VIA EMAIL

August 6, 2025

NAME
FIRM
ADDRESS
EMAIL

RE: _____

Dear Manufacturers, Importers, and Distributors of Animal-Derived Thyroid Products:

The Food and Drug Administration (FDA or we) intends to take action against marketed unapproved animal-derived thyroid (ADT) products (sometimes described as desiccated thyroid extract (DTE) products). ADT products require an approved biologics license application (BLA) under section 351 of the Public Health Service (PHS) Act in order to be legally marketed in the U.S. (42 U.S.C. 262(a)(1)). There are no FDA-approved BLAs for the ADT products currently on the market.

As described in more detail below, FDA intends to take action against marketed unapproved ADT products. To provide notice to manufacturers, importers, and distributors, we are issuing this letter. This notice also serves to promote compliance with FDA's premarket approval requirements. In addition, the timing further discussed below is intended to provide patients currently using these products sufficient time to work with their healthcare providers to transition to an FDA-approved thyroid hormone replacement product.

BACKGROUND

Overt hypothyroidism, a condition of decreased thyroid hormone production from the thyroid gland, affects approximately 2% of the adult population in the U.S.[1] Thyroid hormone replacement products treat hypothyroidism by replacing the hormones that patients need to

[1] Wyne KL et al, 2022, Hypothyroidism Prevalence in the United States: A Retrospective Study Combining National Health and Nutrition Examination Survey and Claims Data, 2009–2019, J Endocr Soc, 7(1): bvac172.

maintain normal circulating thyroid hormone levels and thereby prevent or improve symptoms of hypothyroidism, such as fatigue, weight gain, constipation, cold intolerance, or depressed mood, among others. In general, thyroid hormone replacement products have a narrow therapeutic index, meaning that tight dose regulation is needed to maintain circulating thyroid hormone levels within a narrow therapeutic range.[2]

ADT products were the first pharmacological treatments developed for replacement or supplemental therapy in patients with hypothyroidism and have been in use for this purpose since the late 19th century.[3,4] ADT is a naturally derived mixture from animal thyroid glands. Initially, these products were derived from bovine (cow), ovine (sheep), or porcine (pig) thyroid glands, but currently most ADT products are porcine-derived thyroid extracts.

ADTs are no longer the predominant source of thyroid hormone replacement. Synthetic liothyronine sodium (LT3 or synthetic liothyronine) and synthetic levothyroxine sodium (LT4 or synthetic levothyroxine) became commercially available following FDA approval in 1956 and 2002, respectively.[5,6] These synthetic products provide an approved safe and effective alternative to ADT products for treatment of hypothyroidism. In 2024, approximately 94% of the 24 million patients receiving thyroid hormone replacement were prescribed synthetic levothyroxine sodium, while only 6% (1.5 million patients) received unapproved ADT products.[7] FDA is unaware of any studies demonstrating the safety and effectiveness of ADT products, meaning the benefits and risks of treatment with ADT products have not been adequately assessed.

Certain safety and effectiveness concerns about unapproved ADT products guided current recommendations by professional medical societies and shifted prescribing practices. These concerns include inconsistent potencies from batch to batch of the unapproved ADT products, the

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[2] FDA, Guidance for Industry: Levothyroxine Sodium Tablets – In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing (December 2000). FDA guidances are available on the FDA guidance web page. FDA updates guidances periodically. To make sure you have the most recent version of a guidance, check the guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] FDA, Older Therapies Aren't Necessarily Better for Thyroid Hormone Replacement, https://www.fda.gov/consumers/consumer-updates/older-therapies-arent-necessarily-better-thyroid-hormone-replacement.

[4] Connelly KJ, Park JJ, and LaFranchi SH, 2022, History of the Thyroid, Horm Res Paediatr, 95(6): 546-556.

[5] NDA 010379. Drugs@FDA: FDA-Approved Drugs; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=010379.

[6] NDA 021402. Drugs@FDA: FDA-Approved Drugs; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021402.

[7] Symphony Health. Metys. Data extracted February 2025. Percentages shares may sum to more than 100 percent due to patients who may have received more than one product category in a calendar year.

potential for viral contamination due to the animal source, and supraphysiological levels of the thyroid hormone triiodothyronine (T3) provided by the ADT products, which may result in symptoms of hyperthyroidism.[8,9,10,11,12,3,13]

LEGAL AND REGULATORY HISTORY

ADT products meet the definition of a "biological product" in section 351(i)(1) of the PHS Act (42 U.S.C. 262(i)(1)) because ADT (the drug substance) is a "protein" or because it is "analogous" to a protein. FDA's regulations define "protein" to mean "any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size" (21 C.F.R. 600.3(h)(6)). ADT is derived from animal (usually porcine) thyroid glands and is a naturally derived mixture that necessarily contains thyroglobulin, an alpha amino acid polymer with a specific defined sequence consisting of 2,770 amino acids. In animal thyroid preparations such as porcine-derived ADT, the thyroid hormones T3 and thyroxine (T4) are incorporated into the thyroglobulin by peptide bonds, and ADT also may contain free T3 and free T4.[14] Following oral administration of an ADT tablet, for example, the proteolytic enzymes of the gastrointestinal tract release iodothyronines and iodotyrosines (including T3 and T4) from the thyroglobulin.[10] ADT that is composed primarily of protein components (e.g., thyroglobulin) is a "biological product" because it falls within the Agency's interpretation of the statutory term "protein" (see 21 C.F.R. 600.3(h)(6)).

Alternately, ADT is "analogous" to a protein, and, thus, a "biological product" because it includes an identified biological product component (i.e., thyroglobulin) that is necessary for the activity of the product and contributes to achieving the intended therapeutic effect and also may include identified non-biological product components (e.g., free T3 and free T4) that can contribute to the product's activity.

