abbvie

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Division of Dockets Management (HFA-305)
Food and Drug Administration Department
of Health and Human Services
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Citizen Petition

AbbVie Inc. (AbbVie) respectfully submits this Citizen Petition pursuant to 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs take the actions set forth below with respect to unlicensed desiccated thyroid extract (DTE) products. AbbVie is the manufacturer of Armour Thyroid® (thyroid tablets, USP), an unlicensed DTE product that has been used in the United States since the early 1900s to manage hypothyroidism and other thyroid conditions.[1]

Action Requested

AbbVie requests that the U.S. Food and Drug Administration (FDA or the Agency) prohibit manufacturers who lack active investigational new drug applications (INDs) and robust clinical development programs from commercializing unlicensed DTE products. We also request that the Agency stop DTE manufacturers from promoting and making false and misleading statements about their unlicensed products.

Statement of Grounds

I. Summary

More than a million patients in the United States rely on DTE products to manage hypothyroidism and other thyroid conditions. These products have been marketed for decades, although no DTE available for use today has been approved by FDA.

The Agency has historically considered DTE products to be "new drugs" requiring approved new drug applications (NDAs), but the Agency has also, historically, exercised enforcement discretion with respect to their marketing. Specifically, in a formal published compliance policy, FDA explained how it would permit commercialization of

[1] "AbbVie" also refers to the predecessor Armour Thyroid sponsors Allergan and Forest Laboratories. AbbVie also markets Synthroid (levothyroxine sodium), an approved product containing synthetic levothyroxine (T_4) indicated for treatment of hypothyroidism.

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unapproved drugs based on risk-based priorities for enforcement action, while also encouraging companies to pursue scientific trials to get their products approved.

As discussed below, this compliance policy applied only to drugs subject to the NDA requirement in the Federal Food, Drug, and Cosmetic Act (FDCA). On March 23, 2010, however, DTE products were reclassified as biological products, which made them (as of March 23, 2020) subject instead to the Public Health Service Act's (PHSA's) biologics license application (BLA) requirement. Further, in late 2020, the compliance policy was withdrawn, although FDA has publicly stated since then that it would continue to use its existing risk-based approach to prioritizing regulatory and enforcement actions against unapproved new drugs.

Following these developments, and after more than a decade with no new DTE product entrants, multiple companies in 2023 and 2024 have launched into interstate commerce new (never before marketed) DTE products which lack licensure. These companies do not appear to be seeking licensure and their products are nevertheless promoted directly to patients as equivalent to other DTE products, sometimes as even superior to non-DTE products that FDA has approved to treat hypothyroidism and other thyroid conditions.

Accordingly, FDA now faces a new direct challenge to its new product approval framework regarding the proliferation of unlicensed biological products. The Agency must address this challenge as a matter of public health. Manufacturing DTE products is a complex process, and finished DTE products have a narrow therapeutic range and a patient population requiring accurate dosing. FDA oversight through the IND process is necessary to protect patients taking these medically necessary drugs until FDA licenses a DTE product.

The Agency balanced two goals with its compliance policy for unapproved new drugs: encouraging companies that had been marketing unapproved products (in many cases for decades) to perform the research needed to secure approval, on the one hand, while protecting the public health by removing products that are marketed in direct challenge to the regulatory framework, on the other hand — and achieving both goals without burdening patients or disrupting the market with unnecessary enforcement actions. This Petition asks FDA to achieve these same goals for unlicensed DTE products, mirroring the approaches taken in the 2000s with unapproved pancreatic enzyme products and in the 1990s with unapproved small molecule drugs intended to manage hypothyroidism.

II. Background

A. Desiccated Thyroid Extract (DTE) Products

More than 1,000,000 patients rely on DTE products every day to manage hypothyroidism or another thyroid-related condition.[2] In hypothyroidism, the thyroid gland is underactive and unable to produce a sufficient amount of thyroid hormones. Without enough thyroid hormones, bodily functions slow, resulting in symptoms such as

[2] *E.g.,* certain types of goiters and thyroid cancer.

weight gain, fatigue, constipation, and muscle weakness.[3] The goal of treatment is to replicate normal thyroid functioning.[4]

The main ingredient in DTE products is desiccated, defatted powdered porcine thyroid gland, Thyroid Powder (or Thyroid USP).[5] Thyroid Powder contains the protein thyroglobulin, which is hydrolyzed in the body to yield two thyroid hormones: levothyroxine ($C_{15}H_{11}I_4NO_4$) (also known as T_4) and liothyronine ($C_{15}H_{12}I_3NO_4$) (also known as T_3). These two hormones provide the drug's therapeutic effect. DTE products have a narrow therapeutic range, and proper manufacturing is critical to prevent patients from receiving subpotent or superpotent doses.

