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Alliance for Pharmacy Compounding

December 20, 2022

Dockets Management Staff: Docket No. [FDA-2015-N-0030]
Food and Drug Administration 5630
Fishers Lane, Room 106
Rockville, MD 20852

Re: FDA Letters Regarding Desiccated Thyroid Extract Preparations

To Whom it May Concern:

I write today in my role as CEO of the Alliance for Pharmacy Compounding (APC), formerly the International Academy of Compounding Pharmacists (IACP). APC is the voice for pharmacy compounding, representing compounding pharmacists and technicians in both 503A and 503B settings, as well as prescribers, educators, researchers, and suppliers.

APC has serious concerns with the legal reasoning taken by FDA in its September 26, 2022, letter to the National Association of Boards of Pharmacy and subsequent follow up dated November 16, 2022, in which the FDA proclaims that therapies containing desiccated thyroid extract (DTE) are biological products subject to licensure under section 351 of the Public Health Service Act (PHS Act). We are alarmed by the manner in which this letter was distributed. Unlike the transparency that FDA provided in its publication of the List of Approved NDAs for Biological Products That Were Deemed to be BLAs on March 23, 2020 – including multiple public comment periods on issues surrounding FDA's transition of drug products to biologics and FDA's interpretation of what is considered a biologic – no such public process was followed here.[1] Instead, the FDA sent a letter to be distributed to its state counterparts announcing a new policy to the effect of "compounding DTE products is a violation of law." In turn, the pharmaceutical supply chain, which provides millions of patients in America necessary medications, ceased providing DTE to compounders for fear of state or federal action. In response to becoming aware of the letter's effect, FDA sent another letter to the same stakeholders asserting that DTE products continue to be available. *We respectfully request that*

[1] *See* Docket ID: FDA-2015-D-4750 containing multiple notices and guidance for public comment on implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009; *see also* Docket ID: FDA-2014-D-1525 containing multiple notices and guidance for public comment on Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application; *see also* Docket ID: *FDA-2018-N-2732* Definition of the Term "Biological Product" providing stakeholders an opportunity to comment. Commenter is not commenting on the legal merits of whether the proper administrative process was followed for any of these subjects including the subject of this comment. Commenter is solely providing examples of FDA's typical longstanding process by which FDA provides at least some form of public comment prior to announcing a new policy position.

the FDA immediately retract these letters and issue a correction: DTE is not a biological product because it does not meet FDA's definition of biologic product.

DTE is not a biologic because the active ingredient does not meet the definition of a biologic product.

Section 351(1) of the PHS Act defines "biological product" as follows:

> (1) The term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

In FDA guidance FDA asserts that a drug product that contains a protein **only as an inactive ingredient** is not considered to be a "protein" for purposes of the statutory definition of "biological product."

FDA has made clear that a drug product that contains a protein only as an inactive ingredient (e.g., a drug product formulated with human serum albumin as an inactive ingredient) is not considered to be a "protein" for purposes of the statutory definition of "biological product."[2]

> FDA interprets the statutory definition of "biological product" such that any amino acid polymer composed of 40 or fewer amino acids (i.e., a "peptide") is outside the scope of the term "protein." A "peptide" is not a "biological product" and will continue to be regulated as a drug under the FD&C Act unless the peptide otherwise meets the statutory definition of a "biological product" (e.g., a peptide vaccine) (see Q. II.1 in FDA's draft guidance for industry New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2) (December 2018) (Biosimilars Q&A Draft Guidance)). **Moreover, a drug product that contains a protein only as an inactive ingredient (e.g., a drug product formulated with human serum albumin as an inactive ingredient) is not considered to be a "protein" for purposes of the statutory definition of "biological product" and the transition provision of the BPCI Act.[3]**

If FDA is intending to depart from its Guidance document in effect since March 2020, the FDA should issue a revised Guidance document instead of unilaterally informing state regulators that DTE is a biologic product—even though, based on FDA's own Guidance document, DTE is not a biologic product.

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[2] *See* The "Deemed To Be a License" Provision of the BPCI Act Questions and Answers Guidance for Industry, at 5 (March 2020).

