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Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION AND PETITION FOR ADMINISTRATIVE STAY OF ACTION

Jones Pharma, Inc. (Jones), a subsidiary of King Pharmaceuticals, Inc., submits this petition and request for administrative stay pursuant section 505 of the Federal Food, Drug, and Cosmetic Act (the "Act" or "FDCA") (21 U.S.C. § 505) and in accordance with 21 C.F.R. §§ 10.30 and 10.35(b). Jones is the manufacturer of Levoxyl® (levothyroxine sodium tablets, USP) indicated for thyroid hormone replacement or supplemental therapy for hypothyroidism.

I. Actions Requested

1. Jones requests that FDA refrain from approving or accepting for filing any abbreviated new drug application (ANDA) or supplemental ANDA for levothyroxine sodium tablets that attempts to establish bioequivalence with any reference drug in accordance with the standards for establishing bioequivalence set forth in FDA's February 2001 Guidance for Industry: *Levothyroxine Sodium Tablets - In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing* (the "February 2001 Guidance") or as announced by FDA at the March 12-13 meeting of the Pharmaceutical Science Advisory Committee;

2. Jones requests that FDA convene a joint meeting of the Pharmaceutical Science Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee to evaluate, in a public forum, appropriate methodologies for establishing bioequivalence between levothyroxine sodium tablet drug products;

3. Jones requests that FDA stay approval or acceptance for filing of any ANDA or supplemental ANDA for levothyroxine sodium tablets basing

bioequivalence on the standards set forth in the February 2001 Guidance or the methodology announced at the March 12-13 meeting of the Pharmaceutical Science Advisory Committee until such time as the joint advisory committee meeting referred to above has convened, FDA has established a new bioequivalence methodology consistent with this Petition, and bioequivalence studies in accordance with the new methodology have been submitted, or until FDA responds to this Petition.

II. Brief Statement of Grounds

Pursuant to section 505(j)(2)(A)(iv) of the FDCA, any ANDA must contain, among other things, information demonstrating that the generic drug is bioequivalent to the reference listed drug.[1] Such bioequivalence is often established through a showing of equivalent bioavailability to the reference listed drug. In the February 2001 Guidance, FDA set forth criteria for conducting in vivo bioavailability and dose-form proportionality studies in levothyroxine sodium tablet products. These criteria call for measurement of overall plasma levels of L-thyroxine (T_4) and 3,5,3 triiodothyronine (T_3) without adjustment for baseline levels of endogenous T_3 and T_4. Bioavailability and dose-form proportionality are demonstrated if the 90 percent confidence intervals of the geometric mean ratio of AUC_{0-t} and C_{max} fall within the 80% to 125% range.[2]

The February 2001 Guidance initially led industry to believe that FDA would accept a showing of bioavailability and dose-form proportionality, as defined by the February 2001 Guidance, as establishing bioequivalence between a generic and its reference drug. Accepting such a method for establishing bioequivalence, however, could create significant adverse consequences for thyroid replacement therapy patients. The presence of endogenous baseline levels of T_4 in healthy patients confounds the establishment of bioequivalence through comparative bioavailability and dose-form proportionality because the standards set forth in the February 2001 Guidance do not account for the contribution of endogenous T_4. Testing by Abbott Laboratories has demonstrated that using the February 2001 Guidance methodology to establish bioequivalence would likely result in FDA approval of generic levothyroxine sodium tablet products that differ in drug content from their reference drugs (at each dose level) by as much as 33%.[3]

At a March 12-13, 2003 meeting of the Pharmaceutical Science Advisory Committee, an FDA Office of Clinical Pharmacology and Biopharmaceutics

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[1] *See* 21 U.S.C. § 533(j)(2)(A)(iv).

[2] *See* February 2001 Guidance, at section III(C).

[3] *See* Abbott Laboratories, Briefing Document: Levothyroxine Bioequivalence, at 1.0, *submitted to* FDA Pharmaceutical Science Advisory Committee Meeting (March 12-13, 2003) (*hereinafter*, "Briefing Document").

