David Behar, M.D.

(b) (6) [redacted]

March 9, 2020

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services, Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Dear Commissioner:

CITIZEN PETITION

This petition is submitted pursuant to 21 C.F.R. § 10.30. This petition requests that the Commissioner of Food and Drugs decommission the REMS program regarding clozapine. This petition also requests that the Commissioner modify the current package insert requirements for clozapine to modify the mandatory monitoring language associated with the Clozapine REMS program to defer entirely to the clinical judgment of the health care provider.

A. ACTION REQUESTED

For the reasons discussed in Section B, this petition requests the Commissioner to do the following:

1. Decommission the Clozapine REMS program.

2. Remove the requirement that health care providers be certified in order to prescribe clozapine.

3. Remove language regarding mandatory blood testing and the Clozapine REMS program, replacing them with the following:

Low white blood cell counts (neutropenia). Low white blood cell counts are very common when taking clozapine and may cause serious infections that can lead to death. Your healthcare provider should check your white blood cell counts before and during treatment.

a. If you develop low white blood cell counts during treatment with clozapine, your healthcare provider may stop your treatment or decrease your dose. Tell your healthcare provider right away if you have signs and symptoms of low white blood cell counts or infections such as fever and chills.

B. STATEMENT OF GROUNDS

1. *Motivation for this Petition*

Petitioner is a board-certified psychiatrist with hundreds of former and dozens of current clozapine patients. Petitioner may legally stand in for his patients' medical interest in federal court. Under the current Clozapine REMS program, in order to be prescribed clozapine currently requires health care professionals to be certified to do so and requires that patients be monitored for changes to their WBC and ANC counts by submitting to weekly blood draws for the first four weeks and thereafter to bi-weekly blood draws. The motivation for this monitoring requirement is the fact that taking clozapine has led to agranulocytosis and neutropenia in 0.1% to 0.8% of patients, which may suppress the patient's immune system and make them susceptible to potentially fatal infection. Based on the historical rationale behind the blood monitoring requirement, the low incidence of fatal side-effects, the existence of dozens of other FDA-approved prescription-only medications for which agranulocytosis and neutropenia are side-effects at the same or higher incident rates than clozapine but for which the FDA has not implemented a REMS program, the significant deterrence in patients' willingness to take clozapine due to the onerous blood monitoring requirement, and the undue burden imposed upon patients by the Clozapine REMS program, Petitioner respectfully requests that the Commissioner decommission the Clozapine REMS program in favor of allowing health care professionals to rely on clinical judgment for treatment and monitoring of clozapine patients.

2. *The Monitoring Requirement Originated as a Medicare Fraud Scheme*

After decades of failed attempts, Sandoz was finally able to obtain FDA approval. Due to a tragic experience in Finland in 1975, in which nine patients died while taking clozapine due to agranulocytosis, Sandoz proposed to introduce clozapine to the US market with a mandatory blood monitoring regimen that is substantially the same as what exists under the Clozapine REMS program today. Following Sandoz obtaining FDA approval, there was massive public outcry owing to the exorbitant pricing imposed by Sandoz for the bundled mandatory blood testing and clozapine medication. On December 18, 1990, twenty-nine states and the District of Columbia filed suit against Sandoz in Federal Court for antitrust violations. In late 1990, Sandoz published full-page advertisements in prominent newspapers declaring that they would unbundle the mandatory blood testing from the medication. However, Sandoz took no such action to implement their published promise. In May 1991, the Senate Subcommittee issued their ruling, finding that both the Sandoz Clozapine monitoring plan and the states themselves were at fault for creating barriers to access. The ruling further ordered the state Medicaid programs to pay for clozapine and associated blood monitoring costs for all eligible patients. In addition, Sandoz was ordered to pay $30 million to settle the class action lawsuit. It is clear from this history that the introduction of clozapine into the US market has its origins in a Medicare fraud scheme under which Sandoz attempted to exact payment at an exorbitant rate both for the mandatory blood testing that it had imposed in order to vitiate concerns about the side-effects of clozapine and for clozapine itself. As such, the current Clozapine REMS program has its roots in criminal fraud.