[3] *Id.* at 5 (emphasis added).

FDA incorrectly categorizes DTE as a biologic product.

In FDA's September 26, 2022 letter, FDA states:

> DTE meets the definition of a biological product because it is a "protein" or "analogous" to a protein. DTE is derived from animal thyroid glands (usually porcine, meaning from a pig) and necessarily contains thyroglobulin, an alpha amino acid polymer with a specific defined sequence, consisting of 2,770 amino acids.

Under sections 501 and 502 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a drug with a name recognized in an official compendium must comply with compendial identity standards or be deemed adulterated, misbranded, or both.[4] Yet, the USP monograph for Thyroid USP does not contain thyroglobulin.[5] Further, the labeling of currently marketed DTE commercial products does not identify or quantify thyroglobulin as a component.[6] FDA's letters in September and November 2022 do not identify amounts of thyroglobulin in DTE used for compounding, nor do these letters identify clinical relevance of thyroglobulin in DTE.

Any amounts of thyroglobulin potentially contained in DTE should be considered an inactive ingredient because thyroglobulin is not intended to furnish pharmacological activity.[7] The published medical literature refers to thyroglobulin as a precursor, polypeptide backbone for synthesis, a substrate, or a vessel for iodine storage.[8]

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[4] *See* sections 501(b) and 502(e)(3)(B) and (g) of the FD&C Act; also 21 CFR 299.5.

[5] USP MONOGRAPH FOR THYROID, UNITED STATES PHARMACOPEIA (May 2016).

[6] Multiple entries for thyroid products are listed in the FDA NDC Directory, indicating that these products are currently marketed.

[7] *See Active pharmaceutical ingredient* means any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body. Active pharmaceutical ingredient **does not include intermediates used in the synthesis of the substance**. 21 CFR 207.1 (emphasis added). *See also* FDA definitions of Active and Inactive ingredient. 21 CFR 210.3 "(7) Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.
(8) Inactive ingredient means any component other than an active ingredient."

[8] For example, Thyroglobulin is the protein precursor of thyroid hormones, which are essential for growth, development and the control of metabolism in vertebrates. *See* Francesca Coscia, et al., *The structure of human thyroglobulin*. 578 Nature 627 (2020). Two apical membrane enzymes dual oxidases (DUOX, producing H_2O_2) and thyroid peroxidase (TPO, oxidising iodide) allow the extracellular iodination of tyrosine residues within the thyroglobulin protein substrate. *Id.* Its main function is to provide the polypeptide backbone for synthesis and storage of thyroid hormones. It also offers a convenient depot for iodine storage and retrieval when external iodine availability is scarce or uneven. *See* Bernard Rousset, et al., *Chapter 2 Thyroid Hormone Synthesis & Secretion*, Endotext (2015). Therefore, not only is thyroglobulin not intended to furnish pharmacological activity but is it is instead a building block for thyroid hormones similar to intermediates used in the synthesis of substances.

FDA must immediately clarify to state boards of pharmacy and other stakeholders that state-licensed pharmacies or physicians may lawfully compound DTE.

Section 503A of the Federal Food Drug and Cosmetic Act provides:

> A drug product may be compounded under subsection (a) if the licensed pharmacist or licensed physician—
>
> (A) compounds the drug product using bulk drug substances, as defined in regulations of the Secretary published at section 207.3(a)(4) of title 21 of the Code of Federal Regulations—
>
> (i) that—
>
> (I) comply with the standards of an applicable United States Pharmacopoeia or National Formulary monograph, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding;

Here, there is no question that a statutory authority exists for licensed pharmacists and licensed physicians to compound drug products using bulk drug substances that comply with the standards of the USP monograph for Thyroid USP. FDA must immediately clarify to State Boards of Pharmacy that compounding using Thyroid USP is a permissible activity because FDA has caused unnecessary confusion in the market and has negatively impacted patient access due to its unwarranted and unprovoked letter to NABP dated September 26, 2022.

If you have questions about this request, please contact me at scott@a4pc.org or 404.844.8607.

Sincerely,

Scott Brunner, CAE
Chief Executive Officer