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ACTAVIS ELIZABETH LLC, TEVA PHARMACEUTICALS USA, INC., SUN
PHARMACEUTICAL INDUSTRIES, LTD., SUN PHARMACEUTICAL
INDUSTRIES, INC., AND SUN PHARMA GLOBAL FZE,

Petitioners,

V.

NOVARTIS AG,

Patent Owner.

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Case IPR2017-00854[1]

U.S. Patent No. 9,187,405

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FOURTH DECLARATION OF WILLIAM J. JUSKO, PH.D.

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[1] Cases IPR2017-01550, IPR2017-01946, and IPR2017-01929 have been joined
with this proceeding.

I, William J. Jusko, Ph.D., declare as follows:

I.   Introduction

1.   I am the same William J. Jusko who submitted two prior declarations in this matter, Exhibits 2005 and 2024 plus a Third Declaration (Ex. 2076) served on December 5, 2017 as supplemental evidence. I submit this Fourth Declaration in support of Novartis's sur-reply, and in particular to address certain opinions by Dr. Leslie Z. Benet (Ex. 1047). I use the same terms and abbreviations here that I used in my prior declarations.

2.   In my Second Declaration (Ex. 2024), I showed that a pharmacologist would have thought the invention claimed in the '405 Patent unlikely to work based on information available in the art in June 2006. The Patent claims a method of treating various aspects of RRMS using a 0.5 mg daily dose of fingolimod. But available data in June 2006 suggested that only doses 1.0 mg or higher would work.

3.   Dr. Benet argues otherwise, relying in part on an "EAE" animal study— the "Kataoka" reference (Ex. 1029)—that he says would have led a pharmacologist to expect 0.5 mg daily to be effective in humans. Kataoka reports that 0.1 mg/kg was the lowest tested dose to have a therapeutic effect on EAE in mice and rats. Dr. Benet uses an FDA Guidance on how to extrapolate from animal to first-in-human doses to argue that 0.1 mg/kg in mice converts to approximately 0.5 mg in humans.

(Ex. 1047 ¶¶ 67-70.) Dr. Benet says that this analysis would have led a person of skill to expect 0.5 mg to be effective in humans.

4.   Dr. Benet's analysis has two major flaws.

- ***First***, a person of skill in June 2006 would not have considered extrapolating from animal to human doses because extensive PK/PD data already existed in humans. The FDA Guidance is expressly designed only to identify a safe first-in-human dose before such data exists. But once human PK/PD data exists, that data would provide far more relevant information for estimating a dose's effects than an estimate based on simple animal dose data. Accordingly, a person of skill would not have used the FDA Guidance to extrapolate a human dose from Kataoka's lowest effective mouse dose.

- ***Second***, even if a person of skill in June 2006 would have considered extrapolating from animal to human doses, no pharmacologist would have limited the analysis to extrapolating from one animal using only one method. A pharmacologist would have made use of the other available human and animal data to scale doses. That more complete analysis would have pointed definitively toward doses of 1.0 mg or higher—a range in line with what other prior art suggested.

II. Analysis

A. Animal Dosing Would Have Been Irrelevant Given the Existing Human PK/PD Data

5. In its opening sentence, the FDA Guidance on which Dr. Benet relies describes its purpose: to "outline[] a process (algorithm) and vocabulary for deriving the maximum recommended starting dose (MSRD) for *first-in-human* clinical trials of new molecular entities in adult healthy volunteers, and recommends a standardized process by which the MSRD can be selected." (Ex. 1049 at 1 (emphasis in original).) As the Guidance states in the next sentence, "[t]he purpose of this process is to ensure the safety of the human volunteers." (*Id.*)

6. In other words, the Guidance describes one process by which drug sponsors can use pre-clinical animal data to identify a dose to test in humans for the first time, before any human PK/PD data is available. The Guidance's stated goal is safety for the first-in-human volunteers, not efficacy for any particular condition. That is why the Guidance suggests starting with "the highest dose level that does not produce a significant increase in adverse effects." (*Id.* at 5.) That dose is then extrapolated to a human equivalent dose using an algorithm designed to be "conservative," as I describe further below. The result is then reduced by a safety factor to further limit the risk to the first human volunteers.

7. By June 2006, however, fingolimod had already been tested in humans in multiple trials for many years. Those trials had generated copious human PK/PD

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data, as reflected in Budde 2002 (Ex. 1008), Kahan 2003 (Ex. 1031), Park 2003 (Ex. 2048), and Park 2005 (Ex. 1019). Given that fingolimod's human safety had already been established, the FDA Guidance would no longer have been relevant or appropriate in June 2006.

8.   The focus then would have been on identifying effective doses for specific conditions.   As the FDA Guidance states, identifying such "pharmacologically active" doses (PAD) "depends on many factors and differs markedly among pharmacological drug classes and clinical indications; therefore, selection of a PAD is *beyond the scope of this guidance*." (Ex. 1049 at 12 (emphasis added).) The FDA Guidance observes that pharmacologically active doses could instead be "derived from appropriate pharmacodynamic models." (*Id*.)

9.   That is exactly the analysis I performed in my Second Declaration. Webb identified a pharmacodynamic efficacy marker (a minimum of 70% lymphocyte suppression for "any efficacy"), and Kahan 2003 and Park 2005 reported on that marker in humans at various doses (with 0.5 mg daily generally achieving less than 50% average suppression). As I pointed out in my Second Declaration (Ex. 2024 ¶ 75), pharmacologists assume that PD markers like lymphocyte suppression apply across species, absent evidence to the contrary. Dr. Benet does not disagree, or identify any evidence that a person of skill in June 2006 would have thought the marker would not also apply to humans too. Just the reverse:

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