3. The Clozapine REMS Program is Unwarranted

A REMS is a required risk management plan that can include one or more elements to ensure that the benefits of a drug outweigh its risks.[1] If FDA determines that a REMS is necessary, they may require one or more REMS elements and may also require elements to assure safe use (ETASU).[2] All REMS should include one or more overall goals, and if the REMS has ETASU, the REMS must include one or more goals to mitigate a specific serious risk listed in the labeling of the drug and for which the ETASU are required.[3] Section 505-1(a)(1) of the FD&C Act as implemented in the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires the FDA to consider the following six factors in making decisions about whether to require a REMS:

a) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
b) The expected benefit of the drug with respect to the disease or condition;
c) The seriousness of the disease or condition that is to be treated with the drug;
d) Whether the drug is a new molecular entity;
e) The expected or actual duration of treatment with the drug; and
f) The estimated size of the population likely to use the drug.

The FDA characterized clozapine as an ETASU in implementing the Clozapine REMS program, with the specific serious risk being agranulocytosis. Each of the six factors is addressed below.

a) *Seriousness of Known or Potential Adverse Events and Background Incidence*

Clozapine carries a black box warning for drug-induced agranulocytosis. Without monitoring, agranulocytosis occurs during the first few months of treatment in about 1% of patients who take clozapine.[4] The risk of agranulocytosis is highest around three months into treatment after which time the risk decreases markedly to less than 0.01% after one year.[5] Due to this risk of agranulocytosis, the current package insert for clozapine requires withholding delivery of clozapine to anyone with white blood cell counts (WBC) below 3500/mm^3 and/or an absolute neutrophil count (ANC) below 2000/mm^3. If a large drop in counts is observed or if a mild leucopenia has taken place (3500/mm^3 > WBC ≥ 3000/mm^3) or a mild granulocytopenia has taken place (2000/mm^3 > ANC ≥ 1500/mm^3), then biweekly blood tests are required until the counts rise to the acceptable threshold level. Moderate leucopenia or moderate granulocytopenia require cessation of clozapine therapy and twice-weekly blood tests until the patient has reached "mild

---

1 *See* section 505-1(e) of the FD&C Act and section 505-1(f) of the FD&C Act.

2 *See* Section 505-1(e)(3) of the FD&C Act.

3 *Id.*

4 Baldessarini RJ, Tarazi FI (2006). Pharmacotherapy of Psychosis and Maa. In Laurence Brunton, John Lazo, Keith Parker (eds.). *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (11th ed.).

5 Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA (1993). Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *N. Engl. J. Med.* 329 (3):162–7.

leucopenia" or "mild granulocytopenia" levels. With severe leucopenia (WBC < 2000/mm^3) or severe granulocytopenia (ANC < 1000/mm^3), clozapine treatment must be permanently discontinued.

In contrast, there are at least seventy other prescription medications that also carry a black box warning for drug-induced agranulocytosis or neutropenia but which are not subject to a REMS program. In particular, Ibrance (palbociclib) has an incident rate of neutropenia of 80% and yet defers monitoring to the discretion of the health care provider. Likewise, the penicillin Methicillin has a 2 to 8% incidence of agranulocytosis but has no comparable safety monitoring. Consequently, the monitoring requirement for clozapine cannot rationally be justified by the incidence of agranulocytosis.

b) *Benefits of Clozapine*

Clozapine is an atypical, second-generation antipsychotic drug indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. Clozapine is traditionally used as a "treatment of last resort" for patients who have failed to improve after two adequate trials of other drugs. Approximately 1.5 million people in the United States suffer from schizophrenia, and up to one third of patients with schizophrenia develop treatment resistance and are unresponsive to first-line antipsychotic therapy.[6] There is no other antipsychotic that has comparable efficacy to clozapine in the treatment of resistant schizophrenia.[7] The FDA approved the use of clozapine in such contexts in 1989. The National Institute of Mental Health notes that clozapine is "a very effective medication that treats psychotic symptoms, hallucinations, breaks with reality, such as when a person believes he or she is the president."[8]

