Concert's patent claims to certain deuterated analogs of ruxolitinib under 35 USC section 102, it is instructive when considering the breadth that such language supports as far as written description under section 112 is concerned when applied to a particular genus or species. That is, depending on the number of potential isotopes implicated, boilerplate language including "isotopes" may support only a genus of all isotopes.

As an example, a specification disclosing ruxolitinib and "all isotopes of atoms" occurring in compounds of the invention (including, but not limited to, deuterium isotopes), and stating that synthetic methods for incorporating radio-isotopes were well-known, was found to support a claim to ruxolitinib "wherein one or more hydrogen atoms are replaced by deuterium."[5]

To support a narrow claim to a specific deuterated compound or small genus of deuterated compounds, more targeted language may be warranted.

Accordingly, practitioners involved in application drafting for discovery programmes should consider specifically disclosing – by chemical name or structure – and exemplifying any deuterated derivatives of interest.

Practitioners involved in due diligence analyses for potential acquisitions, or in portfolio analyses for life-cycle development planning, should be aware of IP issues surrounding deuterated compounds. A full picture of the patent landscape around a key compound will involve any patents or applications related to deuterated analogs, which can signal potential future competition or present an opportunity to invest in IP that protects a drug with potential advantages over existing proteo treatments.

Given the recent approval of the first deuterated drug, case law has not yet developed in the courts from suits between branded and generic companies. However, PTAB decisions rendered thus far in *inter partes* review (IPR) proceedings suggest that nonobviousness arguments of the same types that succeed for proteo NCEs can also be useful for defending the patentability of deuterated compounds. For example, in *Incyte v Concert* (the deuterated ruxolitinib IPR noted above), the PTAB rejected the argument that a person of ordinary skill (POSA) would have selected ruxolitinib as a lead compound based on the Jakafi label's teaching that it was FDA-approved, stating that it was not convinced a POSA would select ruxolitinib over any other compound with known clinical efficacy.[6] Further, even if ruxolitinib were a lead compound, the PTAB found a lack of motivation to modify it with deuterium, eg, the petitioner had not shown ruxolitinib had toxic metabolites, that it was not well-tolerated, or that it had poor bioavailability.[7]

As another example, in *Neptune Generics, LLC v Auspex Pharmaceuticals, Inc,* the PTAB declined to institute IPR for a patent claiming D-9 venlafaxine, a deuterated analog of the active ingredient in the antidepressant Effexor.[8] The petitioner argued that D-9 venlafaxine was obvious because venlafaxine was known to be metabolised to an active O-desmethyl metabolite (ODV) and two inactive desmethyl metabolites, and it was known that deuteration could reduce metabolism.[9] The PTAB disagreed.[10] It held that, because ODV was a desired active metabolite, a POSA would not have had a reason to modify venlafaxine to reduce ODV formation. The PTAB also found that the effect of deuteration was not predictable because of potential alternative rate-limiting steps in venlafaxine's metabolism and the possibility of metabolic switching. It credited evidence submitted by the patent owner showing that deuterium substitution could actually increase metabolism (eg, as observed for certain deuterated paroxetine derivatives) or have no effect (eg, as observed for certain phentermine derivatives), and that deuteration reducing *in vitro* metabolism might not translate into superior *in vivo* potency or pharmacokinetic properties (eg, as observed with a deuterated tramadol derivative). Further, the PTAB held that D-9 venlafaxine would not have been "obvious to try" given that venlafaxine had 27 hydrogen atoms that might be replaced with deuterium, resulting in over 100 million possible deuterated derivatives.

Footnotes

1. B Belleau *et al*, 'Effect of deuterium substitution in sympathomimetic amines on adrenergic responses', 133, *Science* 102 (1961).
2. Charles Schmidt, 'First deuterated drug approved', 35, *Nature Biotechnology* 493 (2017).
3. Memorandum from the CDER Exclusivity Board to the Office of Orphan Drug Products Designation and CDER's Division of Neurology Products in the Office of Drug Evaluation I (31 July 2015).
4. IPR2017-01256, Paper No 9 (19 Oct 2017).
5. PGR2017-00034, Paper No 9 (11 Jan 2018).
6. IPR2017-01256, Paper No 9 at 17.
7. Id at 17-18.
8. IPR2015-01313, Paper No 25 (19 Dec 2015).
9. Id at 9-10.
10. Id at 13-21.

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