

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FLATWING PHARMACEUTICALS, LLC,
Petitioner,

v.

ANACOR PHAMACEUTICALS, INC.,
Patent Owner

Case No. IPR2018-00168
Patent No. 9,549,938

PATENT OWNER'S RESPONSE

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At the 2005 priority date of U.S. Patent No. 9,549,938 (“the ’938 patent,” Ex. 1001), scientists attempting to develop topical treatments for onychomycosis, a fungal infection of the human nail, faced a daunting problem—the nail presented a barrier that was very difficult for drugs to cross. If a drug could not penetrate through the nail, referred to as “transungual delivery” of the drug, it could not treat the infection in the nail or its source in the nail bed and related tissue.

Both before and after the priority date, the scientific literature bemoaned problems with transungual delivery:

- “For the topical therapy to be successful, the drug is required to penetrate across the nail plate and distribute in the nail stratum at therapeutically effective amounts (>MIC). Unfortunately, there are at least two factors that could limit the accumulation and activity of drugs in the nail on topical application. First the physicochemical properties of the drug need to be favorable for absorption through [the] nail matrix. The nail matrix is reported to be relatively more permeable to polar compounds than nonpolar compounds. Second, binding of the drug to keratin reduces the availability of the free drug. Antifungal drugs are reported to possess high-binding affinity to keratin . . . This, most likely, is one of the reasons for prolonged durations of treatment of nail disorders. Moreover, the bound form of the drug does not contrib-

ute to the concentration gradient due to the lack of thermodynamic activity. This decreases the amount of drug penetrating into the deeper nail layers.”¹

- “[C]haracteristics of the nail make it a formidable barrier to drug permeation and the challenge to improve topical delivery of drugs into and through the nail remains formidable as well.”²
- “Currently, topical formulations are available as nail lacquers, creams, ointments, gels, solutions and lotions. However, the efficiency of these formulations is limited due to their inability to deliver a therapeutically effective amount of drug into and across the impermeable nail plate. Therefore, this therapy is limited for the treatment of superficial and minor subungual onychomycosis.”³

¹ Murthy et al., *Iontophoretic Drug Delivery across Human Nail*, J. Pharm. Sci., vol. 96, pp. 305–11, at 305–06 (2007) (Ex. 2008).

² Nair et al., *Alteration of the diffusional barrier property of the nail leads to greater terbinafine drug loading and permeation*, Int’l J. Pharm., vol. 375, pp. 22–27, at 22 (2009) (“Nair et al. 2009a,” Ex. 2004).

³ Nair et al., *A study on the effect of inorganic salts in transungual drug delivery of terbinafine*, J. Pharm. Pharmacol., vol. 61, pp. 431–37, at 431 (2009) (“Nair et al.

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