Since 2002, clozapine has also had an FDA-approved indication for the treatment of recurrent suicidal behavior in schizophrenia and schizoaffective disorder. It is the best-studied medication for specific beneficial effects on suicidal behaviors. Analysis of clozapine patients has shown a 75% to 82% reduction in mortality, due primarily to a decrease in suicide risk.[9] Other analyses have found a 67% reduction in risk for suicide attempts.[10]

---

[6] Mistry H, Osborn D (2011). Underuse of clozapine in treatment-resistant schizophrenia. *Adv. in Psych. Treatment*, Vol. 17, Issue 4, pp. 250-255.

[7] Kelly DL, Kreyenbuhl J, Dixon L, Love RC, Medoff D, Conley RR (2007). Clozapine underutilization and discontinuation in African Americans due to leucopenia. *Schizophr. Bull.* 33(5):1221-4.

[8] National Institutes of Health (2010). Mental Health Medications. NIH Pub. No. 12-3929, p. 2.

[9] Anderson AE (1999). Using medical information psychotherapeutically. *Eating Disorders: A Guide to Medical Care and Complications.* Edited by Mehler PS, Andersen AE. Johns Hopkins University Press, Baltimore, pp. 192-201.

[10] Commerford MC, Licinio J, Halmi KA (1997). Guidelines for Discharging Eating Disorder Patients. *Eating Disorders: The Journal of Treatment and Prevention* 5:69-74.

Off-label beneficial uses of clozapine represent half of all clozapine prescriptions. These uses include treatment of the following: mania, intermittent explosive disorder, post-traumatic stress disorder, and psychosis caused by medication for Parkinson's disease. All uses of clozapine are unified by the severity and treatment-resistance of the patients for whom it is prescribed. There is no question that, therapeutically, clozapine is and has been a stellar success.[11]

c) *Seriousness of Condition that is Treated with Clozapine*

Agranulocytosis is an acute condition involving severe and dangerous leukopenia, most commonly of neutrophils, and thus causing neutropenia in the circulating blood.[12] This may lead to a suppression of the immune system, subjecting the patient to an increased risk of bacterial infection.

d) *Whether Clozapine is a New Molecular Entity*

Clozapine was first identified in 1959 as one of a group of tricyclic compounds based on the chemical structure of the antidepressant imipramine that were synthesized the prior year by Swiss pharmaceutical company Wander AG. Sandoz acquired Wander AG in 1967, and in the early 1970s, clozapine began clinical trials in the US. FDA approval was obtained in or around 1990, and Clozaril entered the US market on February 5, 1990. Hence, clozapine can no longer be considered to be a new molecular entity.

e) *Expected or Actual Duration of Treatment with Clozapine*

Patients treated with clozapine are expected to be on the medication for life.

f) *Estimated Size of Population Likely to use Clozapine*

There are approximately 1.5 million people in the US that suffer from schizophrenia. Of these, about 30% are treatment resistant.[13] Relevant to this petition, **between 19% and 28% of schizophrenics who are treatment resistant and who would benefit from clozapine refuse to take the medication because of the Clozapine REMS program's mandatory weekly blood testing**.[14] This may be attributed to trypanophobia and to the fact that these patients are, by and large, the most paranoid, dangerous schizophrenics and psychotics in the population. The net number of patients who do not take clozapine due to the existence of the Clozapine REMS program is thus estimated to be between 85,000 and 126,000. **These treatment-resistant schizophrenics for whom clozapine represents the *only* medication effective in treating their condition represent a clear and present danger to society and to themselves.**

---

[11] Newman, WJ, Newman, BW (2016). Rediscovering clozapine: Clinically relevant off-label uses. *Current Psychiatry* 15:51-61.

[12] *Stedman Medical Dictionary.*

[13] Mistry H, Osborn D (2011). Underuse of clozapine in treatment-resistant schizophrenia. *Adv. in Psych. Treatment*, Vol. 17, Issue 4, pp. 250-255.

[14] Taylor D, et al., Clozapine -- a survey of patient perceptions. *The Psychiatrist*, 2000. **24**(12): p. 450-452.