Reviewer stated that FDA had accepted Abbott's critique of the February 2001 Guidance methodology regarding correcting for endogenous baseline T_4 levels. As a result, the Reviewer announced that FDA has revised its methodology for establishing bioequivalence to include such a baseline correction (the "Revised Methodology"). As Abbott's study has shown, however, even with several attempts to correct for endogenous baseline T_4 levels, the Revised Methodology cannot distinguish between products that differ in drug content by as much as 12.5%.[4]

Even a 12.5% differentiation, let alone a possible 33% differentiation, in treatment dose can lead to significant adverse consequences for patients. Physicians have found that precise and small dose adjustments of as little as 12 mcg are critical for establishing optimal patient outcomes.[5] In addition, thyroid stimulating hormone (TSH) levels, the true indicator of thyroid hormone imbalance, are highly sensitive to changes in T_4 and T_3 levels and to the rate of change in serum T_4. In a prospective, longitudinal study, Carr, et al. demonstrated that changes from optimum dose of as little as 25 mcg can render a patient hyperthyroid or hypothyroid.[6]

As a result, FDA must refrain from accepting or approving ANDAs or supplemental ANDAs using either the February 2001 Guidance's methodology or the Revised Methodology to establish bioequivalence. In addition, FDA must develop new acceptable criteria for bioequivalence in levothyroxine sodium tablet products. Such a methodology must be capable of distinguishing between drug products that differ by as little as 12.5% in drug content and by rate of absorption and total body distribution. Jones therefore requests that FDA stay approval or acceptance for filing of any ANDA or supplemental ANDA for levothyroxine sodium tablet products that attempts to establish bioequivalence to any reference listed drug through use of the February 2001 Guidance methodology or the Revised Methodology. This stay must remain in effect until such time as (a) FDA has convened a joint meeting of the Pharmaceutical Science Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee to consider appropriate methodologies for establishing bioequivalence, (b) FDA has established a new bioequivalence methodology consistent with this Petition, and (c) bioequivalence studies in accordance with that new methodology have been submitted.

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[4] *See id.*

[5] *See, e.g.*, Comments of Dr. Leonard Warofsky, M.D., March 12-13, 2003 meeting of the Pharmaceutical Science Advisory Committee.

[6] Carr D, et al. Fine adjustment of thyroxine replacement dosage: comparison of the thyrotropin releasing hormone test using a sensitive thyrotropin assay with measurement of free thyroid hormones and clinical assessment. *Clin. Endocrinol (Oxf)* 1988; 28:325-333.

III. Complete Statement of Grounds

A. Levothyroxine Sodium Tablets and Hypothyroidism

Hypothyroidism is a condition wherein the human thyroid gland does not produce sufficient amounts of endogenous T_4 and T_3. A portion of the glandular secretion of T_4 (or that absorbed from oral administration) is converted in the liver and pituitary gland to the active hormone T_3. These two thyroid hormones are then responsible for several critical biological functions including stimulation of cellular oxygen consumption, transcription of critical developmental genes, brain development, cardiac muscle function, and regulation of cholesterol levels.[7] Estimates of potency indicate that T_3 is from 3 to 10 times more active in regulating cell metabolism than T_4, the later serving as a prohormone.[8]

Thyroid hormones (both T_4 and T_3) are produced by the thyroid gland, which in turn is regulated by a feedback loop system. The thyroid gland produces both T_4 and T_3 when stimulated by TSH. Serum levels of T_4 are active on the pituitary gland and after intracellular conversion to T_3 regulate both the synthesis and secretion of TSH in a negative feedback manner , i.e. increasing levels of serum T_4 cause decreasing TSH production.[9] Patients suffering from hypothyroidism do not produce sufficient T_4 and T_3 and as a result the pituitary feedback is deficient and serum TSH levels rise in a characteristic and diagnostic manner. Patients suffering from hyperthyroidism, by contrast, produce excessive amounts of T_4 and T_3 resulting in feedback suppression and diagnostically low levels of TSH. [10]

TSH production is highly responsive to small changes in serum levels of T_3 and T_4. For every two-fold change in free T_4 levels, for instance, TSH levels change 100-fold.[11] As a result, diagnosis of hyperthyroidism or hypothyroidism rests not on a measurement of plasma T_4 or T_3, but on the much more sensitive plasma TSH measurements.[12]

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[7] *See* Briefing Document, at 2.0.

