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**DECLARATION OF BRYAN R. HAUGEN, M.D.**

**In Support of the Citizen Petition of Abbott Laboratories  
Docket No. 2003P-0387/CP1**

Bryan R. Haugen, M.D., under penalty of perjury, declares as follows:

1. I am an Associate Professor of Medicine and Pathology and the Assistant Chief of the Division of Endocrinology, Diabetes and Metabolism at the University of Colorado Health Sciences Center in Denver, Colorado ("Health Sciences Center"). I am the Director of the Quantitative RT-PCR Core Laboratory at the University of Colorado Cancer Center. I also am the Director of the University's Thyroid Tumor Program and Associate Director for the General Clinical Research Center. I have previously served at the Health Sciences Center as an Instructor in Medicine, Assistant Professor of Medicine, and Assistant Professor of Pathology.

2. I am a member of the American College of Physicians, the Western Society for Clinical Investigation, the Endocrine Society, and the American Thyroid Association ("ATA"). Since 1992, I have been a member of the National Thyroid Cancer Treatment Cooperative Study group.

3. Since 1998, I have served on the Editorial Board for the journal *Thyroid*, an ATA-sponsored publication. Since 2001, I have served on the Editorial Board for the *Journal of Clinical Endocrinology and Metabolism*. I also have performed editorial reviews for numerous publications, including: *Annals of Internal Medicine*, *Journal of Clinical Investigation*, *Molecular Endocrinology*, *Endocrinology*, and *Neuroendocrinology*. I have 31 peer-reviewed publications, eight invited articles, and five book chapters, most related to pituitary-thyroid function and thyroid cancer. My curriculum vitae is attached at Tab 1.

4. My clinical area of expertise is endocrinology. In 1993, I completed a fellowship in Endocrinology, Diabetes and Metabolism and have focused my clinical practice and research on pituitary-thyroid disorders and thyroid tumors. I attend a weekly Endocrinology clinic in which I primarily see patients with thyroid disorders and thyroid tumors, as well as teach residents and fellows. I also attend a monthly Thyroid Oncology clinic, which is a multidisciplinary clinic for patients with advanced thyroid and other endocrine cancers. As the Director of the Thyroid Tumor Program, my colleagues and I follow more than 800 patients with thyroid cancer, review pathology and patient management at a weekly conference, and present challenging thyroid cancer patients at a monthly teaching conference.

#### Thyroid Cancer

5. Thyroid cancer (or "carcinoma") is the most common form of endocrine cancer. In the United States alone, there are more than 20,000 new patients diagnosed with thyroid cancer annually.

6. The most important indicator of thyroid cancer is a lump or nodule found in the thyroid gland. Most patients with thyroid cancer do not exhibit any symptoms.

7. Thyroid cancer can occur in any age group, although it is most common after age 40, and its aggressiveness increases significantly in older patients. Women are more likely than men to have thyroid cancer, by a ratio of 3 to 1. Thyroid cancer is more common in people with a history of exposure of the thyroid gland to radiation, people with a family history of thyroid cancer, and people over 40 years of age. For the majority of patients, however, the cause of thyroid cancer is unknown.

8. There are four different types of thyroid cancer: Papillary, follicular, medullary and anaplastic.

9. The most common type of thyroid cancer is papillary, which is found in 70 to 80% of all thyroid cancer patients. About 1 in 1,000 patients in the United States have or have had this form of thyroid cancer. The peak onset of papillary carcinoma is between ages 30 and 50. Papillary carcinoma typically arises as an irregular, solid, or cystic mass from otherwise normal thyroid tissue. Cervical metastasis -- in which the cancer spreads to nodes in the neck -- is present in 50% of small tumors and in over 75% of larger ones. Distant metastasis -- in which the cancer spreads beyond the nodes in the neck -- is uncommon, but the lungs and bones are the most common sites. The prognosis for papillary carcinoma is directly related to the size of the tumor, invasion outside of the thyroid gland, and presence of distant metastases.

