IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

ELI LILLY AND COMPANY,

Plaintiffs/Counterclaim Defendants,

v.

DR. REDDY'S LABORATORIES, LTD. and DR. REDDY'S LABORATORIES, INC.,

Defendants/Counterclaimants.

C.A. No. 1:16-308-TWP-DKL

CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER

EXPERT REPORT OF BRUCE A. CHABNER, M.D.

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I. QUALIFICATIONS AND BACKGROUND.

1. My name is Bruce A. Chabner. I am the Clinical Director Emeritus and the Paul G. Allen Distinguished Investigator at the Massachusetts General Hospital Cancer Center. I am also a Professor of Medicine at Harvard Medical School.

2. I am an expert in the field of medical oncology and in the following fields of special interest: biochemistry and pharmacology of anticancer agents, including antifolates, and the development of new anticancer agents. I have well over 40 years of experience in these areas. My curriculum vitae, which include a list of my publications, are found at Exhibit A.

3. Folates and antifolates have been a major focus of my work throughout my career. I have personally engaged in preclinical research on various antifolates, have been involved with or overseen clinical trials that studied various antifolates, and have prescribed or overseen the prescription of antifolates to patients.

4. After my formal education (B.A. from Yale, M.D. from Harvard), I undertook a series of postdoctoral training posts. One of these posts was as a Research Associate in the Department of Medicine and Pharmacology at Yale University School of Medicine, where I worked under the tutelage of Joseph Bertino, a pioneer in the antifolate field. In 1970-71, in Dr. Bertino's laboratory, I studied the role of a particular enzyme (carboxypeptidase G) in cleaving folates and antifolates, including methotrexate. As part of this research, I discovered that this enzyme could rescue animals from toxicity induced by high doses of methotrexate. It is now approved by the FDA for that clinical use.

5. In 1971, I joined the National Cancer Institute at the National Institutes of Health, the federal government's principal agency for cancer research and training as a senior staff fellow, and one year later became a faculty member in the U.S. Public Health Service. While at

the NCI, I maintained an active laboratory program in cancer pharmacology with a particular focus on the pharmacology and biochemistry of antifolate cancer drugs.

6. One aspect of my NCI research concerned the biochemistry and pharmacological aspects of antifolate cancer drugs, including the investigation of the cellular transport and polyglutamation of antifolate drugs. My laboratory was the first to clone the folate receptor (also called the folate binding protein) and define its role in the transport of folates and antifolates. My close colleagues at NCI were the first to clone the reduced folate carrier, a second transporter of antifolates.

7. My NCI research also involved the clinical evaluation of a number of antifolate cancer compounds, in particular methotrexate. I oversaw clinical studies with methotrexate in a variety of tumor types including breast cancer, ovarian cancer, and lymphomas, and investigated safety aspects of methotrexate, such as determinants of methotrexate toxicity (drug concentration and duration of exposure) to normal and malignant cells. My group published the first clinical report of drug resistance related to gene amplification, which had developed in patients treated with methotrexate, and also discovered that the process of polyglutamation (a process central to the cellular retention and mode of action of methotrexate, pemetrexed, and other antifolates) extended the drug's action and determined treatment outcome.

8. Another aspect of my NCI research involved efforts to improve the clinical utility of methotrexate. For example, we performed pharmacokinetic studies to evaluate the mechanisms by which high-dose methotrexate caused sepsis and renal failure—serious toxicities that resulted from this regimen. We discovered that methotrexate-induced renal failure resulted from precipitation of the drug (and its metabolites) in patients' kidneys, and based on that finding, we developed an in-patient regimen of fluid administration, urine alkalinization, and

drug level monitoring that has since become a standard approach with high dose chemotherapy, preventing the frequent deaths that previously occurred with this important regimen.

9. My tenure at NCI culminated in my service, from 1982 to 1995, as the Director of the Division of Cancer Treatment, the largest of the four divisions at NCI, and the one concerned with drug discovery and development. My responsibilities in that position included overseeing intramural research programs, and supporting grants, cooperative groups, and contracts for extramural anticancer drug development. Our division discovered and developed many important cancer drugs, including paclitaxel, cisplatin, and the first anti-AIDS drugs, AZT, DDI, and DDC.

10. In 1995, I joined the academic faculty at Harvard Medical School as Professor of Medicine. I served as Chief of MGH's Division of Hematology and Oncology from 1995 to 2006, Clinical Director of MGH's Cancer Center from 1995 to 2010, and Director of Clinical Research from 2010 to 2015. In addition, from 1999 to 2010, I was the Associate Director for Clinical Sciences at the Dana Farber-Harvard Cancer Center. My responsibilities at MGH have focused on supervision of cancer treatment services, cancer clinical investigations, and training of medical oncology fellows. Throughout this time, I also have served as an attending physician for the inpatient general medicine service and for oncology. I have been responsible for overseeing the prescription of ALIMTA® to patients, and have been an investigator in a high-dose ALIMTA® study for lymphomas of the central nervous system.

11. I am an author of approximately 500 peer-reviewed publications, reviews, chapters, monographs, and editorials, of which a substantial number are related to antifolates. I am an editor of over twenty books and textbooks for the medical and scientific community, including the standard text, Cancer Chemotherapy and Biotherapy, now in its fifth edition. I

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