Waiver to Allow Participation in a Food and Drug Administration Advisory Committee

DATE: February 7, 2018

TO: Rachel Sherman, M.D., M.P.H.
Principal Deputy Commissioner
Office of the Commissioner, Food and Drug Administration

THROUGH: Russell Fortney
Director (Acting), Advisory Committee Oversight and Management Staff
Office of Special Medical Programs

FROM: Jayne E. Peterson, B.S.Pharm., J.D.
Director, Division of Advisory Committee and Consultant Management
Center for Drug Evaluation and Research

Name of Advisory Committee Meeting Member: **Darrell Pardi, MD, MSc, AGAF, FACG, FACP**

Committee: Gastrointestinal Drugs Advisory Committee

Meeting date: March 8, 2018

Description of the Particular Matter to Which the Waiver Applies:

Dr. Darrell Pardi is a standing voting member of the Gastrointestinal Drugs Advisory Committee (GIDAC). The Committee's function is to review and evaluate available data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of gastrointestinal diseases and make appropriate recommendations to the Commissioner of Food and Drugs.

The committee will meet on March 8, 2018, to discuss supplemental new drug application (sNDA) 203214, supplement 18, Xeljanz (tofacitinib) 5 mg and 10 mg tablets, submitted by Pfizer Inc., proposed for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have demonstrated an inadequate response, loss of response or intolerance to corticosteroids, azathioprine, 6-mercaptopurine or tumor necrosis factor (TNF) inhibitor therapy. The topic of this meeting is a particular matter involving specific parties.

Type, Nature, and Magnitude of the Financial Interests:

Dr. Darrell Pardi is Professor of Medicine at Mayo Clinic College of Medicine, Vice Chair of the Division of Gastroenterology and Hepatology, and Associate Dean of Medicine and Pediatrics at Mayo School of Graduate Medical Education.

Dr. Pardi's employer, Mayo Clinic, is participating in a clinical trial funded by (b) (4) : *Correlation of Infliximab Levels with Outcomes In Ulcerative Colitis* (NCT02438410). Infliximab is used for the treatment of UC and would compete with the drug under review by the advisory committee. Dr. Pardi is the Principal Investigator for this study at Mayo Clinic. The study began in 2015 and is anticipated to end in 2018. The total funding amount to Mayo Clinic for this study is between $0 - $50,000 per year. Dr. Pardi does not receive any personal remuneration or salary support for his role.

Additionally, Dr. Pardi is a member of (b) (4) Advisory Board for (b) (4) for the treatment of UC. He participated in one advisory board meeting on (b) (4), 2017, and received between $5,001 - $10,000. Dr. Pardi's term on the Advisory Board is from May 18, 2017, to May 17, 2018, so he potentially could receive additional payments for his services related to (b) (4), a drug product that would compete with the drug product under review by the advisory committee.

Basis for Granting the Waiver:

The primary issue for discussion at this Gastrointestinal Drugs Advisory Committee meeting will be the benefit/risk assessment of the use of tofacitinib 10 mg twice a day dosing, beyond the 8 weeks of initial induction treatment. The proposed dose is above the maximum recommended dosage for the current approved uses, therefore the key discussion point will be whether safety and efficacy data supports the long-term use of the 10 mg twice daily dosage in refractory (prior tumor-necrosis factor inhibitor failure) UC patients.

Inflammatory bowel disease (IBD) involves chronic inflammation of the digestive tract, which includes UC. UC is a disease affecting the colon and the primary endpoint for trials for drugs intended to treat UC includes measurement of findings on colonoscopy. A fruitful discussion of these matters depends upon having strong expertise in this area and hearing many perspectives. Dr. Pardi is currently involved in research studies in IBD and has specific expertise in clinical trials for IBD therapeutics, both biologics and small molecules. This expertise is essential in understanding and interpreting data, and the limitations of data, from IBD clinical trials such as the matter being discussed at this Advisory Committee meeting. Further, he has published extensively on the clinical and research aspects of IBD. As a recognized expert in this field, his input will be invaluable in assessing the potential risks and benefits of the proposed new treatment for the UC population.

Dr. Pardi has unique qualifications and specialized expertise needed for this particular matter.

