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VEPACHEDU EDUCATIONAL FOUNDATION

The Andhra Journal of Industrial News

IP and Industry News

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Editor: Miss Krishna Claudia Vepachedu

Issue 132

Indo-Swiss Collaboration
ANDA for New Polymorphs

Indo-Swiss Collaboration¹

The Indian drug-discovery company Curadev Pharma Private Ltd. and the Swiss biopharmaceutical company Roche² have entered into a research collaboration and exclusive license agreement for the development and commercialization of IDO1 and TDO inhibitors. The agreement covers the development of the lead preclinical immune tolerance inhibitor and research collaboration with Roche's research and early development organization to further explore the IDO and TDO pathways. IDO1 and TDO are enzymes that mediate cancer-induced immune suppression. As a result of the deal, Curadev will receive an upfront payment of \$25 million and be eligible to receive up to \$530 million in milestone payments.

IDO1 (indoleamine-2, 3-dioxygenase-1) and TDO (tryptophan-2, 3-dioxygenase) are enzymes that mediate cancer-induced immune suppression. This mechanism is exploited by tumor cells as well as certain type of immune cells, limiting the anti-tumor immune response. Dual inhibition of the IDO1 and TDO pathways promises to maintain the immune response, prevent local tumor immune escape and potentially avoid resistance to other immunotherapies when used in combination, and could lead to new treatment options for cancer patients. Curadev's preclinical lead-compound, a small-molecule that shows potent inhibition of the two rate-limiting enzymes in the tryptophan to kynurenine metabolic pathways, has the potential for mono therapy as well as combination with Roche's broad oncology pipeline and portfolio.

Curadev Pharma Pvt. Ltd³, founded in 2010, is a drug-discovery company focused on the creation and out licensing of pre-Investigational New Drug assets and Investigational New Drug packages for drug development. Curadev is currently an incubated firm at SIDBI Incubation and Innovation Centre (SIIC)⁴, at The Indian Institute of Technology Kanpur⁵, which acts as a Technology Transfer Office of the Institute and provides professional aid, guidance and management structure to facilitate development of entrepreneurship.

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NIBR⁶ is a global organization of approximately 6,000 scientists, physicians and business professionals from around the world that offers many opportunities for individual professional growth and development.

ANDA for New Polymorphs

Differences in polymorphic forms do not render drug substances different active ingredients for the purposes of ANDA approvals within the meaning of the Hatch-Waxman Act. Section 505(j)(2) of the Act specifies that an ANDA must contain, among other things, information to show that the active ingredient in the generic drug product is the "same as" that of the reference listed drug (RLD). FDA recommendations⁷ assess sameness when the drug substance exists in polymorphic forms. Crystalline forms have different arrangements and/or conformations of the molecules in the crystal lattice. Amorphous forms consist of disordered arrangements of molecules that do not possess a distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent. If the incorporated solvent is water, the solvate is commonly known as a hydrate. Drug substance polymorphic forms can also exhibit different physical and mechanical properties, including hygroscopicity, particle shape, density, flowability, and compactibility, which in turn may affect processing of the drug substance and/or manufacturing of the drug product. The effect of polymorphism on pharmaceutical processing also depends on the formulation and the manufacturing process. Polymorphic forms of the drug substance can undergo phase conversion when exposed to a range of manufacturing processes, such as drying, milling, micronization, wet granulation, spray-drying, and compaction. Therefore, an ANDA applicant should demonstrate that the generic drug product can be manufactured reliably using a validated process.

The Act allows a generic drug manufacturer submit a statement called a "Paragraph IV Certification" with its ANDA stating that any patents that the brand company listed in the FDA's Orange Book are invalid, unenforceable, or will not be infringed by the generic company's proposed product. As a result, despite the best intentions of the law makers, the Act instigates litigation, which is expensive. So contrary to the so-called legislative intent to provide cheaper drugs to patients, the innovator companies, forced to fight the generic companies, incur expenses which must be passed on to patients, employers and tax payers, through increased health insurance premiums.

