David Behar, M.D.

[redacted]

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April 9, 2012

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 create a national patient registry to provide a means for patients suffering from treatment-resistant schizophrenia who also have benign ethnic neutropenia ("BEN") to be treated with clozapine despite such patients having normally low white blood cell ("WBC") counts and absolute neutrophil counts ("ANC") that fall below the minimum thresholds for which clozapine treatment is currently allowed. This petition also requests that the Commissioner modify the current package insert requirements for clozapine to provide an exception to the current delivery thresholds for patients having BEN and to lower the monitoring and discontinuation WBC and ANC thresholds for such patients.

A. ACTION REQUIRED

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

1. Create a national registry for patients suffering from treatment-resistant schizophrenia who also have benign ethnic neutropenia ("BEN") to allow such patients to be treated with clozapine.

2. Require that package inserts for clozapine include language substantially similar to the following:

> Patients who have low WBC or ANC counts because of benign ethnic neutropenia should be given special consideration and may only be started on clozapine with the agreement of a hematologist. If a patient or candidate for clozapine treatment has $3500/mm^3 > WBC \geq 3000/mm^3$ and/or $2000/mm^3 > ANC \geq 1500/mm^3$ and the patient or candidate has African or Mediterranean ethnic origins, than a hematology consultation for the diagnosis of benign ethnic neutropenia (BEN) should be obtained. If the hematologist diagnoses BEN, then the patient or candidate should be enrolled in a registry of Clozapine Patients with Benign Ethnic Neutropenia. Such patients or candidates will then receive a waiver to obtain the usual supply of clozapine from a pharmacy while their WBC remains at or above $3000/mm^3$ and their ANC remains at or above $1500/mm^3$. Such patients or candidates will not be required to obtain more frequent blood tests, nor will their use of clozapine be discontinued.

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3. Require that package inserts and FDA regulations governing the administration of clozapine be modified to accommodate patients with BEN by decreasing the monitoring and therapy discontinuation thresholds of both WBC and ANC counts by 0.5 mm^3/l (i.e., by $0.5x10^9/l$).

B. STATEMENT OF GROUNDS

1. *Motivation for this Petition*

Petitioner is a board-certified psychiatrist with dozens of clozapine patients. Many of Petitioner's patients have origins in Africa and around the Mediterranean and consequently have naturally low WBC and ANC counts, a "condition" commonly known as benign ethnic neutropenia ("BEN"). Current FDA regulations concerning the administration of clozapine have led to mandatory discontinuation of this effective treatment despite the fact that these patients do not have an elevated risk of agranulocytosis. This petition requests that the FDA adopt the regulatory policies and procedures held by numerous European countries with respect to clozapine and patients having BEN, in particular by establishing a registry for such patients and by relaxing the WBC and ANC threshold values for discontinuing its use so that such patients can be treated with clozapine.

2. *Overview 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.[1] There is no other antipsychotic that has comparable efficacy to clozapine in the treatment of resistant schizophrenia.[2] 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."[3]

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

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

[2] 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.

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

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.[4] Other analyses have found a 67% reduction in risk for suicide attempts.[5]

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.

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.[6] 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.[7] 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 ($3500/mm^3 > WBC \geq 3000/mm^3$) or a mild granulocytopenia has taken place ($2000/mm^3 > ANC \geq 1500/mm^3$), 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 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.

3. *Benign Ethnic Neutropenia: a Non-Condition*

Benign ethnic neutropenia ("BEN") has been defined as "the occurrence of neutropenia, defined by normative data in white populations, in individuals of other ethnic groups who are otherwise healthy and who do not have repeated or severe infections."[8] BEN has also been called ethnic neutropenia, psuedoneutropenia, benign familial neutropenia, nongenetic neutropenia, "benign" neutropenia of the black, familial neutropenia, benign hereditary neutropenia, benign hereditary leucopenia-neutropenia, benign familial leucopenia and neutropenia, and chronic benign

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4 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.

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

6 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.).

7 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.