[8] *See* Irwin Klein, M.D., *Disorders of the Thyroid*, at 1325, *in* Internal Medicine (Jay H. Stein, M.D., ed., Mosby 1998).

[9] *See* Briefing Document, at 2.0.

[10] *See id.*

[11] *See id.*

[12] *See* Irwin Klein, M.D., *Evaluation of Bioequivalence and Efficacy of L-thyroxine Preparations in the Treatment of Human Thyroid Disease*, February 7, 2003, at 4.0, *submitted to* FDA Pharmaceutical Science Advisory Committee Meeting (March 12-13, 2003).

Hypothyroidism is treated through thyroid hormone replacement therapy. Levothyroxine sodium tablets are the primary means of introducing replacement T_4 into the bloodstream. Dose levels are adjusted through monitoring of TSH levels until TSH levels are moved into the "normal" range.[13] There are currently seven levothyroxine sodium tablet products approved by FDA. Each comes in twelve different dosage strengths ranging from 25 mcg to 300 mcg.

B. Statutory and Regulatory Background: Bioequivalence

Pursuant to Section 505(j)(2)(A)(iv) of the FDCA, any ANDA must contain, among other things, information demonstrating that the generic drug is bioequivalent to the reference listed drug.[14] The Act further states that, for purposes of an ANDA, bioequivalence is established if:

> the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.[15]

The statute defines "bioavailability" as "the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action."[16] As a result, generic drugs often attempt to establish bioequivalence through what is essentially a showing of equivalent bioavailability to the reference listed drug. FDA's regulations appear to sanction this approach stating:

> Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose.[17]

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[13] *See id.*

[14] *See* 21 U.S.C. § 533(j)(2)(A)(iv).

[15] 21 U.S.C. § 533(j)(8)(B)(i).

[16] 21 U.S.C. § 533(j)(8)(A).

[17] 21 C.F.R. § 320.23(b).

C. FDA's February 2001 Guidance

FDA's February 2001 Guidance establishes criteria for testing bioavailability and dose-form proportionality of levothyroxine sodium tablet formulations in NDAs. The Guidance calls for a crossover study of healthy volunteers comparing a 600 mcg dose of the test compound to a 600 mcg dose of the reference listed compound. Mean plasma/serum concentration-time profiles of T_4 and T_3 are measured to determine bioavailability.[18] Dose-form proportionality is assessed through analysis of log-transformed AUC_{0-t} and C_{max}. Dose-form proportionality is established if the 90 percent confidence intervals fall within the 80% to 125% range.[19]

Because the February 2001 Guidance establishes FDA-sanctioned procedures for assessing bioavailability and dose-form proportionality for levothyroxine sodium tablets in NDAs, some manufacturers initially believed that FDA would permit generic drug manufacturers to use that methodology to establish bioequivalence with a reference listed levothyroxine sodium tablet product. As is discussed below, however, that methodology was not intended to, and is incapable of, accurately measuring bioequivalence among levothyroxine sodium tablet products. Use of the February 2001 Guidance to establish bioequivalence would lead to FDA approval of generic drug products that may differ from their reference drugs in overall drug content by as much as 33% at each dose level.

D. The February 2001 Guidance Methodology Is not Sufficiently Sensitive to be Used to Establish Bioequivalence Among Levothyroxine Sodium Tablet Products

The February 2001 Guidance methodology calls for testing in healthy volunteers. Such healthy volunteers possess varying levels of endogenous baseline T_4.[20] This potentially confounds bioequivalence testing. Thyroid replacement therapy in healthy volunteers can be expected to reduce TSH production in the pituitary that is already producing T_4. This reduction in TSH can lead to a reduction in thyroid production of endogenous T_4.[21] A recent study conducted by Abbott Laboratories confirms this fact.

In its study, Abbott sought to determine if the February 2001 Guidance's methodology for establishing bioavailability and dose-form proportionality could be used to establish bioequivalence between a generic levothyroxine sodium tablet product and its reference listed drug.[22] Abbott's study design was a single-dose, open label

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[18] *See* February 2001 Guidance, at section III.