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As usual, the case law surrounding polymorphs is complex, fact-specific, and subjective and subject to interpretation by courts. Although different polymorphic forms of an active ingredient do not constitute different active ingredients for the purpose of FDA approval, a new polymorphic form of a known active ingredient would not be obvious unless the prior art suggested the new polymorphic form and methods of making the new form⁸. Bioequivalency for the purpose of FDA approval is not to be confused with the doctrine of equivalency (DOE) for infringement of a patent claim⁹. A specific new polymorph is not inherently anticipated by a prior art reference describing a process that does not result in the specific new polymorph¹⁰. When a patent claim describes an invention by reciting a PXRD pattern, the alleged infringing product must exhibit the same PXRD pattern¹¹; however, an expert may rely on fewer than all of the claimed peaks¹², and patent claim language defining a polymorph by its PXRD pattern was broadly construed to account for measurement errors, different measurement conditions, and did not require an identical order of intensity of the peaks as recited in the claim¹³. Presence of a patented polymorph in a commercial embodiment of a new polymorph may establish infringement. However, the amount of the patented polymorph in the new polymorph sufficient to constitute infringement is open for interpretation¹⁴. On the other hand, mere characterization by XPRD of a crystalline form sold in the market would not negate on-sale bar¹⁵. Therefore, determination of the risks of infringement and validity of polymorphs is not simple, thanks to the case law, which only adds to the cost of both branded and generic drugs, .e.g., the cost of developing a prescription drug that gains market approval is about \$ 3 billion, a 145% increase, correcting for inflation, over the estimate the Tufts Center for the Study of Drug Development (CSDD) made in 2003¹⁶.

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Source: The primary sources cited above, New York Times (NYT), Washington Post (WP), Mercury News, Bayarea.com, Chicago Tribune, USA Today, Intellihealthnews, Deccan Chronicle (DC), the Hindu, Hindustan Times, Times of India, AP, Reuters, AFP, womenfitness.net, about.com, mondaq.com, etc.

Om! Asatoma Sadgamaya, Tamasoma Jyotirgamaya, Mrityorma Amritamgamaya, Om Shantih, Shantih, Shantih!

(Aum! Lead the world from wrong path to the right path, from ignorance to knowledge, from mortality to immortality, and peace!)

¹Curadev Pharma Private Ltd, <http://www.prnewswire.com/news-releases/curadev-announces-research-collaboration-and-licensing-agreement-to-develop-cancer-immunotherapeutic-500630711.html>

² Explore the Novartis Institutes for BioMedical Research: <https://www.nibr.com/>

³ Curadev Pharma Pvt. Ltd. <http://www.iitk.ac.in/siic/d/content/curadev-pharma-pvt-ltd>

⁴ SIDBI Incubation and Innovation Centre (SIIC): <http://www.iitk.ac.in/siic/d/content/incubator-policies-and-procedures>

⁵ The Indian Institute of Technology Kanpur is a public research college located in Kanpur, Uttar Pradesh.: <http://www.iitk.ac.in/>

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⁶ Novartis Institutes for BioMedical Research: <https://www.nibr.com/about-us/our-people>

⁷ Guidance for Industry ANDAs: Pharmaceutical Solid Polymorphism:

www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072866.pdf

⁸ *Bristol-Myers Co. v. U.S. Int'l Trade Comm'n*, 1989 WL 147230 (Fed. Cir. 1989) (unpublished): Bristol-Myers Squibb's (BMS's) Duricef® (Cefadroxil monohydrate) is a new crystalline form of a known compound.

⁹ A later U.S. patent application claims priority to a foreign patent application, any forms in the foreign patent application that are not claimed in the U.S. patent are dedicated to the public. *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009)

¹⁰ *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043 (Fed. Cir. 1995) ("Novopharm I"). *In re Armodafinil Patent Litigation Inc.*, 939 F. Supp. 2d 456 (D. Del. 2013)

¹¹ When a patent claim recites a 37-peak PXRD pattern, proving an accused infringer's product exhibits 22 of those 37 peaks does not prove infringement. *Zenith Laboratories, Inc. v. Bristol-Myers Squibb Co.*, 19 F. 3d 1418 (Fed. Cir. 1994). Under § 271(e)(2), courts may properly look to evidence beyond the ANDA to determine whether the ANDA applicant's ultimate product would infringe the patent claim. *Glaxo, Inc. v. Novopharm Ltd.*, 110 F.3d 1562 (Fed. Cir. 1997) ("Novopharm II")

¹² *Schering Corp. v. Apotex Inc.*, Case No. 09-cv-06373, 2012 BL 152438 (D.N.J. June 15, 2012)

¹³ *Bristol-Myers Squibb Co. v. Apotex Corp.*, Case No. 10-cv-05810, 2013 BL 83014 (D.N.J. March 28, 2013)

¹⁴ *Glaxo Group Ltd. v. TorPharm, Inc.*, 153 F.3d 1366 (Fed. Cir. 1998). Even small amounts of the claimed compound may infringe a claim to a specific polymorph. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331 (Fed. Cir. 2005)

¹⁵ *Abbott Labs. v. Geneva Pharm., Inc.*, 182 F.3d 1315 (Fed. Cir. 1999)

¹⁶ Tufts Study Finds Big Rise In Cost Of Drug Development: <http://cen.acs.org/articles/92/web/2014/11/Tufts-Study-Finds-Big-Rise.html> ; <http://www.scientificamerican.com/article/cost-to-develop-new-pharmaceutical-drug-now-exceeds-2-5b/?print=true>

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