May 25, 2018

U.S. Food and Drug Administration
Division of Dockets Management
Dockets Management Staff (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Docket No. FDA-2018-D-1067**
*Draft Guidance for Industry - Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act.*

Dear Sir or Madam,

DYNALABS appreciates the opportunity to provide a formal comment to the Food and Drug Administration (FDA) regarding the recent draft guidance titled "*Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Guidance for Industry.*" DYNALABS is a provider of contract laboratory testing and consulting services for more than 2700 pharmacies and outsourcing facilities. As the first contract laboratory dedicated to testing compounded drug products, DYNALABS is committed to improving patient safety, reducing health care cost, and fostering and environment of business success for our clients.

DYNALABS understands the challenges facing the FDA regarding the need to design and implement meaningful regulation that aims to increase patient safety while both, protecting the integrity of drug approval process and maintaining patient access to medications that are not commercially available. Working closely with clients around the country, DYNALABS knows that clear and defined regulations not only help our 503B clients maintain compliant operations, but also ensure harmonization throughout the industry. Likewise, DYNALABS understands the challenges facing our 503B clients and the significant financial constraints that are placed on them to build and maintain cGMP compliant operations. As outlined below, we strongly feel that the language in the FDA's draft guidance promotes an environment which places uncertainty on the use of bulk drug substances that can potentially lead to increases in healthcare costs, as well as decreased patient access. Furthermore, we believe that certain language in the draft guidance requires clarification.

## 1. Section II. BACKGROUND – (A)(3) – Lines 75-76:

*"…and (3) the bulk drug substance must be accompanied by a valid certificate of analysis."*

The Agency should define what they consider a valid certificate of analysis (COA) or define how a firm would establish the validity of a certificate of analysis. DYNALABS fully supports a requirement for firms to qualify all raw materials used in compounding, however the regulation should define what level of testing is to be required to confirm the validity of a manufacturer's COA. In the Draft Guidance titled, *"Current Good Manufacturing Practice – Interim Guidance for Human Drug*

*Compounding Outsourcing Facilities Under Section 503B of the FD&C Act,"* an alternative approach to rely on a supplier filed DMF is mentioned as a potential part of the qualification process is proposed, but not given as an absolute mechanism for approval. If a firm obtains and maintains a letter of confirmation that an active DMF is on file, would the Agency consider this adequate, in lieu of full monograph conformational testing? Regardless of the final determination, what is needed and requested from many of our clients is clear requirements for the qualification and testing of bulk drug substances.

## Section II. BACKGROUND – (C) Lines 124-125:

*"In general, compounding using bulk drug substances presents a greater risk than compounding using FDA approved drug products."*

Producing any drug product poses inherent risks, but there is no validity in the statement that compounding from bulk drug substances poses a greater risk, when such compounds are produced in a cGMP facility. The interim draft guidance on the cGMP requirements for Outsourcing Facilities, does not provide exemptions from the requirement to comply with 21 CFR Parts 210 & 210, therefore such products should be produced in manner consistent with the requirements for manufactured approved drug products. Specifically, the only exemptions from the requirement of the FD&C Act, that apply to conventionally-manufactured drugs are:

- Labeling with adequate directions for use (section 502(f)(1))
- Premarket approval requirements (section 505)
- Drug supply chain security requirements (section 582)

**Validation is Validation…**

The use of approved products vs raw materials in a cGMP facility should be no different, as cGMP is inherently based on the validation of processes to ensure product quality specifications are consistently met. DYNALABS believes that the assumption that compounding using approved drug products as ingredients is somehow less risky than starting with raw materials is not based in fact and is not supported by any statistical data. If a facility validates their raw materials, sterilization method, aseptic processes, manufacturing process, personnel, etc., within an established cGMP compliant quality system, then risk is mitigated to the same standard as a pharmaceutical manufacturer. It should be mentioned that the current cGMP guidance for 503B facilities, does not exempt a 503B facility from performing the validation as previously stated, and the same requirements for validation would be necessary for a compound produced from approved drug products.