For most of the 20th century, DTE products were the mainstay of thyroid hormone replacement therapy. Today, clinical practice guidelines developed by the American Thyroid Association recommend treating hypothyroid patients first with laboratory-made (synthetic) levothyroxine (referred to as L-T_4) products.[6] Most patients respond satisfactorily to these products.[7] But even with synthetic levothyroxine treatment, some patients with hypothyroidism remain symptomatic.[8] These patients may seek out alternative therapies, such as the addition of synthetic liothyronine to the synthetic levothyroxine monotherapy, or they may abandon synthetic products altogether in favor of DTE products.

B. Regulatory History of DTE Products

1. Drugs Predating 1938 and 1962 Legislation

DTE products have been marketed in the United States since well before passage of the FDCA in 1938, but none of the currently marketed DTE product has ever been approved. Until recently, DTE products were among the many unapproved older products long considered by FDA to be "new drugs" requiring NDAs, but which the Agency allows to be marketed without an approved application, provided manufacturers meet certain conditions.

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[3] Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet. 2017 Sep 23;390(10101):1550–62.

[4] American Thyroid Association, *Thyroid Hormone Treatment* (here) (all links lasted visited Mar. 26, 2024).

[5] The current USP monograph establishing product specifications for "Thyroid" has been in effect since 2016.

[6] Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. Thyroid. 2014 Dec 1;24(12):1670–751.

[7] Ettleson MD, Bianco AC. Individualized therapy for hypothyroidism: Is T4 enough for everyone? J Clin Endocrinol Metab. 2020 Sep 1;105(9):e3090–104.

[8] The exact prevalence of L-T_4-treatment-refractory hypothyroidism is not known. *E.g.*, Centanni M, Benvenga S, Sachmechi I. Diagnosis and management of treatment-refractory hypothyroidism: An expert consensus report. J Endocrinol Invest. 2017 Dec; 40(12):1289–1301. Some place the number as high as 15% to 20%. *E.g.*, Quiroz-Aldave J, Concepción-Zavaleta MJ, et al. Refractory hypothyroidism: Unraveling the complexities of diagnosis and management. Endocr Prac. 2023 Dec; 29(12):1007–16.

The presence of unapproved older products on the market stems from the piecemeal evolution of the drug approval scheme over the course of the 20th century. Congress required NDAs based on safety data beginning in 1938, but it grandfathered certain products that had been marketed before 1938, and in 1962 it added the requirement that new drugs also be proven effective. This last requirement applied retroactively, so FDA had to review the effectiveness of thousands of products that had reached the market under safety-only NDAs between 1938 and 1962. This review was called the Drug Efficacy Study Implementation (DESI).[9]

FDA did once approve an NDA (and later an ANDA) for thyroglobulin, but those products are no longer marketed. As part of DESI, FDA reviewed Proloid, a thyroglobulin product that reached the market in 1940 under a safety-only NDA. In 1969, the agency found Proloid effective for treatment of certain conditions relating to inadequate endogenous thyroid production,[10] and in 1977, the agency announced that "identical, related, or similar products" would require abbreviated NDAs to be marketed.[11] The Proloid NDA was withdrawn in 1993, and a separate thyroglobulin ANDA was withdrawn in 2001.[12] To AbbVie's knowledge, no other thyroglobulin product nor any identical, related, or similar product has ever been approved by FDA.

2. FDA's Compliance Policy

The sheer number of drugs to be reviewed under DESI meant that many drugs would continue to be marketed without approval while the process played out. Accordingly, in 1976 FDA issued a Compliance Policy Guide (CPG) stating that it would defer enforcement action against a DESI drug unless it received significant new information questioning the drug's safety or effectiveness.[13]

FDA's compliance policy has evolved over the last several decades — for example, the Agency reissued the CPG in 2006 and again in 2011.[14] As recently as 2021, however, FDA confirmed the principles according to which it will exercise enforcement

[9] *See* 31 Fed. Reg. 9426 (July 9, 1966) (launching DESI).

[10] 34 Fed. Reg. 14775 (Sept. 25, 1969).

[11] 42 Fed. Reg. 61313 (Dec. 2, 1977) (providing notice to "all persons who manufacturer or distribute a drug product . . . that is identical, related, or similar" to thyroglobulin). *See also* 37 Fed. Reg. 23185 (Oct. 31, 1972) (final rule that every DESI notice applies not only to the drug with the NDA but also to all identical, related, and similar products), codified then at 21 C.F.R. § 130.40 (now § 310.6).