4. *Why the Current FDA Regulations Must be Changed*

Discrimination in medicine is a medical practice that includes both differential treatment on the basis of a protected class (disparate-treatment discrimination) and treatment on the basis of inadequately justified factors that disadvantages a particular group (disparate-impact discrimination).[15] Disparate treatment involves intentional discrimination and is per se unconstitutional. Statistical disparity is sufficient for a legal showing of discrimination.[16] In contrast, a determination as to the legality of disparate-impact discrimination depends upon whether the practice is supported by a sufficiently compelling reason and whether alternative processes exist that would not give rise to disparities. Disparate-impact liability mandates the "removal of artificial, arbitrary, and unnecessary barriers . . ."[17]

Petitioner contends that the current FDA regulations governing the use of clozapine are unconstitutional because they discriminate against individuals with mental illness, prohibiting such groups of individuals from being prescribed what often is *the only* effective medication available to treat or control their symptoms.

In terms of disparate impact, the current FDA regulations have the effect of discriminating against individuals with mental illness by prohibiting them from the use of an effective treatment. There is no compelling reason why such a prohibition should exist, especially given the fact that FDA-approved medications exist that exhibit a far greater risk of agranulocytosis but which are not subject to a REMS program.

Petitioner also contends that the current FDA regulations governing the use of clozapine are unconstitutional because they constitute an undue burden by placing a substantial obstacle in the path of patients seeking treatment. In *Planned Parenthood of Southeastern Pennsylvania v. Casey*, the Supreme Court defined undue burden as an invalid provision of law whose purpose or effect is to place a substantial obstacle in the path of a patient seeking treatment.18 The Supreme Court futher refined the definition in *Whole Woman's Health v. Hellerstedt*, 136 S. Ct. 2292, 2309 (2016), in which the Court held that it was "wrong to equate the judicial review applicable to the regulation of a constitutionally protected personal liberty with the less strict review applicable [in other contexts]."19 In other words, the undue burden test is a form of heightened scrutiny that rejects the judicial deference to legislative claims afforded under the rational basis test even if the beneifts are minimal or the laws is unnecessary to achieve them. The test articulated in *Whole Woman's Health* has three requirements: 1) the law must actually further a valid state interest; 2) the benefits of the law must outweigh the burdens imposed by the law; and 3) there must be an evidence-based inquiry based on reliable methodology. While the Supreme Court's holdings were

---

[15] National Research Council (2004). *Measuring Racial Discrimination.* The National Academies Press, Washington, DC. p. 40. *Available at* http://www.nap.edu/catalog.php?record_id=10887 (last accessed Feb. 20, 2012).

[16] *Texas Dept. of Housing and Community Affairs v. Inclusive Communities Project, Inc*., 576 US ____ (2015).

[17] *Griggs v. Duke Power Co*., 401 US 424, 431 (1971).

[18] *Planned Parenthood of Southeastern Pennsylvania v. Casey*, 505 US 833 (1972).

[19] *Whole Woman's Health v. Hellerstedt*, 136 S. Ct. 2292, 2309 (2016).

issued in the context of a woman's right to seek an abortion, they are broadly applicable to cases in which laws limit individual rights when their constitutionality depends on whether the law is actually advancing valid interests in a way that justifies the harm placed on the individual. Here, it may be argued that the regulations at issue further a valid state interest in that they seek to minimize the number of deaths caused by agranulocytosis; however, two facts undermine the legitimacy of this supposed interest: there is no evidence that discretionary monitoring by the prescribing physician would result in more adverse outcomes, and no other medication with a potential side-effect of agranulocytosis is subject to a REMS monitoring program, even though other medications present an exponentially higher risk. In terms of the benefit/burden analysis, clozapine being a drug of last resort, the target population being among the most volatile and potentially dangerous that exists within society, and the severe and possibly deadly repercussions of cessation of treatment make it clear that the burden imposed by the Clozapine REMS monitoring program are not outweighed by its benefits. With respect to the third requirement, the Court held that "The statement [] that legislatures, and not courts, must resolve questions of medical uncertainty is also inconsistent with this Court's case law." Thus, Petitioner believes the Clozapine REMS program constitutes an undue burden and consequently an unconstitutional regulation.

