

UNITED STATES PATENT AND TRADEMARK OFFICE

---

BEFORE THE PATENT TRIAL AND APPEAL BOARD

---

MYLAN INSTITUTIONAL INC.  
Petitioner,

v.

FRESENIUS KABI USA, LLC,  
Patent Owner.

U.S. Patent No. 9,006,289 to Jiang et al.  
Issue Date: April 14, 2015  
Title: Levothyroxine Formulations  
Case: IPR2017-00645

U.S. Patent No. 9,238,238 to Jiang et al.  
Issue Date: October 27, 2015  
Title: Levothyroxine Formulations  
Case: IPR2017-00643

U.S. Patent No. 9,238,239 to Jiang et al.  
Issue Date: October 27, 2015  
Title: Levothyroxine Formulations  
Case: IPR2017-00644

---

**DECLARATION OF JAMES E. KIPP, PH.D**

## TABLE OF CONTENTS

I.	Introduction .....	1
II.	Background and Qualifications .....	2
III.	List of Materials Considered .....	8
IV.	Legal Standards .....	11
V.	Summary of Opinions .....	15
A.	Claims 1-21 of the '289 Patent Would Have Been Obvious .....	15
B.	Claims 1-30 of the '238 patent Would Have Been Obvious .....	15
C.	Claims 1-15 of the '239 patent would have been obvious .....	16
VI.	The Jiang Patents .....	17
VII.	Level of Ordinary Skill in the Art .....	23
VIII.	The Subject Matter of Claims 1-21 of the '289 Patent, Claims 1-30 of the '238 Patent, and Claims 1-15 of the '239 Patent Would Have Been Obvious .....	25
A.	Scope and Content of the Prior Art .....	25
i.	Levothyroxine Sodium Compositions .....	25
ii.	Instability of Levothyroxine Sodium Compositions .....	26
iii.	Mannitol was the Most Commonly Used Bulking Agent and was Used in Lyophilized Levothyroxine Sodium Compositions .....	34
iv.	Mannitol's Degradation of Moisture-Sensitive Compounds .....	37
B.	Obviousness Based on the Abbott Label, Brower, Baheti, and Collier .....	45
i.	Independent Claims of the Jiang Patents .....	45
a.	Independent Claims 1 and 14 of the '289 Patent .....	45
b.	Independent Claims 1, 11, and 21 of the '238 Patent .....	47
c.	Independent Claim 1 of the '239 Patent .....	49
d.	It Would Have Been Obvious to Use 100 Micrograms of Levothyroxine Sodium .....	49

	e.	It Would Have Been Obvious to Reduce the Amount of Mannitol Below 10 Milligrams .....	50
ii.		Dependent Claims of the '289 Patent .....	74
	a.	Amount of Levothyroxine Sodium: Claims 2 and 3 .....	74
	b.	Amount of Mannitol: Claims 2, 3, and 15 .....	74
	c.	Phosphate Buffer and Amount: Claims 4, 9, and 16.....	75
	d.	Lyophilization Process: Claim 5, 10, and 17 .....	79
	e.	Amount of Levothyroxine Sodium Converted to Liothyronine: Claims 6–8, 11–13, and 18–21 .....	80
iii.		Dependent Claims of the '238 Patent .....	88
	a.	Amount of Levothyroxine Sodium Converted to Liothyronine: Claims 2, 3, 12, 13, 22, and 23 .....	88
	b.	Amount of Mannitol: Claim 4, 14, and 24.....	90
	c.	Pharmaceutically Acceptable Liquid Carrier: Claims 5, 15, and 25 .....	90
	d.	Concentration of Levothyroxine in Pharmaceutical Solution: Claims 6, 16, and 26 .....	91
	e.	Method of Providing Levothyroxine to a Patient in Need: Claims 7, 17, and 27 .....	92
	f.	Dosage of Levothyroxine Sodium: Claims 8, 9, 18, 19, 28, and 29 .....	92
	g.	Phosphate Buffer: Claim 10, 20, and 30.....	93
iv.		Dependent Claims of the '239 Patent .....	94
	a.	Amount of Levothyroxine Sodium Converted to Liothyronine: Claims 2-5 .....	94
	b.	Amount of Mannitol: Claim 6 .....	99
	c.	Phosphate Buffer and/or Amount: Claims 7 and 8 .....	100
	d.	Levothyroxine Sodium: Claim 9 .....	100
	e.	Pharmaceutically Acceptable Liquid Carrier: Claim 10 .....	101
	f.	Concentration of Levothyroxine in Pharmaceutical Solution: Claim 11 .....	101
	g.	pH of the Solution: Claim 12 .....	101
	h.	Method of Providing Levothyroxine to a Patient in Need: Claim 13 .....	108
	i.	Dosage of Levothyroxine Sodium: Claims 14 and 15.....	108
C.		Obviousness Based on the APP Label, Brower, Baheti, and Collier.....	109
	i.	Independent Claims of the Jiang Patents .....	109