[12] 58 Fed. Reg. 12042 (March 2, 1993); 66 Fed. Reg. 43017, 43109 (Aug. 16, 2001); FDA, List of Withdrawn Applications for Biological Products That Were Removed From FDA's Orange Book on March 23, 2020, at 5 (here).

[13] FDA, Transmittal No. 76-127, Compliance Policy Guides, 7132c.08: Marketed New Drugs Without Approved NDA's or ANDA's, at 1–2, 4–5 (Oct. 6, 1976) ("1976 CPG").

[14] *See* FDA, Guidance for FDA Staff and Industry: Marketed Unapproved Drugs — Compliance Policy Guide, Sec. 440.100 Marketed New Drugs Without Approved NDAs or ANDAs, at 7 (June 2006) (here) ("2006 CPG"); FDA, Guidance for FDA Staff and Industry: Marketed Unapproved Drugs — Compliance Policy Guide, Sec. 440.100 Marketed New Drugs Without Approved NDAs or ANDAs, at 8 (Sept. 19, 2011) (here) ("2011 CPG"). In 2020, HHS published a notice stating that it was withdrawing CPG 440.100, 85 Fed. Reg. 75331 (Nov. 25, 2020), but the next year HHS and FDA jointly issued a statement withdrawing the earlier withdrawal notice. 86 Fed. Reg. 28605 (May 27, 2021).

discretion for unapproved drugs, including drugs that predate the current approval scheme.[15] These principles prioritize enforcement actions against unapproved (1) drugs with potential safety risks; (2) drugs that lack evidence of effectiveness; (3) "health fraud drugs," including drugs deceptively promoted as safe and effective without scientific evidence to support that promotion, especially if the drugs present a direct risk to health; (4) drugs that "present direct challenges" to the new drug approval and OTC drug monograph systems, including unapproved drugs that compete with drugs that have approved NDAs; (5) drugs that violate the FDCA in some other way; and (6) drugs reformulated to evade FDA enforcement action.[16] This risk-based approach is meant to prioritize "drugs that pose the highest risk to public health, without imposing undue burden on patients or unnecessarily disrupting the availability of drugs on the market."[17]

FDA has explained its overall goal as either encouraging the manufacturers of unapproved products to obtain the required evidence and comply with the FDCA or removing the products from the market, and in either case doing so "without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market."[18] Thus, in addition to taking a risk-based approach to enforcement that prioritizes removal of products that raise public health concerns, FDA encourages companies to complete the research necessary for approval of applications. Encouraging the completion of this research "benefits the public health by increasing the assurance that marketed drugs are safe and effective" and also "reduces the resources that FDA must expend on enforcement."[19]

3. The BLA Transition

On March 23, 2010, changes to the PHSA were enacted reclassifying proteins as biological products.[20] By virtue of this statutory change, unapproved DTE products became subject exclusively to the BLA requirement in section 351 of the PHSA rather than the NDA requirement in section 505 of the FDCA. The actual transition occurred on March 23, 2020, following a ten-year period during which either NDAs or BLAs could have been submitted to FDA for approval of any DTE product.[21]

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[15] HHS and FDA stated in May 2021 that FDA "will continue to exercise its existing general approach to prioritizing regulatory and enforcement action, which involves risk-based prioritization in light of all the facts of a given circumstance." 86 Fed. Reg. at 28608.

[16] 2006 CPG, *supra* note 14, at 3–4; 2011 CPG, *supra* note 14, at 4–5.

[17] FDA, Unapproved Drugs (June 2, 2021) (here).

[18] 2011 CPG, *supra* note 14, at 3; *see also* 2006 CPG, *supra* note 14, at 2 (stating that FDA has "an interest in taking steps to either encourage the manufacturers of these products to obtain the required evidence and comply with the approval provisions of the Federal Food, Drug, and Cosmetic Act . . . or remove the products from the market" and that it wants "to achieve these goals without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market").

[19] 2011 CPG, *supra* note 14, at 7; *see also* 2006 CPG, *supra* note 14, at 5.

[20] Biologics Price Competition and Innovation Act of 2009 (BPCIA), Pub. L. No. 111-148, § 7002(b), 124 Stat. 119, 814 (2010) (amending definition of "biological product").

[21] For ten years, between March 23, 2010, and March 23, 2020, a protein could be the subject of an NDA or BLA if FDA had approved at least one NDA for a protein in the same "product class" before March 23,

The transition in 2020 also removed DTE products from the scope of the formal compliance policy discussed above, because this policy and its predecessors applied only to new drugs that "require" NDAs.[22] Biological products, however, do not require NDAs. Instead, they must be licensed under the PHSA; that is, they "require" approved BLAs.[23] Thus, as of March 23, 2020, DTE products were no longer subject to the express terms of FDA's formal compliance policy providing for enforcement discretion.

