

**BIOLOGICS
AND
COMPOUNDING**

**ALLIANCE FOR PHARMACY COMPOUNDING
PRESENTATION**

DECEMBER 2, 2020

Karla L. Palmer and Sara Koblitz
Hyman, Phelps & McNamara, P.C.
-and-
Matt Martin, Professional
Compounding Centers of America



WHAT IS A BIOLOGIC?

- Biological products defined as “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” (see section 351(i)(1) of the PHS Act).
 - *Protein* is any alpha amino acid polymer with a defined sequence greater than *a total number of 40* amino acids (even if comprised of several shorter polypeptide chains)

WHAT IS A BIOLOGIC?

- “Biological product” definition revised in BPCIA of 2009 to include “protein”
 - Initially, this definition excluded “any chemically synthesized polypeptide,” but Congress revised again in early 2020 to remove exception
- Now, FDA uses “bright-line rule” based on number of amino acids in amino acid polymer regardless of method of manufacture
 - But FDA uses fact-specific, case-by-case analysis for amino acid chains not found in naturally occurring proteins

WHAT IS A BIOLOGIC?

- Most biologics are complex mixtures
 - Are not easily identified or characterized
- Tend to be heat sensitive and susceptible to microbial contamination
- In to contrast to most conventional drugs, aseptic principles must be used from initial manufacturing steps
 - Manufacturing process is integral to safety, purity, potency, and effectiveness of biological products

WHAT IS A PEPTIDE?

- Peptides are distinct from proteins in FDA parlance
 - Peptide refers to smaller, simpler chains of amino acids while proteins are longer, more complex chains
 - FDA draws the line at 40 amino acids

WHAT IS A “TRANSITIONED” BIOLOGIC?

- The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) requires that a marketing application for a “biological product” (that previously could have been submitted under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)) must be submitted as a biologics license application (BLA) under section 351 of the Public Health Service Act (PHS Act).
- This requirement is subject to certain exceptions during a 10-year transition period **ending on March 23, 2020.**

BIOLOGICS TRANSITION

- Opened up specific products to competition through biosimilars pathway
- In 2019, FDA identified about a hundred products
- Includes different insulins, and products containing chorionic gonadotropin, follitropin alfa, hyaluronidase, menotropins, pancrelipase and somatropin, among others.
- After March 23, 2020, all sponsors seeking approval of a biologic that previously could have been approved under Section 505 will need to submit an application under Section 351 of the PHS Act (either a standalone BLA, or a proposal for a biosimilar product)

TRANSITION...

- FDA and Congress believed that the 10-year transition period provided sponsors of biological products affected by the transition with time to prepare for the transitions and allowed ample time for approval of the transitioned BLA.
- Recognized that some protein products (insulin, HGH, pancreatic enzymes, and reproductive hormones) had historically been approved via Section 505's NDA route
- Remember what compounders can use in compounding under Section 503A

COMPOUNDING: WHAT HAPPENED?

- Compounders that engage in “lawful” compounding under section 503A of the FDCA are entitled to certain exemptions:
- 502(f)(1) – adequate directions for use
- 501(a)(2)(B) – FDA’s cGMP regulations
- 505 – new drug application requirements
- Compounders are **NOT** exempted from biologics approval (BLA) provisions at section 351 of the PHS Act.

COMPOUNDING WITH A BIOLOGIC SUBSTANCE?

- List of transitioned products is linked [here](#); was updated in 2018, 2019
- Issue was raised concerning proteins and peptides and amino acids.
- FDA stated that if the peptide has less than 40 amino acids then it is still regulated as a drug under Section 505.
- But ...



COMPOUNDING WITH A BIOLOGIC SUBSTANCE?

- **Just because it's still a “drug” regulated under Section 505, does not mean that the peptide may be used in compounding.**

Under Section 503A compounders may only compound drug products if they meet certain conditions set forth in Section 503A.

SECTION 503A

(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 [DRUG] monograph, if a monograph exists**, and the United States Pharmacopoeia chapter on pharmacy compounding;

(II) if such a monograph does not exist, are drug substances that are **components of drugs approved by the Secretary**; or

(III) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a **list developed by the Secretary** through regulations issued by the Secretary under subsection (d);

These “disjunctive” requirements prescribe compounders’ limits when compounding from bulk substances.

WHAT HAPPENED NEXT?

- January 2020 – Compounders filed comments and sent letters. Requested that:

“FDA immediately clarify that approved NDAs for biological products that will be deemed to be a license (“Deemed BLAs”) on March 23, 2020 will continue to be regulated as “drugs” for purposes of compounding pursuant to Section 503A and Section 503B of the Federal Food, Drug, and Cosmetic (“FD&C”) Act. This includes but is not limited to the following products: insulin, human chorionic gonadotropin (HCG), and hyaluronidase.”

- A USP/NF Drug Monograph exists for Insulin, HCG and Hyaluronidase.
- Products have been compounded for 50 years.

