

UNITED STATES PATENT AND TRADEMARK OFFICE

---

BEFORE THE PATENT TRIAL AND APPEAL BOARD

---

FRONTIER THERAPEUTICS, LLC

Petitioner

v.

MEDAC GESELLSCHAFT FÜR KLINISCHE  
SPEZIALPRÄPARATE MBH

Patent Owner

---

*Inter Partes* Review Case No. Unassigned

Patent No. 8,664,231

Title: Concentrated Methotrexate Solutions

---

**DECLARATION OF M. ERIC GERSHWIN, M.D.**

## TABLE OF CONTENTS

I.	INTRODUCTION .....	1
II.	MY EXPERIENCE AND QUALIFICATIONS.....	1
III.	MATERIALS REVIEWED .....	6
IV.	BACKGROUND OF METHOTREXATE.....	9
V.	PERSON OF ORDINARY SKILL IN THE ART.....	15
VI.	THE '231 PATENT .....	15
VII.	CLAIM CONSTRUCTION.....	17
A.	Claims of the '231 Patent .....	18
i.	“subcutaneously” .....	18
VIII.	CERTAIN REFERENCES DISCLOSE OR SUGGEST THE FEATURES RECITED IN THE '231 PATENT CLAIMS.....	19
A.	Grint discloses all elements of claims 1, 2, 4, 5, 6, 17, and 22.....	19
1.	Grint discloses “a method for treating inflammatory autoimmune diseases in a patient in need thereof” (Claim 1).....	20
2.	Grint discloses “subcutaneously administering to said patient a medicament comprising methotrexate” (Claim 1).....	20
3.	Grint discloses that the methotrexate is “in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml” (Claim 1) .....	21
4.	Grint discloses that the methotrexate is “present at a concentration of more than 30 mg/ml to 100 mg/ml” (Claim 2).....	21
5.	Grint discloses the “[p]harmaceutically acceptable solvent [] selected from water, water for injection purposes, water comprising isotonic additives and sodium chloride solution” (Claim 4) .....	22
6.	Grint discloses “the inflammatory autoimmune disease is	

selected from rheumatoid arthritis, juvenile arthritides, vasculitides, collagenoses, Crohn’s disease, colitis ulcerosa, bronchial asthma, Alzheimer’s disease, multiple sclerosis, Bechterew’s disease, joint arthroses, or psoriasis” (Claim 5) and “wherein the inflammatory autoimmune disease is rheumatoid arthritis” (Claim 6).....23

7. Grint discloses that “the sodium chloride solution is isotonic sodium chloride solution” (Claim 17) .....24

8. Grint discloses methotrexate “present at a concentration of from 40 mg/ml to 80 mg/ml” (Claim 22).....24

B. Grint In View Of Alsufyani Teaches Every Element of Claim 18 .....24

C. The PDR (Ex. 1007) or Hospira (Ex. 1009) in view of Brooks (Ex. 1008) teach each element of Claims 1-5, 17, and 22 of the ’231 patent .....26

1. PDR (Ex. 1007) .....26

2. Hospira (Ex. 1009) .....28

3. Brooks (Ex. 1008) .....29

IX. Secondary Considerations.....32

A. A. Any toxicity associated with MTX after subcutaneous injection is dose, not concentration dependent .....32

B. The bioavailability of MTX after subcutaneous injection is dose, not concentration dependent.....35

C. Applicants’ evidence of unexpected results is not based on a comparison of the claimed invention to the closest prior art.....36

D. Zackheim does not teach away from the claimed invention.....39

X. CONCLUSION.....40

## **I. INTRODUCTION**

1. I, Dr. M. Eric Gershwin, M.D., have been retained by Frontier Therapeutics, LLC (“Petitioner”) as an independent expert consultant in this proceeding before the United States Patent and Trademark Office.

2. I understand that this proceeding involves U.S. Patent No. 8,664,231 (“the ’231 patent”) (Ex. 1001). I further understand that the ’231 patent claims priority to German Application No. DE 10 2006 033 837.5, filed July 21, 2006. Ex.1001 at Front Cover. I further understand that the ’231 patent is assigned to medac GmbH.

3. I have been asked to provide information regarding the use of methotrexate (“MTX”) to treat inflammatory autoimmune diseases, particularly rheumatoid arthritis, and the various routes of administration used for MTX prior to July 2006. I have also been asked to consider whether certain references disclose or suggest the features recited in the claims of the ’231 patent. My opinions are set forth below.

## **II. MY EXPERIENCE AND QUALIFICATIONS**

4. My curriculum vitae, which includes a detailed summary of my background and experience and a list of my publications and patents is attached as Exhibit 1031.

5. I am a Distinguished Professor of Medicine, and Chief of

Rheumatology, Allergy and Clinical Immunology in the School of Medicine at the University Of California, Davis. My official title is Distinguished Professor of Medicine.

6. I received my A.B. degree (summa cum laude) in Zoology from Syracuse University in 1966. In 1975, I graduated with an M.D. from Stanford University School of Medicine in Palo Alto, California. I was an intern and medical resident from 1971-1973 at Tufts-New England Medical Center, Boston, MA. From 1973 to 1977, I was a Clinical Associate, Immunology, National Institute of Health, Bethesda, MD.

7. From 1975-1977, I was an Assistant Professor of Medicine (Rheumatology and Clinical Immunol.), University of California, Davis.

8. From 1976-1979, I was the Director of the Tissue Typing Laboratory at the University of California, Davis.

9. From 1977-1981, I was an Associate Professor of Medicine in the Division of Rheumatology/Allergy and Clinical Immunology at the University of California, Davis.

10. From 1981 to the present time, I have been a Professor of Medicine, Division of Rheumatology/Allergy and Clinical Immunology, University of California, Davis.

11. From 1982 to the present time, I have been the Chief of the Division

# 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.