In 2020, the Department of Health and Human Services (HHS) issued a notice withdrawing the policy, but in 2021 HHS and FDA jointly issued a statement withdrawing the earlier withdrawal notice and confirming the risk-based principles according to which FDA will continue to exercise enforcement discretion for unapproved drugs.[24]

III. Rationale for Acting Now

This Petition asks FDA to prohibit DTE manufacturers without active INDs and robust clinical development programs from commercializing unlicensed products. In determining whether a particular DTE development program is robust, FDA should consider "the degree of attention, continuous directed effort, and timeliness" as may be expected of an applicant seeking licensure.[25] We also request that FDA stop manufacturers from promoting and making false and misleading statements about DTE products.

There is a compelling public health reason for FDA to grant AbbVie's request now. After more than a decade without a single new entrant, at least five *new and never before marketed* unlicensed DTE products have entered the market since the start of 2023. AbbVie believes that a perception that DTE products can be marketed and promoted without manufacturers being required to invest in clinical studies and seek licenses has contributed to a rash of opportunistic new market entrants.[26] These new

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2010. BPCIA § 7002(e)(2)(A), 124 Stat. at 817. Due to the prior approval of Proloid, DTE products could therefore have been the subject of NDAs until March 23, 2020.

[22] *E.g.*, 2011 CPG, *supra* note 14, at title page & 2 (referring to "marketed new drugs without approved NDAs or ANDAs" and "enforcement discretion with regard to drugs . . . that do not have required FDA approval for marketing"); 2006 CPG, *supra* note 14, at 1 (same); 1976 CPG, *supra* note 13, at 2 ("The sequence for regulating drugs for which a final determination has been made regarding new drug status and for which a Federal Register notice has been published requiring ANDA or NDA approval . . . [is] outlined in part (A) of this section . . . . Part (B) of this section deals with the regulation of those drugs for which no determination has been made.").

[23] 42 U.S.C. § 262(a)(1)(A) ("No person shall introduce or deliver for introduction into interstate commerce any biological product unless a biologics license under this subsection or subsection (k) is in effect for" such product). Once they are licensed, biological products are expressly exempt from the NDA requirement. 42 U.S.C. § 262(j).

[24] *Supra* notes 14–15 and accompanying text.

[25] *Cf.* 72 Fed. Reg. 60860, 60861 (Oct. 26, 2007) (factors considered for assessing due diligence of manufacturers in pursuing development programs) and discussion *infra*.

[26] Until recently, two products made up nearly the entire prescription DTE market: AbbVie's Armour Thyroid® (thyroid tablets, USP) and Acella Pharmaceuticals, LLC's (Acella) NP Thyroid® (thyroid tablets, USP). AbbVie and its predecessors have marketed Armour Thyroid for nearly 100 years. Acella began marketing NP Thyroid in late 2010. There have been other unlicensed DTE products over the years,

entrants began commercializing unlicensed DTE products shortly after the 2020 transition requiring BLAs for DTE products and the HHS notice withdrawing FDA's formal compliance policy providing for enforcement discretion.

In February 2023, Azurity Pharmaceuticals, Inc. began marketing Adthyza® (thyroid tablets, USP).[27] In June 2023, ANI Pharmaceuticals, Inc. began marketing Thyroid Tablets, USP.[28] In July 2023, Nivagen Pharmaceuticals, Inc. began marketing Niva Thyroid (thyroid tablets, USP).[29] In January 2024, Vitruvias Therapeutics began marketing APur Thyroid (thyroid tablets, USP).[30] And most recently, on March 1, 2024, LGM Pharma Solutions, LLC began marketing Thyroid Tablets, USP.[31] All five of the new entrants are described in labeling as "porcine thyroid gland" products containing "levothyroxine" and "liothyronine."

AbbVie anticipates even more new entrants in the near future as AbbVie has very recently received an unsolicited overture from a source previously unfamiliar to AbbVie offering to supply AbbVie with enough DTE active pharmaceutical ingredient (API) to satisfy the demand of nearly the entire DTE market.

A. FDA Must Address this Direct Challenge to its New Product Approval Framework in Order to Protect Public Health

The rapidly accelerating pace of new market entrants presents FDA with a direct challenge to its new drug and biological product approval framework that the Agency must address as a matter of public health.

FDA has long encouraged the manufacturers of unapproved DTE products to pursue approval for their products. AbbVie holds an active IND, is actively pursuing a robust clinical development program for Armour Thyroid, and plans to seek licensure of Armour Thyroid upon completing the development program.[32] We have found no publicly available information to indicate that the manufacturer of any other on-market DTE product has submitted an IND and is actively pursuing the studies needed to obtain approval of a BLA.

