UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE PATENT TRIAL AND APPEAL BOARD SANDOZ INC., Petitioner, v. PHARMACYCLICS LLC, Patent Owner. Case IPR2019-00865 U.S. Patent No. 9,795,604

DECLARATION OF DR. JOHN KORETH, M.B.B.S., D. Phil.



TABLE OF CONTENTS

I.	INTF	INTRODUCTION9					
II.	PRO	PROFESSIONAL BACKGROUND AND QUALIFICATIONS					
III.	МАТ	MATERIALS CONSIDERED					
IV.	BACKGROUND OF GRAFT VERSUS HOST DISEASE						
	A.	cGVHD Is a Major and Life-threatening Complication of HCT	14				
	B.	cGVHD Is Distinct From and Treated Differently Than aGVHD	16				
	C.	The Pathogenesis of cGVHD Is Complex and Incompletely Understood	18				
	D.	Treatment of cGVHD Is Difficult, Especially in Steroid-Dependent/Refractory, Steroid-Resistant, or Refractory cGVHD Patients	23				
	E.	Before 2013 There Were Many Treatment Failures and No FDA Approved Drugs for cGVHD	28				
V.	THE	'604 PATENT	32				
	A.	The Specification	32				
	B.	The Claims	35				
VI.	PERS	SON OF ORDINARY SKILL IN THE ART	38				
VII.	CLAIM CONSTRUCTION						
	A.	Legal Standards for Claim Construction	39				
	В.	Claims 1 and 55: "method of treating chronic graft versus host disease (GVHD)" and "thereby treating the chronic GVHD in the patient"	41				
	C.	Claims 6-8, 29-31, 44-46, and 51-53: the "wherein" efficacy limitations	44				



	D.	Claim 1: "therapeutically effective amount"			
	E.	The clinical efficacy limitations are not inherent to the claimed methods	46		
VIII.	THE ASSERTED REFERENCES				
	A.	The '085 Publication (Ex. 1002)	47		
	B.	Shimabukuro-Vornhagen (Ex. 1003)	51		
	C.	Herman (Ex. 1004)	54		
	D.	Uckun (Ex. 1005)	55		
IX.	LEGAL STANDARDS FOR PATENTABILITY				
	A.	Anticipation	57		
	B.	Obviousness	58		
X.	THE '085 PUBLICATION DOES NOT DESCRIBE THE CLAIMED METHODS OF TREATING CHRONIC GVHD WITH IBRUTINIB (GROUND 1)				
	A.	The '085 Publication Does Not Anticipate the Challenged Claims	59		
	В.	The '085 Publication Does Not Enable Treating cGVHD With Ibrutinib Without Undue Experimentation (Claims 1, 4, 6-10, 13, 15, 24, 28-31, 35, 39, 43-46, 50-53, and 55)	60		
		1. The Nature of the Invention / Relative Level of Skill	61		
		2. The State and Unpredictability of the Prior Art	62		
		3. The Quantity of Experimentation / The Lack of Direction or Guidance / The Absence of Working Examples	63		
	C.	The '085 Publication Does Not Describe the Subject Matter of Claims 4, 13, and 15 and the Claims that Depend From Them (Claims 28-31, 43-46, and 50-53)	67		



	D.			ublication Does Not Disclose the Specific Efficacy of Claims 6-8, 29-31, 44-46, and 51-53	70
XI.	IBRU REA DEP	JTINII SONA ENDE	B TO T ABLY I NT/RI	O NOT HAVE BEEN MOTIVATED TO USE TREAT cGVHD, AND WOULD NOT HAVE EXPECTED SUCCESS IN TREATING, STEROID-EFRACTORY, STEROID-RESISTANT, AND CGVHD	72
	A.			The '085 Publication and a POSA's Knowledge Do Obvious Claims 4, 13, 15, 28-31, 43-46, and 50-53	72
	В.	Shim	abuku	The Combination of the '085 Publication, ro-Vornhagen, and Herman Does Not Render aims 4, 13, 15, 28-31, 43-46, and 50-53	77
		1.		e of The Cited References Contain Any <i>In Vitro</i> , linical, or Clinical Data for Ibrutinib in cGVHD	80
		2.	Invol Focu	habukuro-Vornhagen's Disclosures Regarding B-Cell lyement and Rituximab Do Not Provide a Reason to s on Ibrutinib With a Reasonable Expectation of ess	81
			a.	The role of B cells in cGVHD pathogenesis was complex and incompletely understood in 2013	81
			b.	Rituximab and ibrutinib are very different drugs	85
			c.	Covalent BTK inhibitors and drugs targeting both B and T cells raised significant safety concerns in steroid-dependent/refractory, steroid-resistant, or refractory cGVHD patients	88
			d.	A POSA would have been skeptical of the rituximab studies referenced in Shimabukuro-Vornhagen	91
		3.		nan's Disclosures Regarding Cytokines Do Not Fill Gaps in the Asserted References	95



	C.	Ground 4: The Combination of the '085 Publication, Shimabukuro-Vornhagen, and Uckun Does Not Render Obvious Claims 4, 13, 15, 28-31, 43-46, and 50-539					
		1.	Uckun, Like the '085 Publication and Shimabukuro- Vornhagen, Does Not Contain Any <i>In Vitro</i> , Preclinical, or Clinical Data for Ibrutinib in cGVHD	99			
		2.	Uckun Shows that LFM-A13 Alone Demonstrated Limited Efficacy in Preventing aGVHD	99			
		3.	aGVHD Is Distinct From cGVHD and GVHD Prophylaxis Cannot be Conflated with GVHD Treatment	101			
XII.	REAS	ROUNDS 2-4 DO NOT PROVIDE MOTIVATION OR A EASONABLE EXPECTATION OF SUCCESS TO ACHIEVE THE ETHODS OF CLAIM 110					
XIII.	OVE	R ANY	8, 29-31, 44-46, AND 51-53 ARE NOT OBVIOUS OF THE ASSERTED REFERENCES BECAUSE OF CCIFIC CLINICAL EFFICACIES	104			
XIV.	ANY	REAS	BINED ASSERTED REFERENCES DO NOT PROVIDE SON TO TARGET A DAILY DOSE OF 420 MG/DAY ED IN CLAIMS 24, 28, 35, 39, 43, 50, AND 55	107			
XV.	ADDITIONAL OBJECTIVE EVIDENCE DEMONSTRATES THAT THE CLAIMED METHODS ARE NOT OBVIOUS11						
	A.	Treat	ment of cGVHD Is Replete With Failures	111			
	B.	The C	Claimed Methods Fulfilled a Long-Felt But Unmet Need	113			
	C.	The C	Claimed Methods Achieved Unexpected Results	118			
	D.	Praise	e and Industry Acclaim for Imbruvica®	119			
	E.		e Is a Nexus Between the Claimed Invention and the etive Evidence	123			
XVI	CON	CLUS	ION	141			



DOCKET

Explore Litigation Insights



Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time** alerts and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.

