IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ICEUTICA PTY LTD and IROKO PHARMACEUTICALS, LLC,	)	
Plaintiffs,	)	
v.	)	C.A. No. 14-1515-SLR-SRF
LUPIN LIMITED and LUPIN PHARMACEUTICALS, INC.,	)	
Defendants.	)	

DECLARATION OF DR. MANSOOR M. AMIJI, PH.D., RPH IN SUPPORT OF DEFENDANTS' ANSWERING CLAIM CONSTRUCTION BRIEF

I, Mansoor M. Amiji, do hereby declare as follows:

1. I submit this declaration in support of Defendants Lupin Limited and Lupin Pharmaceuticals, Inc. (collectively, "Lupin") Answering Claim Construction Brief. I have personal knowledge of the matters set forth in this declaration, and if I am called upon to testify, I could and would testify competently thereto.

I. INTRODUCTION AND QUALIFICATIONS

2. I am currently the Bouvé College Distinguished Professor and Chair of the Department of Pharmaceutical Sciences in the School of Pharmacy at Northeastern University. I have been Chair of that department since 2006 and have been a full-time faculty member in that department since 1993. I am also a registered pharmacist in the Commonwealth of Massachusetts.

3. In addition, I am currently an Affiliate Faculty Member in the Department of Chemical Engineering and the Department of Biomedical Engineering at Northeastern

University. I am also currently a Distinguished Adjunct Professor in the Faculty of Pharmacy at King Abdulaziz University in Jeddah, Saudi Arabia.

4. I earned my B.S. in Pharmacy (magna cum laude) at Northeastern University in June 1988 and my Ph.D. in Pharmaceutics from Purdue University in July 1992. Prior to beginning my professorship at Northeastern University in 1993, I served as a Senior Research Scientist at Columbia Research Laboratories, in Madison, Wisconsin.

5. I have been fortunate enough to receive a number of distinctions for my work in pharmaceutical chemistry, including: the "Nano Science and Technology Institute (NSTI) Fellowship Award for Outstanding Contributions towards the Advancement, in Nanotechnology, Microtechnology, and Biotechnology" in 2006; the "Meritorious Manuscript Award" from the American Association of Pharmaceutical Scientists (AAPS) in 2007; and the "Tsuneji Nagai Award from the Controlled Release Society in 2012.

6. I am also a member of various professional societies, including the American Association of Pharmaceutical Scientists (Fellow), Controlled Release Society (Fellow), American Association of College of Pharmacy, and the Phi Lambda Sigma, Pharmacy Leadership Society (Honorary Member).

7. I have served as an editor of seven textbooks related to pharmaceutical chemistry. I have authored, or co-authored, over 180 peer-reviewed articles and roughly 40 book chapters, including numerous publications related the use of nanotechnology in drug delivery.

8. Currently, the primary focus of my laboratory research is on the development of biocompatible materials from natural and synthetic polymers, target-specific drug and gene delivery systems for cancer and infectious diseases, and nanotechnology applications for medical diagnosis, imaging, and therapy.

9. My *curriculum vitae* is included as Appendix I. In the last four years I testified in the following cases: 1:10-CV-00329 (D. Del.), 11-CV-840 (N. D. Cal.), 2011-CV-12226 (D. Ma.), 11-CV-02038 (S.D.N.Y.), 12-CV-05615 (S.D.N.Y.), 13-CV-00139 (S. D. Cal.), 13-CV-1674 (D. Del.), 14-CV-0422 (D. Del.), 1:13-6502 (D.N.J.), and 1:14-3653(D.N.J.).

10. I am being compensated at my normal consulting rate of $870 per hour. I have no personal financial interest in any of the entities involved in this litigation, and my compensation does not depend in any way on my testimony, my conclusions or the outcome of my analysis.

II. MATERIALS REVIEWED

11. Appendix II is a list of materials I reviewed in preparation of this declaration.

III. BACKGROUND AND STATE OF THE ART

A. NSAIDs and Diclofenac

12. The patents-in-suit relate to diclofenac, a compound that is classified as a nonsteroidal anti-inflammatory drug, or NSAID. Like other NSAIDs, diclofenac has long been used as an anti-inflammatory and analgesic agent, or pain killer. Ex. 1 (Moore at 164-165).