[19] *See id.*

[20] *See* Klein, *supra* note 12, at 6.0.

[21] *See id.*

[22] *See* Briefing Document, at Appendix A.

study, conducted with healthy volunteers with a three-period, randomized cross-over.[23] The three regimens employed doses of 600 mcg, 450 mcg, and 400 mcg, respectively, of Synthroid®, an approved levothyroxine sodium tablet. Abbott employed a washout period of at least 44 days between the three study periods.[24] Abbott then collected blood samples for total T_4, T_3, and TSH assays and determined serum concentrations of T_4 and T_3. In its first set of tests, as per the February 2001 Guidance's established methodology, Abbott did not correct for baseline endogenous T_4.[25]

Abbott's results demonstrate that using the February 2001 Guidance methodology to demonstrate bioequivalence would likely lead FDA to find two drug products to be bioequivalent even though they differed in drug content by as much as 33%. For each of the comparator pairs (450 mcg/600 mcg, 400 mcg/600 mcg, and 400 mcg/450 mcg), the 90% confidence intervals from the analysis of natural logarithms of C_{max} and AUC_{48} fell within the 80% to 125% range.[26] Thus, the February 2001 Guidance methodology was unable to distinguish between a 600 mcg dose and a 400 mcg dose. This represents a difference of 33%. Indeed, the 90% confidence interval for the 400 mcg/600 mcg comparator pair was 0.890 - 0.968 for C_{max} and 0.927 - 0.982 for AUC_{48}, respectively, suggesting that even larger disparities are possible.[27]

The costs of such imprecise measurements would be borne by patients. Dosing for thyroid replacement therapy is precise and is measured in small doses. Most approved levothyroxine sodium tablet products come in twelve different dose strengths ranging from 25 to 300 mcg with prescribed doses typically beginning at a lower dose and increasing in small increments until normal TSH levels are achieved.[28] If generic products are approved using the February 2001 Guidance methodology, however, a patient receiving a 100 mcg dose of a generic product could actually be getting the equivalent of a 75 mcg dose of its reference listed drug. This level of variance puts patients at significant risk for atrial fibrillation, altered lipid levels, cardiac contractility, and accelerated atherosclerosis.[29]

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[23] *See id.*

[24] *See id.*

[25] *See id.*

[26] *See id.*, at 3.2.1.

[27] *See id.*

[28] *See* Klein, *supra* note 12, at 6.0; Briefing Document, at 4.2. The very availability of multiple product presentations that increase in dosage strength incrementally by only 12-13 mcg within the 75-150 mcg product range is indicative of the importance of precise titration for these narrow therapeutic index drug products.

[29] *See* Klein, *supra* note 12, at 6.0.

E. Even With its Correction for Endogenous T_4, the Revised Methodology Still Leads to Unacceptable Variances Between a Generic and its Reference Listed Drug

During the March 12-13 meeting of the Pharmaceutical Science Advisory Committee, an FDA Office of Clinical Pharmacology and Biopharmaceutics Reviewer stated that FDA had accepted Abbott's critique of the February 2001 Guidance methodology regarding correcting for endogenous baseline T_4 levels. He announced, therefore, that FDA now maintains that bioequivalence can be established in levothyroxine sodium tablet products using the methodology set forth in the February 2001 Guidance with a correction for endogenous baseline T_4 (i.e., the Revised Methodology).[30] As discussed below, however, Abbott's study has already shown that even this Revised Methodology is an inadequate measure of bioequivalence because it is incapable of distinguishing between drug products that differ in drug content by as much as 12.5%.

In a second phase of the Abbott study, Abbott employed three different corrections for baseline endogenous T_4 levels in healthy volunteers. Although the 400 mcg/600 mcg and 450 mcg/600 mcg pairs no longer fell within the 80% to 125% range, the Revised Methodology remained incapable of distinguishing between a 400 mcg dose and a 450 mcg dose. The 90% confidence interval for the 400 mcg/450 mcg comparator pair remained within the 80% to 125% range for all three methods of correcting for baseline endogenous T4.[31] Thus, even with correction for baseline endogenous T_4, FDA's Revised Methodology is incapable of discerning between products that differ in drug content by 12.5%.