WHAT HAPPENED NEXT?

- FDA's Response: Public Notice
- **Notice to Compounders: Changes that affect compounding as of March 23, 2020**

A change to the law will impact compounding of certain products beginning on March 23, 2020. On that date, biological products that were approved under the Federal Food, Drug, and Cosmetic (FD&C) Act will transition to being licensed under the Public Health Service (PHS) Act. This transition affects compounding under sections 503A and 503B of the FD&C Act because, beginning on March 23, these transitioning biological products will not be eligible for the exemptions for compounded drugs under sections 503A and 503B of the FD&C Act.

WHAT ELSE DOES FDA SAY ABOUT THIS?

- Outsourcing facilities have recently reported using four bulk drug substances that are affected by the transition: human chorionic gonadotropin, hyaluronidase, follicle stimulating hormone (FSH or urofollitropin) and menotropins. One of these products – hyaluronidase – was on [category 1](#) of the list of substances under our [503B bulks interim policy](#). As stated in the 503 bulks interim policy, biological products subject to approval under section 351 of the PHS Act are not eligible for the 503B bulks list because such products are not eligible for the exemptions in section 503B of the FD&C Act. Accordingly, as of March 23, hyaluronidase will be removed from category 1.

OPTIONS?

- Can peptides be marketed as a **cosmetic**?
- The FDA defines cosmetics by their “intended use,” as **"articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance"** [FD&C Act, sec. 201 (i)]. Cosmetics do not generally need FDA approval.
- Consider the “intended use” of the product.
- Consider claims made

COSMETICS VS. DRUGS

- The FD&C Act defines drugs, in part, by their intended use, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals" [FD&C Act, sec. 201(g)(1)].
- If claim on labels, advertising, marketing promotion that the cosmetic prevents, cures, treats a condition or disease, then FDA would consider the product a drug.
 - FDA may also impute "drug" status when active ingredient commonly is used in drugs

WHAT ABOUT A DIETARY SUPPLEMENT?

- Congress defined "dietary supplement" in the Dietary Supplement Health and Education Act (DSHEA) of 1994.
- "Dietary supplement" is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet.
- "Dietary ingredient" as a vitamin; mineral; herb or other botanical; amino acid; dietary substance for use by man to **supplement the diet by increasing the total dietary intake**; or a concentrate, metabolite, constituent, extract, or combination of the preceding substances.

DIETARY SUPPLEMENTS

- Dietary supplements are manufactured by FDA-registered facilities pursuant to cGMP and via a comprehensive regulatory scheme.
- Unlike drugs, *supplements are not intended to treat, diagnose, prevent, or cure diseases*. That means supplements should not make claims, such as “reduces pain” or “treats heart disease.”
- Claims like these can only legitimately be made for drugs, not dietary supplements.

WHAT IF I CONTINUE TO SELL COMPOUNDED BIOLOGICS? PEPTIDES?

- What will FDA really do about it?

WHAT WILL FDA DO ABOUT IT?

- Warning Letters concerning compounding of peptides:
- April 1, 2020:
- *For example, the investigators noted that your firm compounded drug products using Follistatin, GHRP-2, GHRP-6, Endurobal, AOD 9604, BPC 157, Bremelanotide (PT-141), Cerebrolysin, DSIP, Epitalon, GHK-Cu, IGF1-LR3, Ipamorelin, LL-37, Melanotan II, PEG-MGF, Selank, Semax, CJC 1295, SARMS, LGD-4033, and MK 677. Drug products compounded using these bulk drug substances are not eligible for the exemptions provided by section 503A(a) because they are not the subject of an applicable USP or NF monograph, are not a component of an FDA-approved human drug, and do not appear on the 503A bulks list*

WHAT WILL FDA DO?

- February 2019:
- *For example, the investigator noted that your firm compounded drug products using Growth Hormone Releasing Peptide 2 (GHRP-2), Growth Hormone Releasing Peptide 6 (GHRP-6), and chromium picolinate. Drug products compounded using Growth Hormone Releasing Peptide 2 (GHRP-2), Growth Hormone Releasing Peptide 6 (GHRP-6) and chromium picolinate are not eligible for the exemptions provided by section 503A(a), because Growth Hormone Releasing Peptide 2 (GHRP-2), Growth Hormone Releasing Peptide 6 (GHRP-6) and chromium picolinate are not the subject of an applicable USP or NF monograph, are not components of an FDA-approved human drug, and do not appear on the 503A bulks list.*

WHAT CAN YOU DO?

- Do not compound biological products that have been transitioned
- That some may be in shortage is likely of no matter to FDA
- Communicate with FDA concerning the safe compounding and use of peptides and biological products; seek “enforcement discretion” ?
- Contact your member of Congress; tell them that Sections 503A and 503B need amendment to permit another exemption: Section 351 of the PHS Act, which would permit compounding of transitioned products

QUESTIONS?

THANK YOU!