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Axinn IP Update: Federal Circuit Applies Lead Compound Analysis and Confirms Obviousness of Deuterated Derivatives of Ruxolitinib

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PRACTICE AREAS

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Patents

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On August 22, 2023, the Federal Circuit affirmed an IPR Final Written Decision holding claims to deuterated derivatives of ruxolitinib unpatentable as obvious and rejected the patentee's argument that a skilled artisan would not have been motivated to modify the undisputed lead compound based on prior art teaching the general benefits of deuteration. *Sun Pharm. Indus., Inc. v. Incyte Corp*., No. 2019-2011, Dkt. No. 117, at *15 (Fed. Cir. Aug. 22, 2023).

Ruxolitinib, shown below, is sold under the brand name Jakafi and is a small molecule inhibitor of JAK1/JAK2. FDA first approved ruxolitinib in 2011 to treat "intermediate or high-risk myelofibrosis." *Id*. at *3.

Concert Pharmaceuticals, Inc. (later merged with Sun Pharmaceutical Industries, Inc.) held U.S. Patent No. 9,249,149 ("the '149 patent"), which was directed to deuterated derivatives of ruxolitinib. Deuterium (H2 or D) is a stable isotope of hydrogen (H1 or H), and "[d]euteration involves replacing one or more hydrogen atoms of a drug with deuterium," which can positively affect a drug's pharmacokinetics without affecting its potency and selectivity. *Id*. at *3. The '149 patent claimed ruxolitinib derivatives that replaced various hydrogen atoms on ruxolitinib's cyclopentyl ring (i.e., the upper right-hand ring in the above structure) for deuterium atoms. See '149 patent at claims 1–15.

Incyte Corporation petitioned for IPR, and ultimately, the PTAB held all claims unpatentable as obvious. See *Incyte Corp. v. Concert Pharms., Inc*., IPR2017-01256, Paper 119, at *51–52 (PTAB Apr. 8, 2019). The PTAB performed a lead compound analysis to assess obviousness, which involves asking (1) whether a POSA would select the prior art compound for further development and (2) whether a POSA would have motivation to modify that compound in a manner that leads to the claimed compound with a reasonable expectation of success. *Id*. at *20. Neither party disputed the former prong, and thus, the PTAB focused on the latter. In finding

obviousness, the PTAB relied on three prior art references—one that disclosed ruxolitinib itself, one that disclosed that ruxolitinib's cyclopentyl ring is a metabolic hotspot, and one that disclosed the benefits of deuteration *in general* (i.e., not specific to ruxolitinib). *See Sun*, No. 2019-2011, at *6–7.

On appeal, Sun argued that the PTAB erred as to motivation to modify ruxolitinib using deuteration, as to motivation to deuterate ruxolitinib's cyclopentyl ring *in particular*, and as to reasonable expectation of success. In affirming the PTAB, the Federal Circuit recognized that the three prior art references, as well as expert testimony, provided substantial evidence that a POSA would have had "motivation to deuterate ruxolitinib, at its *metabolic hotspots*, in order [to achieve the benefits of deuteration]." *Id.* at *10–11 (emphasis added). The Federal Circuit also held that substantial evidence demonstrated that a POSA "would have reasonably expected . . . that deuterium modification *could*" result in improved pharmacokinetics, even if the precise benefit could not be predicted beforehand. *Id*. at *12–13 (emphasis added).

The Federal Circuit also rejected Sun's argument that the claimed invention achieved an unexpected result. It agreed that any pharmacokinetic benefit achieved by deuteration was merely a "difference in degree" and "did not indicate a marked superiority." *Id*. at *14.

Ultimately, this case highlights that obviousness challenges may be used to invalidate a compound patent at least where the prior art identifies an undisputed lead compound and teaches the benefit of a proposed modification, even generally, with a reasonable expectation of success.