The IND framework facilitates FDA oversight of manufacturing and quality for drugs (including biological products) that have not yet been fully reviewed and approved.

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including Nature-Throid (thyroid tablets, USP) and WP Thyroid (thyroid tablets, USP), both made by RLC Labs, Inc. These products exited the market when the manufacturer recalled all lots in September 2020, after FDA found samples subpotent. RLC Labs, Inc., Issues Voluntary Nationwide Recall of All Lots of Nature-Throid® and WP Thyroid® with Current Expiry Due to Sub Potency (Sept. 3, 2020) (FDA publication of company announcement) (here).

[27] National Library of Medicine, Adthyza Labeling (here).

[28] National Library of Medicine, Thyroid Tablets, USP Labeling (here).

[29] National Library of Medicine, NIVA Thyroid Labeling (here).

[30] National Library of Medicine, APur Thyroid Labeling (here).

[31] National Library of Medicine, Thyroid Tablets, USP Labeling (here).

[32] *See* Protocol ID M21-341, *A Study to Assess the Safety and Efficacy of Oral Armour Thyroid Compared to Synthetic T4 for the Treatment of Primary Hypothyroidism in Adult Participants* (anticipated study completion date of June 3, 2028) (here).

In an IND application, the sponsor must provide a description of the composition, manufacture, and control of the drug substance and the drug product, including a description of the acceptable limits and analytical methods used to ensure the identity, strength, quality, and purity of each.[33] FDA reviews this information to ensure that the company can adequately produce and supply consistent batches of the drug.[34] Each IND drug must also comply with current good manufacturing practice "to assure that such drug meets the requirements of [the FDCA] as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."[35] Ensuring FDA oversight of manufacturing and quality is particularly important here because DTE products are characterized by their narrow therapeutic range, meaning small changes in dose can have significant safety implications. As FDA is aware, both subpotent and superpotent DTE products have made their way into the marketplace already, posing a risk to patients — too much medication can cause significant side effects, and too little can be ineffective.[36] Moving forward, to protect patient safety, FDA should ensure that all marketed DTE products are subject to the IND framework and its guardrails.

Moreover, there is widespread promotion of unapproved DTE products in violation of the FDCA and FDA's IND regulations in particular.[37] At least two companies promote their unapproved DTE products as superior to FDA-approved synthetic levothyroxine sodium products. At least one fails to sufficiently disclose in its promotional materials that its DTE product is unapproved. And at least one falsely implies that its product is a substitutable equivalent for Armour Thyroid.

The DTE market-share leader, Acella, uses a large, dedicated sales force to promote NP Thyroid as a first-line treatment that is superior to FDA-approved synthetic levothyroxine sodium and other DTE products.[38] Acella also maintains a promotional website for NP Thyroid directed to healthcare providers, describing the product as a "go-to [treatment] for patients with hypothyroidism."[39] This phrasing implies that NP Thyroid should be a first-line treatment, that is, for use before FDA-approved options for hypothyroidism. The company also promotes NP Thyroid to patients as an option "for

[33] 21 C.F.R. § 312.23(a)(7)(i) & (iv).

[34] FDA, Investigational New Drug (IND) Application (here).

[35] FDCA § 501(a)(2)(B).

[36] *See, e.g.*, Acella Pharmaceuticals, LLC, Issues Voluntary Nationwide Recall of Certain Lots of NP Thyroid® (Thyroid Tablets, USP) Due to Sub Potency (Apr. 29, 2021) (FDA publication of company announcement) (here) (citing 43 reports of serious adverse events that could possibly be related to 38 lots of subpotent product); FDA, Warning Letter to Bioiberica SAU (June 30, 2022) (here) (indicating that the safety and quality of the product is a continuing concern).

[37] *See* 21 C.F.R. § 312.7(a) ("A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug."). To the extent claims are false or misleading, they render the relevant products misbranded. FDCA § 502(a); 42 U.S.C. § 262(j).

[38] Information based on market research performed by AbbVie.

[39] Acella Pharmaceuticals, LLC, NP Thyroid, For Practitioners (here).

people who have yet to be treated for hypothyroidism," which similarly suggests that first-line treatment is appropriate.[40] Both the website for healthcare providers and the website for patients strongly imply that NP Thyroid is superior to FDA-approved synthetic options,[41] when to our knowledge there are no data to support a superiority claim. None of these materials adequately discloses the fact that the company's DTE product is unapproved.