Petitioner is confident that should the FDA refuse to decommission the Clozapine REMS program, the current regulations would not withstand a disparate-impact discrimination challenge brought by Petitioner on behalf of his patients under Title II of the Americans with Disabilities Act Amendments Act of 2008. Should Petitioner's petition be denied, Petitioner also intends to pursue an undue burden challenge, which, given recent jurisprudence, Petitioner believes the Clozapine REMS program will not survive. Petitioner prays that wisdom will prevail, making initiation of such a challenge unnecessary.

5. *Sudden Interruption of Clozapine Treatment Can Be Catastrophic*

Under the current regulations, patients may experience repeated, random interruptions in treatment of varying duration, depending on when their WBC and ANC counts rebound to "acceptable" levels. It is ironic that if infected, the counts will jump to high levels, and clozapine may again be dispensed.

The following have been reported as effects of sudden discontinuation of clozapine: bad flu-like symptoms with headaches and vomiting lasting a week; delirium; the return of original psychotic symptoms; the return of suicidal ideas; and abnormal movements ("These subjects had severe limb-axial and neck distonias and dyskinesias 5 to 14 days after clozapine withdrawal. Two subjects were unable to ambulate and 1 had a lurching gait.") These are immediate, acute effects, which remit quickly with the resumption of clozapine.[20]

---

[20] Ahmed S., Chengappa KN, Naudu VR, Baker RW, Parepally H, Schooler NR (1998). Clozapine withdrawal-emergent dystonias and dyskinesias: a case series. *J Clin. Psychiatry* 59(9):472-7.

Stanilla JK, de Leon J, Simpson GM (1997). Clozapine withdrawal resulting in delirium with psychosis: a report of three cases. *J Clin. Psychiatry* 58(6):252-5.

Miodownik C, Lerner V, Kibari A, Toder D, Cohen H (2006). The effect of sudden clozapine discontinuation on management of schizophrenic patients: a retrospective controlled study. *J Clin. Psychiatry* 67(8):1204-8.

The more disturbing consequence is evidence of brain damage necessitating higher doses and taking longer to work: "the discontinuation of clozapine treatment leads to a deterioration in the quality of remission, with a need for an increased dose of clozapine."[21] Duration of under-treatment also correlates with measurable losses of grey matter. A proper analogy would be the ease of treating a microscopic breast cancer lump versus a tumor the size of a baseball which has been allowed to grow untreated.

Interruption in clozapine treatment may also lead to relapse, in some cases with dramatic aggravation of the psychotic symptomatology, a phenomenon known as "super-sensitivity" psychosis.[22] Treatment resistance to clozapine in prior clozapine responders has also been reported; patients whose clozapine treatments have been interrupted due to temporarily low WBC counts have experienced decreased effectiveness when treatment is resumed.[23] Discontinuation of clozapine has also been found to have a marked negative impact on clinical status, including decreases in function and increases in time spent in mental facilities.[24] It is clear from these and other studies that the current regulations mandating cessation of clozapine treatment based solely upon WBC and ANC counts without concern for other factors, including the potentially severe negative consequences to patients of such cessation are not sufficiently refined to be considered thoughtful, responsible regulations: in many published cases, patients have experienced severe consequences as a direct result of the current regulations, leaving those patients in a worse condition than they were before clozapine treatment began.

6. *Public Benefit of Action*

The decommissioning of the Clozapine REMS program will have great public benefit. "Given the high costs of medication discontinuation, rehospitalization and inadequate treatments for schizophrenia, the underutilization of clozapine in the United States is particularly noteworthy."[25] Adoption of the requests made herein will have an immediate impact on those patients with treatment-resistant schizophrenia and schizoaffective disorder; Petitioner finds it difficult to put into words how significant the increase in quality of life for those patients will be. The savings in terms of societal and social costs are difficult to quantify but would be significant. In addition, adopting these requests will decrease the disparity that currently exists with respect to the use of second-generation antipsychotics in the treatment of schizophrenia, which, as noted above, is an acute problem in the United States; as the Department of Health and Human Services noted, "'the combined costs of health inequalities and premature death in the United States were $1.24 trillion' between 2003 and 2006."[26] Finally, the requests herein are fully aligned with the HHS's goals

---

[21] Bangalore SS, Gloria DD, Nutche J, Diwadkar VA, Prasad KM, Keshavan MS. Untreated illness duration correlates with gray matter loss in first-episode psychoses. *Neororeport*, April 3, 2009.