**Compounding from Approved Drug Product is NOT Less Complicated And More Safe**

When producing compounds from approved drug products, a 503B facility losses the ability to control ALL inactive ingredients that may be put into the compound. An approved drug product may contain inactive ingredients that are not listed, so by utilizing both active and inactive bulk drug substances a 503B facility has greater control over final drug product quality. In addition, when bulk drug substances are used in compounded and manufactured product, the "as is" or "as found" assay values are utilized to determine the amount of material needed to achieve the labeled ingredient concentrations in the final product. When an approved drug product is utilized, often the only value used to determine the amount needed for a particular batch formulation is the labeled approved drug product concentration. This value does not take into account, the

actual amount of active ingredient present in the product and the subsequent lot variability with regard to product assay, often allowable from 90.0% - 110.0%. When you account for the potential potency variation, along with fill volume variability of approved products, it is simply not possible to ensure that a compound from an approved product will meet the established finished product specification for every container produced.

The pooling of approved drug products into a bulk container for subsequent injection into finished product containers, such as the sterile-to-sterile production of IV admixture is a common practice compounding from approved products. However, this compounding process ensures that finished product samples are NOT representative of the entire lot. A filling error can occur in an individual container, resulting in single or multiple individual containers either be sub-potent or super-potent. There is no sampling scheme to ensure that potency samples are representative of the entire lot, making validation of such processes inherently difficult. In a production process where bulk drug substances are utilized to produce a bulk formulation, which is then sterilized and filled into finished product containers, any sample pulled would be representative of the entire bulk formulation.

**Automation Should Be Encouraged**

Encouraging an environment of "sterile-to-sterile" compounding discourages the use of automation. Due to limitations and scalability of using approved finished drug products as ingredients, automation is rarely integrated, because it's not a cost-effective manner in which to produce these products. This leads to highly manual processes which are inherently more difficult to validate due to high operator variability. As the 503B industry grows, facilities have begun to incorporate more automated processes. Any environment in which a greater investment in automation and enhanced process controls of pharmaceuticals is discouraged, whether intentional or not, should be avoided. Therefore, the language that compounding from bulk drug substances poses greater risk, should be stricken from the document, as it propagates a negative view on an industry that has improved significantly since the implementation of the DQSA.

## The Practice of Medicine and Determination of Clinical Need

The original intent of the FD&C Act was to regulate the food and drug supply chain and in no way regulate the "Practice of Medicine." The compounding industry is based on the premise that medications are produced which fulfill a clinical need at request of a medical practitioner. Understandably, it is important to also protect the drug approval process which is adequately addressed in the finalized guidance titled, *"Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act,"* however, the FDA is not in a position to provide an assessment of clinical need. The criteria in which the FDA is in a position to assess for inclusion on the bulks list is as follows:

- Does an official monograph exist for the nominated substances?
- Is the bulk drug substance produced by an FDA registered facility pursuant to the cGMP requirements for production of bulk drug substances?
- Has the drug substance been shown to pose a public safety risk and been withdrawn from the market.

In the draft guidance regarding compounds that are essentially copies of approved drug products, there is a requirement to obtain a statement of clinical difference for each order of compounded drug product by a physician or

hospital. The Agency further states that the "FDA generally does not intend to question the determinations of clinical difference that are documented in a prescription or order…" If the Agency does not intend to question the clinical determination of practitioner upon the ordering of a compounded product, how do they intend to question the clinical need of a drug substance to be used in compounded products? It should also be noted that practitioners who cannot obtain compounded medications from 503B outsourcing facilities, due to limitations of the bulks drug list, will seek to obtain those products from 503A facilities who are otherwise not prohibited from using those bulk drug substances. This will undermine the purpose of creating the designation of 503B facilities, and statements made by the Agency, encouraging practitioners and hospitals to purchase compounded products from 503B facilities.

To close, DYNALABS believes that the draft guidance contains language that undermines the intent of Section 503B of the FD&C Act by implying that compounded drug products produced from approved finished products are safer than those produced from bulk drug substances. By making this statement, 503A facilities will be discouraged from registering as 503B facilities, thereby circumventing the intent of 503B designation and FDA oversite of compounding. Further, this guidance provides regulation that will impact a physician's ability to practice medicine as they see fit and, in many ways, represents the Agency's intent to regulate the practice of medicine. Based on the aforementioned information, and on behalf of our many 503B clients, we recommend that any such language be stricken from the draft guidance and a new revision be created for review and public comment.

Sincerely and Respectfully,

Kristopher V. Le, PharmD.
VP & Principal Consultant
DYNALABS, LLC