Darrell Pardi, MD, MSc, AGAF, FACG, FACP, is Professor of Medicine at Mayo Clinic College of Medicine, Vice Chair of the Division of Gastroenterology and Hepatology, and Associate

Dean of Medicine and Pediatrics at Mayo School of Graduate Medical Education. He received his medical degree from University of Rochester School of Medicine and went on to complete a three-year fellowship in Gastroenterology and Hepatology at Mayo Graduate School of Medicine. After his fellowship, Dr. Pardi attained a Master of Biomedical Sciences in Clinical and Translational Science from the Mayo Graduate School. Dr. Pardi is board certified in Gastroenterology and Hepatology.

Dr. Pardi's research program focuses on the clinical features, epidemiology and treatment of inflammatory bowel disease, specifically microscopic colitis, pouchitis, and clostridium difficile (C. difficile). He has conducted a wide array of research ranging from the use of different agents in UC patients, both biologics and small molecules, validation of the UC colonoscopic index of severity, and the complications of surgical intervention in UC. Dr. Pardi is a recognized expert in IBD and has published extensively on the clinical and research aspects of IBD.

It is particularly important to include Dr. Pardi in the upcoming GIDAC meeting given his experience in adult gastroenterology, microscopic colitis, colonoscopy, as well as in depth knowledge in the validity and reproducibility of endoscopic scoring index. His comprehensive background in clinical features, epidemiology, and endoscopic healing of IBD will add a different perspective to the panel as the committee considers the questions before them regarding the risk-benefit profile and medication safety of tofacitinib.

Multiple experts are needed.

There are several gastroenterologists scheduled to atttend this meeting. It is necessary for the committee to include multiple gastroenterologists, ideally both those who treat adults as well as pediatric patients, to help provide a balanced assessment of the acceptability of the known and anticipated risks associated with the proposed treatment, tofactinib, for UC. Dr. Pardi brings a different perspective, allowing for a diversity in expertise and a robust and productive discussion of the meeting topic.

The particular matter is not sensitive.

The meeting topic is not considered to be sensitive. The Division does not expect that the meeting is likely to receive significant public interest, (non-trade) press interest, or Congressional interest.

Dr. Pardi's expertise in this particular matter is necessary in the interest of public health.

UC is a chronic, idiopathic inflammatory disease that affects the colon, most commonly afflicting adults aged 30–40 years and resulting in disability. It is characterized by relapsing and remitting mucosal inflammation, starting in the rectum and extending to proximal segments of the colon. The annual direct and indirect costs related to UC are estimated to be as high as $8 to $15 billion in the USA.

Although several treatment options are available, none of them are curative. Therefore most patients experience periods of illness after intervals of remission. The goals of treatment are

induction and maintenance of remission of symptoms to provide an improved quality of life, reduction in need for long-term corticosteroids, and minimization of cancer risk. Currently, agents approved for moderate-severe active UC that have demonstrated an inadequate response, loss of response or intolerance to corticosteroids, are azathioprine, 6-mercaptopurine (6-MP) or TNF inhibitor therapy, include infliximab, vedolizumab, golimumab, and adalimumab. These agents require intravenous or subcutaneous administration while tofacitinib, the product at issue, is an oral medication proposed to be administered twice daily. If approved, tofacitinib represents the first systemic immunosuppressant in a new drug class, and the first oral treatment option available to patients with severe UC disease.

As a recognized expert in IBD and related complications, Dr. Pardi's vast experiences in gastroenterology, endoscopy, colonoscopy, and IBD coupled with his in-depth knowledge in epidemiology and clinical trials for IBD therapeutics will ensure a fruitful discussion and a broader public health consideration.

Any potential for a conflict of interest is greatly outweighed by the strong need for Dr. Pardi's expertise in this matter.

Dr. Pardi's participation at this advisory committee meeting is essential – it would add to the diversity of experiences on the panel, allow for a comprehensive discussion of the meeting topic, and would ensure the presence of an expert with significant experience to be part of the discussion. As such, any potential for a conflict of interest is significantly outweighed by the need for Dr. Pardi's expertise on this panel.

Accordingly, I recommend that you grant Dr. Darrell Pardi, a standing, voting member of the Gastrointestinal Drugs Advisory Committee, a waiver from the conflict of interest prohibitions of 18 U.S.C. § 208(a).

Certification:

_X_ The individual may participate, pursuant to 18 U.S.C. 208(b)(3) – The need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved.

Limitations on the Regular Government Employee's or Special Government Employee's Ability to Act:

_____ Non-voting

_____ Other (specify):

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_____

_____ Denied – The individual may not participate.

Kathleen Davies -S

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for Rachel Sherman

February 15, 2018

Rachel Sherman, M.D., M.P.H.
Principal Deputy Commissioner
Office of the Commissioner, Food and Drug Administration

Date