8 Haddy TB, Rana SR, Castro O (1999). Benign ethnic neutropenia: what is a normal absolute neutrophil count? *J. Lab. Clin. Med.* 133:15–22.

idiopathic neutropenia.[9] Between 25% and 50% of Africans and certain other ethnic groups in the Middle East, including Yemenite Jews, Jordanians, and Afro-Caribbean groups, have BEN, making it the most common form of neutropenia in the world.[10] BEN has only been reported in ethnic groups that have tanned or dark skin.[11] Subjects with BEN do not exhibit an increased incidence of infections, and their response to infections is similar to those without BEN.[12]

4. *Why the Current FDA Regulations Must be Changed to Recognize BEN*

Medical literature is rife with examples of health disparities that correlate with social categories of race and ethnicity.[13] Most current health disparities have little or nothing to do with genetics and instead arise due to socioeconomic and other environmental factors.[14] However, clozapine has been expressly recognized as one of a few dozen medications for which biological differences associated with "race" or "ethnicity" have led to disparities in access to health care.[15] In addition, there is evidence that some ethnic groups, particularly African Americans, are less likely to be prescribed clozapine as a matter of course, demonstrating a persistent gap in the quality of care for patients with schizophrenia.[16]

Racial discrimination in medicine is a medical practice that includes both differential treatment on the basis of race that disadvantages a racial group (disparate-treatment racial discrimination) and treatment on the basis of inadequately justified factors other than race that disadvantages a

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[9] Hoffman R (ed.) (2000). *Haematology: Basic Principles and Practice* (3d ed.). Churchill Livingstone, London. p. 748.

[10] Shoenfeld Y *et al.* (1988). Benign familial leukopenia and neutropenia in different ethnic groups. *Eur. J. Haematol.* 41(3): 273-277.

[11] Haddy, *supra.*

[12] *Id.*

[13] *See, e.g.,* U.S. Dep't of Health & Human Svcs. (April 2011). HHS Action Plan to Reduce Racial and Ethnic Disparities: A Nation Free of Disparities in Health and Health Care. U.S. Department of Health and Human Services, Washington, D.C. *Available at* http://1.usa.gov/HHSActionPlanDisparities (last accessed Feb. 20, 2012); *see also* Inst. of Med. (2002). Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care. *Available at* http://www.nap.edu/openbook.php?isbn=030908265X (last accessed Feb. 20, 2012).

[14] Cooper, RS (2001). Social inequality, ethnicity and cardiovascular disease. *Int. J. Epidemiol.* 30 Suppl 1, S48–S52.

[15] Tate SK, Goldstein DB (2004). Will tomorrow's medicines work for everyone? *Nat. Genetics* 36, S34-S42.

[16] *See, e.g.,* Kuno E, Rothbard AB (2002). Racial disparities in antipsychotic prescription patterns for patients with schizophrenia. *Am. J. Psychiatry* 159:567-72. *See also* Horvitz-Lennon M, McGuire TG, Alegria M, Frank RG (2009). Racial and ethnic disparities in the treatment of a Medicaid population with schizophrenia. *Health Serv. Res.* 44(6): 2106-2122. *Additionally, see* Mallinger JB, Fisher SG, Brown T, Lanberti JS (2006). Racial disparities in the use of second-generation antipsychotics for the treatment of schizophrenia. *Psychiatr. Serv.* 57:133-36.

racial group (disparate-impact racial discrimination).[17] Disparate treatment involves intentional discrimination and is per se unconstitutional. In contrast, a determination as to the legality of disparate-impact racial discrimination depends upon whether the practice is supported by a sufficiently compelling reason and whether alternative processes exist that would not give rise to racial disparities.

Petitioner respectfully contends that the current FDA regulations governing the use of clozapine are unconstitutional because they discriminate against individuals from ethnic groups having BEN, prohibiting such groups of individuals from being prescribed what often is *the only* effective medication available to treat or control their symptoms, and doing so solely on the basis of purely racial attributes. It is undisputed that both WBC and ANC counts are normally lower for certain ethnic groups, particularly individuals of African and Mediterranean descent—ethnic groups who invariably have tanned or dark skin.[18] Ethnic groups exhibiting BEN do not suffer from any increased risk of agranulocytosis when treated with clozapine.[19] The current denial of clozapine as a treatment option for individuals with BEN is due to the WBC and ANC threshold counts having been based upon the "normal" counts of a Caucasian population; the existence of other ethnic groups having normally lower WBC and ANC counts was not taken into consideration by the FDA when the regulations regarding clozapine were adopted.