Azurity promotes Adthyza as a treatment option for patients who have persistent symptoms despite treatment with FDA-approved synthetic levothyroxine sodium products. For example, the healthcare provider website states that Adthyza "may help patients get back to life without persistent symptoms of hypothyroidism despite treatment with levothyroxine (T_4) alone."[42] The patient website states that "[i]f you are still experiencing persistent hypothyroidism symptoms, ADTHYZA® may be a natural option."[43] Other claims imply that Adthyza could be an attractive alternative to synthetic levothyroxine sodium, without specifying that the latter should be tried first. For example, one page on the patient website contrasts Adthyza to "synthetic T_4 monotherapies," implying that it may be a suitable first-line treatment.[44]

At least one company uses wording that implies their DTE products are generic equivalents of Armour Thyroid. For example, the ANI Pharmaceuticals website page for its unbranded "Thyroid Tablets USP" states "Compare To: Armour® Thyroid," which creates the misimpression that the two are equivalent and interchangeable.[45] These statements create the impression that FDA has found the products bioequivalent, pharmaceutically equivalent, and therapeutically equivalent to each other — none of which is true.

In short, these companies are promoting and commercializing unapproved DTE products in direct challenge to FDA's product approval framework. These companies do not appear to hold effective INDs and therefore are not subject to that framework's

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[40] Acella Pharmaceuticals, LLC, NP Thyroid May Help You Get in Tune (here).

[41] The HCP-facing webpage provides a link for HCPs to learn about "the rising interest in therapies alternate to L-T_4 monotherapy among healthcare professionals, and patient preference data for DTE therapy." *See* here. The section entitled "Why Desiccated Extract (DTE)?" emphasizes that "up to 15% of patients receiving L-T_4 alone fail to achieve normal serum T_3 levels" and that "L-T_4 monotherapy may not address the needs of every patient living with hypothyroidism." *See* here. These claims imply superiority of NP Thyroid over FDA-approved synthetic hormone. The patient-facing webpage provides a guide for discussing hypothyroidism with doctors, which encourages patients to ask about DTE products and displays statistics purporting to show patient preference for DTE products over FDA-approved synthetic hormone. *See* here. A separate downloadable patient brochure leads with a large, bolded statement "CHANGE YOUR PERSPECTIVE," which is followed by statistics again purporting to show patient preferences for DTE products over FDA-approved synthetic hormone. *See* here.

[42] Azurity Pharmaceuticals, Inc., Adthyza HCP Website (here).

[43] Azurity Pharmaceuticals, Inc., Adthyza Patient Website, Get to Know Adthyza (here).

[44] *Id.* ("ADTHYZA tablets contain a combination of T_4 and T_3 thyroid hormones. Synthetic T_4 monotherapies do not provide T_3, but rely on the body to convert T_4 to T_3, which doesn't happen naturally for everyone in the same way. Combination therapy, which includes both T_4 and T_3, was the first treatment for hypothyroidism.").

[45] ANI Pharmaceuticals, Inc., Thyroid Tablets USP (here).

manufacturing and quality protections; they do not appear to be conducting research that would lead to licensure of their products; and they promote their products as preferable to FDA-approved products that are understood to be first-line treatment. These companies are therefore directly and openly challenging the drug approval scheme entrusted to and administered by FDA.

B. AbbVie's Request Aligns with FDA's Longstanding Policy for New Drugs and Has Precedent

We urge FDA to require a manufacturer to file an IND and have in place a robust clinical development program in order to commercialize any unlicensed DTE product. There is precedent for doing so: measures taken with respect to pancreatic enzyme products (PEPs) (products used to treat exocrine pancreatic insufficiency) in the 2000s and measures taken in the late 1990s with respect to synthetic levothyroxine sodium products.

With respect to PEPs, on April 28, 2004, FDA announced that manufacturers who wished to continue marketing these products must submit NDAs.[46] Like DTE products, PEPs are derived from glands harvested from pigs, and like the marketing of DTE products, marketing of PEPs predated passage of the FDCA in 1938. Between 1938 and 1996, no PEPs in the market had approved NDAs. Although a PEP was approved in 1996, by 2004 it was no longer being sold, leaving on the market only products without approved NDAs.[47] In 2004, FDA announced a four-year grace period for the manufacturers of those PEPs to obtain NDA approval. The Agency subsequently extended the grace period for receiving NDA approval from four years to six years, but it required that manufacturers have an open IND for their PEP by April 28, 2008 (six months after the notice's publication), and an approved NDA by April 28, 2010. The Agency also required that manufacturers pursue approval "with due diligence as determined by FDA."[48] This process was successful, and FDA ultimately approved six NDAs for PEPs. Like DTE products, PEPs qualify as biological products because they are proteins, so under the BPCIA all the approved PEP applications were deemed to be BLAs under section 351 of the PHSA on March 23, 2020.[49]