a.	Independent Claims 1 and 14 of the '289 Patent .....	109
b.	Independent Claims 1, 11, and 21 of the '238 Patent.....	111
c.	Independent Claim 1 of the '239 Patent .....	112
d.	It Would Have Been Obvious to Reduce the Amount of Mannitol Below 10 Milligrams .....	113
ii.	Dependent Claims of the '289 Patent .....	120
a.	Amount of Levothyroxine Sodium: Claims 2 and 3 ....	120
b.	Amount of Mannitol: Claims 2, 3, and 15 .....	120
c.	Phosphate Buffer and Amount: Claims 4, 9, and 16....	121
d.	Lyophilization Process: Claim 5, 10, and 17 .....	123
e.	Amount of Levothyroxine Sodium Converted to Liothyronine: Claims 6–8, 11–13, and 18–21 .....	123
iii.	Dependent Claims of the '238 Patent .....	124
a.	Amount of Levothyroxine Sodium Converted to Liothyronine: Claims 2, 3, 12, 13, 22, and 23 .....	124
b.	Amount of Mannitol: Claim 4, 14, and 24.....	125
c.	Pharmaceutically Acceptable Liquid Carrier: Claims 5, 15, and 25 .....	125
d.	Concentration of Levothyroxine in Pharmaceutical Solution: Claims 6, 16, and 26 .....	126
e.	Method of Providing Levothyroxine to a Patient in Need: Claims 7, 17, and 27 .....	127
f.	Dosage of Levothyroxine Sodium: Claims 8, 9, 18, 19, 28, and 29 .....	127
g.	Phosphate Buffer: Claim 10, 20, and 30.....	128
iv.	Dependent Claims of the '239 Patent .....	128
a.	Amount of Levothyroxine Sodium Converted to Liothyronine: Claims 2-5 .....	128
b.	Amount of Mannitol: Claim 6.....	130
c.	Phosphate Buffer and/or Amount: Claims 7 and 8 .....	130
d.	Levothyroxine Sodium: Claim 9 .....	131
e.	Pharmaceutically Acceptable Liquid Carrier: Claim 10 .....	131
f.	Concentration of Levothyroxine in Pharmaceutical Solution: Claim 11 .....	131
g.	pH of the Solution: Claim 12 .....	132
h.	Method of Providing Levothyroxine to a Patient in Need: Claim 13.....	132

	i.	Dosage of Levothyroxine Sodium: Claims 14 and 15.....	132
D.		Obviousness Based on the Abbott Label, APP Label, Brower, Baheti, and Collier .....	133
	i.	Independent Claims of the Jiang Patents .....	133
	a.	It Would Have Been Obvious to Reduce the Amount of Mannitol Below 10 Milligrams .....	134
	ii.	Dependent Claims of the '289 Patent .....	135
	a.	Amount of Levothyroxine Sodium: Claims 2 and 3 ....	135
	b.	Amount of Mannitol: Claims 2, 3, and 15 .....	135
	c.	Phosphate Buffer and Amount: Claims 4, 9, and 16....	136
	d.	Lyophilization Process: Claim 5, 10, and 17 .....	137
	e.	Amount of Levothyroxine Sodium Converted to Liothyronine: Claims 6–8, 11–13, and 18–21 .....	137
	iii.	Dependent Claims of the '238 Patent .....	139
	a.	Amount of Levothyroxine Sodium Converted to Liothyronine: Claims 2, 3, 12, 13, 22, and 23 .....	139
	b.	Amount of Mannitol: Claim 4, 14, and 24.....	139
	c.	Pharmaceutically Acceptable Liquid Carrier: Claims 5, 15, and 25 .....	140
	d.	Concentration of Levothyroxine in Pharmaceutical Solution: Claims 6, 16, and 26 .....	140
	e.	Method of Providing Levothyroxine to a Patient in Need: Claims 7, 17, and 27 .....	141
	f.	Dosage of Levothyroxine Sodium: Claims 8, 9, 18, 19, 28, and 29 .....	141
	g.	Phosphate Buffer: Claim 10, 20, and 30.....	142
	iv.	Dependent Claims of the '239 Patent .....	143
	a.	Amount of Levothyroxine Sodium Converted to Liothyronine: Claims 2-5 .....	143
	b.	Amount of Mannitol: Claim 6.....	144
	c.	Phosphate Buffer and/or Amount: Claims 7 and 8 .....	144
	d.	Levothyroxine Sodium: Claim 9 .....	145
	e.	Pharmaceutically Acceptable Liquid Carrier: Claim 10 .....	145
	f.	Concentration of Levothyroxine in Pharmaceutical Solution: Claim 11 .....	146
	g.	pH of the Solution: Claim 12 .....	146
	h.	Method of Providing Levothyroxine to a Patient in Need: Claim 13 .....	147

# 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.