In terms of disparate impact, it is undisputed in the medical literature that the current FDA regulations have the effect of discriminating against certain racial groups who have BEN by prohibiting them from the use of an effective treatment solely by virtue of their race. Petitioner is unaware of any compelling reason why such a prohibition should exist, and there is consensus among the medical community that such discrimination is not warranted based on any increased risk of side-effects including agranulocytosis.[20] Additionally, the alternative regulations requested in this petition are an alternative process that, if adopted, would not give rise to racial disparities; in fact, precisely the requests made herein were adopted in several European countries, including Ireland and the U.K., have been in place for years, and have not led to any reported negative repercussions with respect to the use of clozapine such as increased incidence of infections or agranulocytosis.[21] Petitioner is confident that should the FDA refuse to enact the requests proffered herein, the current regulations would not withstand a disparate-impact racial discrimination challenge brought by Petitioner on behalf of his patients under Title II of the Americans with Disabilities Act Amendments Act of 2008. Petitioner prays that wisdom will

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[17] 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).

[18] Alvir, *supra.*

[19] *See, e.g.,* Munroe J, O'Sullivan D, Andrews C, Arana A, Mortimer A, Kerwin R (1999). Active monitoring of 12,760 clozapine recipients in the UK and Ireland. Beyond pharmacovigilance. *Br. J. Psychiatry* 175:576-80.

[20] *See, e.g.,* the Pennsylvania Medical Society's endorsement of such a registry in the United States, attached hereto as Exhibit 1.

[21] The package insert for Irish registry patients is attached hereto as Exhibit 2.

prevail, making the instigation 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.[22]

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."[23] 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.[24] 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.[25] Discontinuation of clozapine has also been found to have a marked negative impact on clinical

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[22] 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.

[23] 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.

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

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

status, including decreases in function and increases in time spent in mental facilities.[26] 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 BEN and 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 establishment of a national registry for clozapine patients with BEN and the contemporaneous modification of the regulations regarding minimum WBC and ANC counts to allow such patients to receive clozapine treatment as requested herein 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."[27] Adoption of the requests made herein will have an immediate impact on those patients with treatment-resistant schizophrenia and schizoaffective disorder who have BEN; 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 racial 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."[28] Finally, the requests herein are fully aligned with the HHS's goals under *Healthy People 2020* "to achieve health equity, eliminate disparities and improve the health of all groups."[29]

6. *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 . . ."[30] This FDA exemption mirrors a similar exemption in the Administrative Procedure Act ("APA").[31] When enacting the APA exemption, Congress stated that the "lack of

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[26] 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.

[27] Kelly, *supra.*

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

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

[30] 21 C.F.R. § 10.40(e)(1).

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

public interest in rule-making warrants an agency to dispense with public procedure."[32] 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]."[33] The environmental assessment fulfills the FDA's obligations under the National Environmental Policy Act of 1969 ("NEPA").[34] NEPA requires all federal agencies to assess the environmental impact of their actions "significantly affecting the quality of the human environment."[35] 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.

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 the petitioners that are unfavorable to the petition.

F. CONCLUSION

For the foregoing reasons, Petitioner requests that this petition be granted and that the Commissioner establish a national registry for clozapine patients with benign ethnic neutropenia and contemporaneously require modifications to package inserts and FDA guidance and regulations to allow patients with BEN to receive the benefit of clozapine treatment.

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

[33] 21 C.F.R. § 25.40; *see also* 40 C.F.R. § 1508.9.

[34] 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).

[35] 42 U.S.C.A. 5 4332.

Respectfully submitted,

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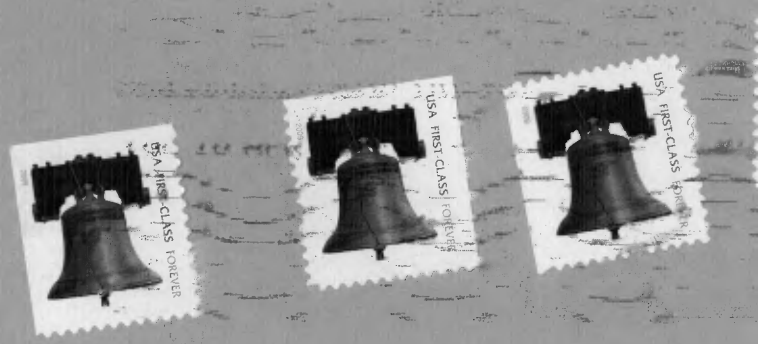

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