FDA should take similar steps to require that all DTE manufacturers diligently pursue licensure for their products. Consistent with measures taken with respect to PEPs, in addition to requiring an active IND, FDA should require that manufacturers implement the type of robust development programs that would be expected of sponsors seeking BLAs.[50] FDA should consider, among other things, whether the manufacturer is conducting its clinical trial or trials in a manner reasonably designed to demonstrate that the DTE product is safe, pure, and potent; the adequacy and completeness of required documents submitted to FDA; "the speed and thoroughness with which the manufacturer

[46] 69 Fed. Reg. 23410 (Apr. 28, 2004).

[47] *See id.* at 23412.

[48] 72 Fed. Reg. 60860, 60861 (Oct. 26, 2007).

[49] *See, e.g.*, Purple Book, *Product Details for: Creon* (BLA 020725) (here).

[50] *Cf.* 72 Fed. Reg at 60861 (discussing factors considered in assessing due diligence).

responds to any FDA requests for information or notifications of deficiencies[;] and any other relevant evidence of whether the manufacturer is making a genuine effort to" obtain a license.[51]

FDA's actions with synthetic levothyroxine sodium products provide another precedent. There were four unapproved levothyroxine sodium products in the market in the late 1990s: two branded and two unbranded. Synthroid, then one of the most heavily prescribed drugs in the country, was not approved, and therefore no drug had been found to be its therapeutic equivalent. Controversy over the results of a bioequivalence study funded by its manufacturer (a company that marketed Synthroid before AbbVie acquired its interest in the drug) prompted Public Citizen to write FDA in May 1996, asking it to require NDAs for the levothyroxine sodium products.[52] On August 14, 1997, FDA announced that any manufacturer wishing to continue marketing an orally administered drug product containing levothyroxine sodium would need to obtain approval of an NDA by August 14, 2000.[53] The Agency later extended this date to August 14, 2001.[54] By June 2001, the Agency had approved two products, which allowed it to begin phasing out unapproved products.[55] Distribution of unapproved levothyroxine sodium ended by August 14, 2003, and FDA has now approved 14 new drug applications for oral levothyroxine sodium products.[56]

Confusion, similar to that which prompted FDA to require approval for levothyroxine sodium products, exists today regarding the interchangeability of DTE products. FDA has not approved any BLAs for DTE products, let alone issued any interchangeability determinations. As discussed below, however, public statements from stakeholders imply FDA approval of, and therapeutic equivalence among, various marketed DTE products. Many participants in the healthcare system characterize certain marketed DTE products as "generic" drugs.[57] As was true with levothyroxine sodium,

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[51] *Cf. id.*

[52] Public Citizen, Letter Urging FDA to Review Safety and Efficacy of Pharmaceuticals Marketed Prior to 1938 (May 29, 1996) (here). The investigator concluded that all four drugs were bioequivalent and interchangeable for most patients, while the company's scientists reached the opposite conclusion. *Id.*

[53] In the alternative, because these drugs had been marketed before 1938, FDA said a manufacturer might choose to file a petition arguing that its product was not subject to the new drug requirements of the statute. 62 Fed. Reg. 43535, 43538 (Aug. 14, 1997). The Agency allowed this because it is "theoretically possible" a marketed drug that would otherwise be subject to the NDA requirement is, instead, grandfathered or otherwise not a new drug. *See* 2011 CPG, *supra* note 14, at 12. No company was able to make this showing, however. There would be no basis for FDA to invite such a showing for DTE products because there is no grandfather (or "generally recognized as . . . safe and effective") exception to the BLA requirement. All biological products require approved licenses.

[54] 65 Fed. Reg. 24488 (Apr. 26, 2000).

[55] FDA planned a gradual phase-out of unapproved products through August 2003 because it would take time for patients to switch to the approved products and for manufacturers of the approved products to scale up their production. 66 Fed. Reg. 36794 (July 13, 2001); FDA, Guidance: Levothyroxine Sodium Products — Enforcement of August 14, 2001, Compliance Date and Submission of New Applications (July 2001) (here).

[56] *See* Search Results for "Levothyroxine Sodium" in the Orange Book Database (here).

[57] *See, e.g., infra* note 63; Rx Saver Listing for NP Thyroid (here) (referring to NP Thyroid as "generic for Armour Thyroid"); WellRx (here) (referring to NP Thyroid as a "generic"); Kaiser Permanente Listing for

clarity around these issues will benefit the public health by ensuring that physicians and patients understand that marketed DTE products have not been reviewed and approved by FDA, let alone found interchangeable with one another.