[22] Llorca PM, Penault F, Lançon C, Dufumier E, Vaiva G (1999). *Encephale* 25(6):638-44.

[23] Grassi B, Ferrari R, Epifani M, Dragoni C, Cohen S, Scarone S (1999). Eur. Neuropsychopharmacol. 9(6):479-81.

[24] Atkinson JM, Douglas-Hall P, Fischetti C, Sparshatt A, Taylor DM (2007). Outcome following clozapine discontinuation: a retrospective analysis. *J Clin. Psychatry* 68(7):1027-30.

[25] Kelly, *supra.*

[26] HHS Action Plan to Reduce Racial and Ethnic Health Disparities, *supra*, p. 2.

under *Healthy People 2020* "to achieve health equity, eliminate disparities and improve the health of all groups."[27]

7. *Request for Action as Direct Final Rule*

FDA regulations at 21 C.F.R. § 10.40(e)(1) provide that "[t]he requirements of notice and public procedure . . . do not apply . . . [w]hen the Commissioner determines for good cause that they are . . . unnecessary . . ."[28] This FDA exemption mirrors a similar exemption in the Administrative Procedure Act ("APA").[29] When enacting the APA exemption, Congress stated that the "lack of public interest in rule-making warrants an agency to dispense with public procedure."[30] Here, as there appears to be no question of law or fact in dispute, the Commissioner may dispense with advance notice and opportunity for comment. Therefore, Petitioner requests that the FDA effect creation of a national registry for clozapine patients having benign ethnic neutropenia and the proposed changes to package inserts and regulations by direct final rule.

C. ENVIRONMENTAL IMPACT

FDA regulations at 21 C.F.R. § 10.30 require Petitioner to prepare an environmental assessment under 21 C.F.R. § 25.40. However, an environmental assessment is not necessary here. 21 C.F.R. § 25.40 defines environmental assessment as "a concise public document that serves to provide sufficient evidence and analysis for an agency to determine whether to prepare an [environmental impact statement] or a [finding of no significant impact]."[31] The environmental assessment fulfills the FDA's obligations under the National Environmental Policy Act of 1969 ("NEPA").[32] NEPA requires all federal agencies to assess the environmental impact of their actions "significantly affecting the quality of the human environment."[33] The requests embodied in the instant petition have no environmental implications. Consequently, no environmental assessment is warranted.

D. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30, information under this section is to be submitted only when requested by the Commissioner following review of the petition.

---

[27] *Id.* at p. 8.

[28] 21 C.F.R. § 10.40(e)(1).

[29] *See* Administrative Procedure Act, 5 U.S.C.A. § 553(b)(B).

[30] *See* S. Doc. No. 248, 79th Cong., 2d Sess. at 200 (1946).

[31] 21 C.F.R. § 25.40; *see also* 40 C.F.R. § 1508.9.

[32] SW Environmental Impact Statements, 38 Fed. Reg. 7001 (Mar. 15, 1973), amended by 42 Fed. Reg. 19986 (Apr. 15, 1977) and 50 Fed. Reg. 16636 (Apr. 26, 1985).

[33] 42 U.S.C.A. § 4332.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to Petitioner that are unfavorable to the petition.

F. CONCLUSION

For the foregoing reasons, Petitioner requests that this petition be granted and that the Commissioner decommission the Clozapine REMS program and contemporaneously require modifications to package inserts and FDA guidance and regulations to allow health care providers to treat patients with the drug using their own clinical judgment.

Respectfully submitted,

David Behar, MD

David Behar, M.D.

(b) (6)