Even a 12.5% difference in drug content can have serious consequences for patients moved from a currently approved product to a presumed to be generically equivalent form. As discussed above, initial prescribed doses of levothyroxine sodium tablet products typically start at a lower dose and are gradually increased in 12 mcg increments until normal TSH levels are reached.[32] Currently approved levothyroxine sodium tablet products come in twelve dose strengths. Three of these dose strengths (88 mcg, 100 mcg, and 112 mcg) differ from one another by less than 12.5%. Thus a patient with doses carefully titrated to 100 mcg to establish normal TSH levels and then switched to a "100 mcg" dose strength of a generic product that utilized the Revised Methodology to establish bioequivalence may actually be receiving the functional equivalent of an 88 mcg or 112 mcg dose. This level of variance could lead to

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[30] FDA also indicated that the Revised Methodology will not consider comparative T_3 measurements in establishing bioequivalence because T_3 is a metabolite of T_4.

[31] *See* Briefing Document, at Appendix A.

[32] *See* Klein, *supra* note 12, at 6.0; Briefing Document, at 4.2.

artificially created hyperthyroidism or hypothyroidism requiring that the patient be put through repeated dose adjustments until normal TSH levels are re-achieved.[33]

Leading physicians and endocrinologists have stressed the importance of such small dose increments. At the March 12-13, 2003 meeting of the Pharmaceutical Science Advisory Committee, for example, Leonard Wartofsky, M.D. noted testimony during the public participation stage of the proceeding. He pointed to testimony from medical professionals representing "hundreds of years of clinical experience from senior members of the Endocrine Society and the American Thyroid Association, seeing tens of thousands of patients and seeing the importance of these minor 12.5 microgram differences that were alluded to."[34] One of the several physician presenters discussed her personal experience with the frequent need to make small dose adjustments in order to maker her patients feel better. Clearly, any test for bioequivalence must be capable of distinguishing between these significant 12 mcg dose levels.

F. The Revised Methodology Does not Adequately Account for the Presence of T_3 in Levothyroxine Sodium Tablet Drug Products

During the March 12-13, 2003 meeting of the Pharmaceutical Science Advisory Committee, FDA stated that the Revised Methodology will not consider comparative T_3 measurements in establishing bioequivalence because T_3 is a metabolite of T_4. This further compromises the ability of the Revised Methodology to adequately establish bioequivalence.

The current USP monograph (USP25-NF20, 2002) allows for up to 2.0% content of T_3 in levothyroxine sodium tablets. Because T_3 is the active form of the hormone, any methodology for establishing bioequivalence between such drug products must also take into consideration comparative measurements of serum T_3 after dosage to more completely assess equivalence of drug products used in thyroid hormone replacement therapy.

IV. Conclusion

As a result of Abbott's findings, it is clear that neither the February 2001 Guidance methodology nor the Revised Methodology can be used to establish bioequivalence in generic levothyroxine sodium tablet products. Neither of these designs are capable of distinguishing between fine dose levels critical for effective patient management. FDA must therefore refrain from approving or accepting ANDAs or supplemental ANDAs for filing until such time as it has established an effective methodology for establishing bioequivalence for levothyroxine sodium tablet products. FDA must establish this methodology with the assistance of a joint meeting of the

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[33] *See* Klein, *supra* note 12, at 6.0; Briefing Document, at Appendix A.

[34] *See* Comments of Dr. Leonard Warofsky, M.D., March 12-13, 2003 meeting of the Pharmaceutical Science Advisory Committee.

Pharmaceutical Science Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee. The new methodology must take into account the need for precise dose titration in hypothyroid and hyperthyroid patients in small, generally 12 mcg, increments. FDA must then accept only those ANDAs and supplemental ANDAs that follow this new bioequivalence methodology.