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[8] Jackson IM and Cobb WE, Why does anyone still use desiccated thyroid USP?, 1978 Am J Med 64(2): 284-288.
[9] Penny R and Frasier SD, 1980, Elevated serum concentrations of triiodothyronine in hypothyroid patients. Values for patients receiving USP thyroid, Am J Dis Child. 134(1): 16-18.
[10] LeBoff MS et al, 1982, Bioavailability of thyroid hormones from oral replacement preparations, Metabolism 31(9): 900-905.
[11] Lev-Ran A, 1983, Part-of-the-day hypertriiodothyroninemia caused by desiccated thyroid, JAMA 250(20): 2790-2791.
[12] MI Surks et al, 1972, A new radioimmunoassay for plasma L-triiodothyronine: measurements in thyroid disease and in patients maintained on hormonal replacement, J Clin Invest. 51(12): 3104-3113.
[13] Jonklaas J et al, 2014, Guidelines for the Treatment of Hypothyroidism: Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement, Thyroid 24(12): 1670-1751.
[14] Idrees T et al, 2020, Liothyronine and Desiccated Thyroid Extract in the Treatment of Hypothyroidism, Thyroid 30(10): 1399-1413.

Although the majority of therapeutic biological products have been licensed under the PHS Act, some protein products historically had been approved under section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act. On March 23, 2010, the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) clarified the statutory authority under which certain products would be regulated by amending the definition of a "biological product" in section 351(i) of the PHS Act to include a "protein" (and products "analogous" to a protein) and describing procedures for submission of a marketing application for certain biological products. As of March 23, 2020, all sponsors seeking approval of a biological product that previously could have been submitted under section 505 of the FD&C Act, including ADT products, must submit a marketing application (i.e., a BLA) under section 351 of the PHS Act.

ADT products marketed without a biologics license under the PHS Act are unapproved biological products. This includes ADT products that are prepared by a licensed pharmacist in a state-licensed pharmacy or a federal facility, a licensed physician, or an outsourcing facility. Biological products subject to licensure under section 351 of the PHS Act are not eligible for the exemptions for compounded drugs under sections 503A and 503B of the FD&C Act, nor is there an exemption under section 351 of the PHS Act from the requirement to have an approved BLA.[15]

SAFETY, EFFECTIVENESS, AND QUALITY CONCERNS WITH UNAPPROVED ADT PRODUCTS

Unlike approved biological products, unapproved ADT products currently on the market have not undergone FDA's premarket evaluation, which involves, among other things, an assessment of manufacturing processes and controls, evaluation of labeling, and examination of ADT supplier suitability. Unapproved ADT products have presented issues with potency, content uniformity, labeling, and impurities identified through inspections, sampling, and patient complaints. These products pose unique risks compared to synthetic thyroid drug products because they are derived from animal thyroid glands, potentially containing process-related impurities, elemental impurities, and ADT-unique impurities (e.g., organic iodine and inorganic iodide) and contaminants (e.g.,

[15] For additional discussion of FDA policies pertaining to the mixing, diluting, and repackaging of approved biological products, see FDA's Guidance for Industry: Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application (January 2018). This guidance is currently available at https://www.fda.gov/media/90986/download. FDA updates guidances periodically. To make sure you have the most recent version of a guidance, check the guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents

viruses and other objectionable microbes). The potency and bioavailability of unapproved ADT products can be highly variable both between batches and within batches, creating uncertainty about the quantity of active hormones delivered, which is particularly concerning given the narrow therapeutic index for thyroid replacement therapies where minor dose changes can lead to serious adverse effects.

Since late 2017, FDA inspections of ADT manufacturers, ADT product manufacturers, and ADT product distributors have identified significant current good manufacturing practice (CGMP) violations, resulting in warning letters, an import alert, and recalls due to issues including, but not limited to: inadequate quality unit oversight, lack of stability data to support labeled expiration dates, failure to investigate out-of-specification results, and manufacturing processes not operating in a state of control. FDA is aware of over 500 adverse event reports associated with ADT products from 1968 through February 2025, with a substantial increase between 2019-2020 that may have been related to several voluntary recalls of subpotent or superpotent ADT products.

Additionally, unapproved ADT products have inconsistent labeling that does not comply with regulatory standards, with some products including the non-metric unit of measurement of “grain” and using different measurements for one "grain" (ranging from 60 mg to 65 mg), creating confusion and potential dosing errors that FDA premarket review could prevent.

RISK-BASED PATIENT TRANSITION PERIOD

FDA understands that a significant number of patients currently take unapproved ADT products. We believe it will require up to 12 months to safely transition patients to an FDA-approved thyroid hormone replacement product. FDA intends to provide adequate time to transition patients to an FDA-approved thyroid hormone replacement product before initiating action against manufacturers, distributors, and importers of ADT and unapproved ADT products intended for commercial distribution. During this time, FDA will continue to apply a risk-based enforcement policy.[16]

It is your responsibility to ensure that your firm complies with all applicable requirements of

[16] See 85 FR 75331 (Nov. 25, 2020) and 86 FR 28605, 28608 (May 27, 2021) (“FDA will continue to exercise its existing general approach to prioritizing regulatory and enforcement action [for marketed unapproved new drugs], which involves risk-based prioritization in light of all the facts of a given circumstance.”).

federal law and FDA regulations. Within 30 working days from the date of receipt, please acknowledge receipt of this letter by emailing FDAADVISORY@fda.hhs.gov. Please include your firm name and the unique identifier "_____" in the subject line of the email.

Sincerely,

U.S. Food and Drug Administration

U.S. Food and Drug Administration
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