13. Diclofenac, like other NSAIDs, inhibits activity of the class of enzyme known as cyclooxygenase (COX). Diclofenac inhibits both the COX-1 and COX-2 enzymes (Ex. 1 (Moore at 165)), with preferential inhibition of the COX-2 enzyme. Ex. 2 (Chuasuwan at 1207-08). Its anti-inflammatory and analgesic properties are hypothesized to stem from inhibiting the COX enzymes in synthesizing prostaglandins and thromboxanes, which are the lipids involved in regulating inflammation and pain receptor sensitivity. Ex. 1 (Moore at 165).

14. Like other NSAIDs, diclofenac usage is associated with an increased risk of gastrointestinal bleeding and serious cardiovascular side effects. Ex. 2 (Chuasuwan at 1208). Because of cardiovascular safety concerns, FDA recommended that all NSAIDs remaining on

the market should be prescribed at the lowest effective dose for the shortest duration possible. Ex. 3 (Jenkins Memo at 15).

15. The scientific literature classifies diclofenac in the biopharmaceutical classification system (BCS) as Class II, meaning it is poorly water-soluble, but highly permeable. Ex. 2 (Chuasuwan at 1214). Thus, diclofenac's poor water solubility becomes the rate-limiting factor in its oral absorption and bioavailability.

16. The first commercially available diclofenac tablet was the sodium salt, marketed in Japan as Voltaren® in 1974 for anti-inflammatory use. Ex. 1 (Moore at 164.) The potassium salt tablet was introduced in the early 1980s for use as an analgesic. *Id.* iCeutica also previously developed diclofenac acid formulations prior to the patents-in-suit. S*ee* Ex. 4 (Payne) and Ex. 5 (Meiser) discussed in paragraphs 24-28 below.

B. <u>Milling Drug Particles to Improve Dissolution Rate and Oral Bioavailability</u>

17. By at least 1993, it was known that a drug with low water solubility "often shows insufficient bioavailability because of the poor solubility in gastrointestinal fluids, which compels said drug to pass through the site of absorption before it completely dissolves in the fluids." Ex. 6 (Samejima, 1:19-24).

18. "An active material's bioavailability is the degree to which the active material becomes available to the target tissue in the body or other medium after systemic administration through, for example, oral or intravenous means." JA22 (1:19-23)[1]. Bioavailability, in turn, depends, to a large extent, on the drug's ability to dissolve in the small intestine

19. The patents-in-suit recognize the importance of reducing particle size to improve dissolution rate and bioavailability: "[i]t is known that the rate of dissolution of a particulate drug

[1] All references to the shared specification are to the '544 patent (JA1-JA57).

will increase with increasing surface area. One way of increasing surface area is decreasing particle size." JA22 (1:32-34).

20. Reducing the particle size of the drug increases the overall surface area of the administered dose of the drug. Dokoumetzidis *et al*. observed "[a]nother factor that influences the dissolution rate is the surface exposed in the solvent. This is primarily affected by the particle size, meaning the smaller the particles, and, therefore, in greater number, the higher their total exposed surface as compared to larger, but fewer, particles of the same total mass. The effect is especially dramatic with poorly soluble compounds." Ex. 7 (Dokoumetzidis at 5).

21. Different milling techniques have been developed over several decades to reduce the particle size of poorly-soluble drug compounds, in order to increase the drug's solubility and bioavailability. Milling is also referred to as grinding in the patents-in-suit, as well as the broader literature. Dry milling and wet milling are milling methods that have been employed to reduce particle size. The distinction between wet milling and dry milling is that wet milling is performed in a liquid medium, whereas dry milling "should be understood to refer to milling in at least the substantial absence of liquids." JA33 (23:24-25). Wet and dry milling each have benefits and drawbacks. One drawback of wet milling is that flocculation, or the clumping together of milled particles, prevents size reduction below certain levels. *See, e.g.*, Ex. 8 (Liversidge '684 at 1:40-43).

22. In 1993, Samejima addressed poor solubility and bioavailability by reducing drug particle size through dry milling. Specifically, Samejima discloses dry milling naproxene (an NSAID like diclofenac, which is marketed in the U.S. as Aleve) to "preferably less than 1 μm [1,000 nm]" to improve dissolution, solubility, and bioavailability. Ex. 6 (Samejima at 2:43-45, 4:14-45).

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