There are several possible ways to accomplish this goal. FDA should consider, among other things, narrowing the confidence interval for bioequivalence testing of levothyroxine sodium tablet drug products. It may also consider requiring bioequivalence testing in athyrodic patients. Studies involving such patients would not present the complications raised by endogenous baseline T_4 levels. FDA might also consider testing TSH levels and T_3 levels in addition to or in lieu of T_4 levels. Although each of these approaches may contain flaws, FDA's current methodology is clearly unacceptable.[35]

At the March 12-13, 2003 meeting of the Pharmaceutical Science Advisory Committee, FDA's Supervising Pharmacist of the Division of Bioequivalence stated that the purpose of the bioequivalence requirement for generic drugs is to insure therapeutic equivalence between a generic and its reference listed drug. As clearly demonstrated above, the variances in functional dose strength between a generic and its reference listed drug resulting from use of the February 2001 Guidance methodology or the Revised Methodology to establish bioequivalence would not promote therapeutic equivalence. While such methodologies might be appropriate for drug products for which precise, small increment dose titration is not necessary, they are not appropriate where, as here, such precise adjustments are critical for patient care. Where FDA's methods for establishing bioequivalence fall short of ensuring therapeutic equivalence, to the detriment of patients, FDA has a duty to establish more precise requirements for bioequivalence testing.

V. Irreparable Harm

If FDA does not grant Jones' request for stay in this matter, Jones will suffer irreparable harm in several respects. Approval of a generic levothyroxine sodium tablet product will result in loss of market share for Jones. It will also create confusion in the marketplace for Jones' product as physicians begin prescribing the generic and patients become aware of its existence. It will not be possible for Jones to recoup this market share even if such a generic is withdrawn from the market after FDA or a court

[35] FDA's Guidance for Industry: *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations*, acknowledges the need for such additional testing in narrow therapeutic range drugs. That guidance states, "[t]his guidance recommends that sponsors consider additional testing and/or controls to ensure the quality of drug products containing narrow therapeutic range drugs. The approach is designed to provide increased assurance of interchangeability for drug products containing specified therapeutic range drugs."

determines that the approval was in error. Patients and physicians, now accustomed to the presence of generic alternatives will not immediately, if at all, move back to Jones' product. Even a temporary loss of market share could have significant economic consequences for the Company.

Approval of a generic levothyroxine sodium tablet product that is not actually bioequivalent to its reference listed drug will lead to a loss of goodwill among patients for Jones' product. Within four to six weeks, some patients switched from reference listed drugs to generic products that established bioequivalence via the Revised Methodology will likely experience adverse clinical responses due to the 12.5% differentiation in actual drug content. These adverse patient outcomes will result in a permanent loss of patient confidence in Jones' product and a resulting loss of sales. This loss in consumer confidence will not be corrected by a later withdrawal of the generic products.

The public interest also favors granting of a stay in this case. The confusion in the marketplace that would be generated from first the appearance, and then disappearance of generic drug products would complicate treatment of a serious medical condition. Furthermore, as discussed in detail above, some patients switched to generic products that may differ in drug content by as much as 12.5% at each dose level from their previous therapy will likely suffer adverse consequences such as atrial fibrillation even if the generic products are removed after a short period of time.[36]

VI. Required Material

A. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R. §§ 25.30 & 25.31(a).

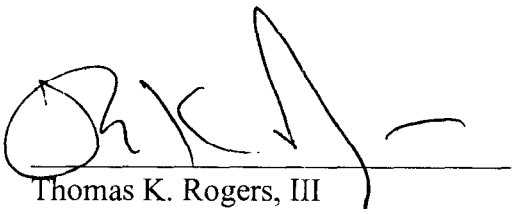
B. Economic Impact

An economic impact statement will be submitted at the request of the Commissioner.

[36] *See* Klein, *supra* note 12, at 6.0.

C. 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 petitioner which are unfavorable to the petition.



Thomas K. Rogers, III

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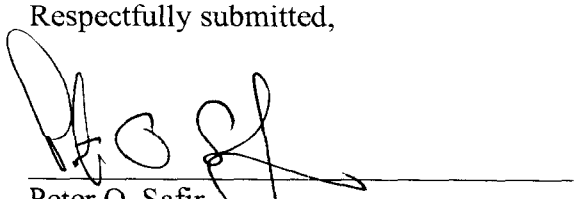
Respectfully submitted,



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