10. Follicular carcinoma is the second most common thyroid cancer. Follicular carcinoma is considered more malignant (*i.e.*, aggressive) than papillary carcinoma. The peak onset of follicular carcinoma is between ages 40 and 60. Distant metastasis is more common than in papillary thyroid cancer -- the lungs, bones, brain, and other organs are potential sites of distant spread. As with papillary thyroid cancer, the prognosis for follicular thyroid cancer is directly related to the size of the tumor, invasion outside of the thyroid gland, and presence of distant metastases.

11. Medullary carcinoma is the third most common thyroid cancer. Unlike papillary and follicular thyroid cancer, which originates from cells that produce thyroid hormone, medullary cancer comes from the parafollicular cells of the thyroid gland (*i.e.*, the "C" cells). Distant metastasis can occur in the liver, bones, brain, and other organs.

12. Anaplastic tumors are the least common, but the most deadly, thyroid cancer. The peak onset for anaplastic thyroid cancer is at age 65 and older. Cervical metastasis occurs in the vast majority (over 90%) of patients at the time of diagnosis, and distant metastasis to the lungs is present in over 50% of patients at the time of diagnosis.

### **Treatment of Thyroid Cancer**

13. The primary therapy for all forms of thyroid cancer is surgery. The generally accepted approach is to remove the entire thyroid gland, or at least as much of it as can safely be removed. After surgical removal of the thyroid gland, radioactive iodine can be used in many patients with papillary and follicular carcinoma to destroy all remaining thyroid cells (normal and cancerous).

14. After removal of the thyroid gland, patients must take synthetic thyroid hormone (levothyroxine) for life.

15. Also after surgery, patients must attend periodic follow-up examinations to check whether the cancer has returned (even after many years). Such examinations include a thorough physical and a blood test to determine whether any change in the patient's levothyroxine dosage is necessary. In particular, clinicians rely on serum thyroid stimulating hormone ("TSH") levels to adjust levothyroxine dosing, and monitor a thyroid cell protein called thyroglobulin, which serves as a cancer marker. The levothyroxine dose is adjusted to lower the TSH level into a very narrow range below normal. If the thyroglobulin level is detectable even when the patient's TSH levels are low, that means there are still potential thyroid cancer cells in the body.

16. Patients with thyroid cancer have another unique levothyroxine dosing requirement: TSH can stimulate the growth of thyroid cancer. These patients, therefore, need to take a precise amount of levothyroxine in order to suppress serum levels of TSH. Chronic excess levothyroxine, however, can lead to complications, including reduced bone mass (osteoporosis) and heart function abnormalities (alterations in cardiac function and rhythm abnormalities). It is thus critical to determine the precise amount of levothyroxine to give a patient and monitor the patient regularly to make sure the serum TSH is slightly below normal, but not oversuppressed. See, e.g., Pujol P et al., *Degree of Thyrotropin Suppression as a Prognostic Determinant in Differentiated Thyroid Cancer*, J. Clin. Endocrinol. Metab. 81:4318-23 (1996) (attached at Tab 2).

17. Careful dosing of levothyroxine in accordance with each individual patient's unique requirements prevents the development of persistent hypothyroidism and decreases the likelihood of cancer recurrence. Patients with thyroid cancer require the correct amount of levothyroxine to avoid symptoms and complications of excess or insufficient thyroid hormone, just as patients with primary hypothyroidism require accurate levothyroxine dosing.

18. In my clinical experience, even variations in the dose of levothyroxine of as little as 12.5% can move the serum TSH level out of the narrow target range in patients with thyroid cancer, thereby putting these patients at risk for long-term complications. For this reason, I would not consider two manufacturers' levothyroxine products that differ in dose by such an amount to be clinically or therapeutically equivalent.

Dated:

Denver, Colorado  
February 5, 2004



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Bryan R. Haugen, M.D.