As an example, First Databank, the most widely used healthcare data compendium, which counts the Centers for Medicare and Medicaid Services (CMS) among its customers, publishes confusing information about DTE products.[58] Specifically, it classifies DTE products as "multi-source" products, Armour Thyroid as the sole "innovator" and all the other DTE products as non-innovators.[59] All of this is misleading, as these terms cannot be applied, either as a matter of law or logic, to products lacking NDAs or BLAs.[60] Compounding the confusion, First Databank categorizes these attributes (i.e., "multi-source") as "Generic Indicators," which is misleading because the term "generic" applies to small molecule drugs, not biological products.[61] The compendium also groups all DTE products under the same "Generic Code Number" (GCN), which is used to group candidates for substitution. This suggests that DTE products are substitutable equivalents of one another. Because of widespread reliance on this classification scheme, unprincipled substitution of DTE products appears to be occurring,[62] and pharmacy benefit managers appear to be making significant patient access decisions based on the perceived "generic" status of certain DTE products.[63]

NP Thyroid (here) (showing a picture of an Armour Thyroid tablet and identifying Armour Thyroid and Adthyza as "Brand name(s)" for NP Thyroid, thus implying NP Thyroid is a generic).

[58] Data compendia are published by third parties and contain drug information summaries that pharmacists, pharmacy benefit managers, and others in the healthcare community use when making decisions about product substitution and formulary placement. *See* First Databank, *Drug Databases That Empower Critical Decisions* ("Millions of people – including physicians, nurses, pharmacists, claims adjudicators, and patients – rely on [First Databank's data] to help them choose, dose, prescribe, and use medications properly. Precise medication information is critical to help ensure the best possible health outcomes.") (here). First Databank's website identifies as its customers 32,000+ retail pharmacies, 3,500+ non-federal hospitals, and 16 top health plans. *See id.*

[59] Among the major healthcare compendia, First Databank is the only one that classifies DTE products as either "multi-source" or "generic."

[60] First Databank's "multi-source" indicator means that all DTE products have identical clinical formulations (including identical potencies). This is not based on any clinical data reviewed by FDA but rather is based solely on First Databank's comparison of DTE product labels (none of which has been reviewed by FDA and, in the case of the "non-innovator" DTE products, all of which appear to be in large part simply copies of Armour Thyroid's label).

[61] *See, e.g.*, FDA, Biosimilars Info Sheet *Level 1: Foundational Concepts* ("[B]iosimilars are not generics, and important differences exist between them.") (here). Although First Databank recently started publishing information that specifically identifies biological products as either reference biologics or biosimilars, nowhere does First Databank identify DTE products as biological products.

[62] *See* Amended Complaint ¶ 20, *Faulkner v. Acella Pharms., LLC*, No. 2:22-CV-092-RWS (N.D. Ga. May 1, 2023) (co-lead plaintiff in class action alleging that, due to compendia classification of DTE products, plaintiff was switched at the pharmacy to a different DTE therapy from the one prescribed by her doctor); *see also* NP Thyroid Product Update released by Acella on March 21, 2024 (here) (stating that Acella is aware that switching of DTE products at pharmacies may be taking place).

[63] *See, e.g.*, Cigna Formulary Update (Apr. 2022) (here) (stating that Armour Thyroid would be removed from its formulary "to encourage use of an alternative generic drug called NP Thyroid"); 2023 Optum Rx Select Standard Formulary (here) (asserting that Optum's guide "tells you if a medication is generic",

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Requiring DTE manufacturers to diligently pursue licensure and follow the IND rules prohibiting promotion of unlicensed products would address the challenges the Agency now confronts with the recent proliferation of unlicensed and marketed DTE products. The relief AbbVie requests in this Petition would prevent the ongoing dissemination of false and misleading promotional claims regarding these products and lead to formal Agency findings of safety and efficacy, accessible listing in the Purple Book, and (where applicable) interchangeability determinations to help guide appropriate substitution and pharmacy practices.

Based on the success of the PEP program in the 2000s and the levothyroxine sodium program in the late 1990s, we recommend that FDA ensure that companies marketing unlicensed DTE products be required to implement robust clinical development programs and diligently seek licenses for their products. AbbVie believes it would be reasonable for the Agency to require that companies marketing unlicensed DTE products obtain an effective IND within three months of Agency action regarding this Petition.

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describing generic medications as "offer[ing] the same effect" as their branded counterpart, and identifying NP Thyroid as generic and Armour Thyroid as brand).

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Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.30.

Economic Impact

Petitioner will submit economic information upon request of the Commissioner.

Certification

The undersigned certify, 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 which are unfavorable to the Petition.

Respectfully submitted,

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