#	Section	Commenter	Comment	Staff Response
1	1736(d)	CA Medical Association	**Requirement to Verify a Preparation Produces a Clinically Significant Difference Interferes with Exercise of Professional Judgment and Exceeds Federal Law (§§ 1735(d), 1735.1(e)(1)(B), 1736(d), 1736.1(e)(1)(B))** CMA reiterates its concern regarding the Board's proposed requirement for pharmacists to "verify" that a compounded drug produces a clinically significant difference for a patient. This proposed requirement creates an undue burden and restricts the professional judgment the Board intended to preserve. Mandating verification for every instance of compounding a commercially available drug that is not on a shortage list establishes a rigid, prescriptive standard. This contradicts the Board's stated goal of maintaining flexibility, and, as such, the language violates the clarity standard because it conflicts with the Board's description of the effect of the regulations in its formal response to members of the public regarding this issue. We refer you to our comment letters dated January 27 and February 21, 2025, for detailed discussions of this issue. To enhance clarity and ensure patients maintain timely access to medications, CMA reiterates its request from our prior comment letter, dated January 27, 2025, to remove "verify and" from proposed sections 1735(d), 1735.1(e)(1)(B), 1736(d), and 1736.1(e)(1)(B) of the third modified text.	Board staff have reviewed the comment and do not recommend a change in the proposed text. Board staff note that the comment is outside the scope of the proposed changes in the fourth modified text. Board staff note that the comment has been previously considered and a response provided. Board staff respectfully refer the commenter to the Board's prior response.
2	1736(e)	CSHP	We once more emphasize that us and others who commented on this section remain concerned with the wording of this section. We appreciate the board's position that the intent is to rely on the professional judgement of the pharmacist. At the same time, we object to the wording of the regulation and wish to point out that this section has the potential to be misinterpreted as written, both currently and in the future. It is important to get this right so that the intent is clear and does not cause confusion.	Board staff have reviewed the comment and do not recommend a change to the proposed text based on the comment received. Board staff note that the comment is outside the scope of the fourth modified text. Board staff believe it is appropriate to note that licensed pharmacists are required by law to exercise professional judgement. The commenter appears to suggest that language in some areas lacks clarity. The Board disagrees. The regulation language is intended to

			The wording of ""Essentially a copy" of a commercially available drug product means a preparation that includes the same active pharmaceutical ingredient(s) (API(s)) as the commercially available drug product," could be interpreted to mean that ANY compound being made is defined as essentially a copy of a commercially available drug product. The trouble here is that any compounded drug that has the same API as a commercially available drug product will violate this regulation. We are deeply concerned that the language as written, will cause additional communication and documentation of the communications for both physicians and pharmacists. We are concerned that board staff's previous response to this concern did not demonstrate their understanding of our concern. In the ISOR, the board states that the FDA guidance document is being utilized to provide guidance regarding this definition. It is important to note that the definition taken from the FDA guidance document and used in this proposed regulation, is only one part of three of the definition in the guidance document. Herewith the guidance document section on "Essentially a Copy" for reference: FDA intends to consider a compounded drug product to be essentially a copy of a commercially available drug product if: • the compounded drug product has the same active pharmaceutical ingredient(s) (API) as the commercially available drug product; • the API(s) have the same, similar, or an easily substitutable dosage strength; and • the commercially available drug product can be used by the same route of administration as prescribed for the compounded drug, unless, as provided by section 503A(b)(2), a prescriber determines that there is a change, made	provide flexibility for a pharmacist, using professional judgement to make the appropriate decision for the patient. The Board's regulations in several areas are also intended to provide facilities with flexibilities to implement the requirements as they believe is appropriate for their specific operations. As an example, the Board's essentially a copy definition relies heavily on a pharmacist's professional judgement in making a determination if a compounded preparation would provide a clinically significant difference for the patient. **Note**: The Board did not include the strikethrough (appears to be track changes) in a sentence in the CSHP comment in this area.

			for an identified individual patient, which produces, for that patient, a significant difference from the commercially available drug product. The proposed regulation definition crucially leaves out the requirements for a same or similar dosage strength and route. By leaving out these clarifying terms, the definition is now so broad that it is inclusive of every single non-sterile and sterile compound being compounded by a pharmacy in the state of California. From our example above, it is open to interpretation by both the regulated public and board staff of what "essentially a copy" is because it will be everything with the same API. By the proposed definition, since diazepam tablets are commercially available, a pharmacy may not compound a diazepam drip from IV vials since the tablets contains an API that is commercially available (even though it is available in a completely different non-sterile dosage form). According to the definition, a hospital making a batch of oral suspension from tablets on a regular basis for its neonatal of pediatric unit, will be making essentially copies of the API in the tablets and will have to call and verify with the prescriber and then document the self-evident information that the change was made for each and every identified individual patient that produces for that patient a clinically significant difference. We are sure that we can all agree that this is not the intent of the regulation. By adding the crucial elements of strength and route it narrows the definition and it is much clearer and is aligned with both the FDA and board's intent. This addition of language provides clarification while still allowing flexibility for the pharmacist to use professional judgement. By adding the components that aligns with FDA guidance, it becomes clear that it will the same as federal statute and guidance, and we recommend that this regulation be deleted. We are concerned that Board staff's previous response	

			to this concern did not demonstrate their understanding of our concern. While all involved currently in the creation and comments for the definition of "essentially a copy" may have a grasp and understanding of the intent of this proposed regulation, we must take the multiple comments from all stakeholders as an indicator that there will be future misunderstanding and misinterpretations of this language. It is of the utmost importance to recognize that ten to fifteen years from now these interpretations and intent will be forgotten, and the only guidance left to enforce are the words as written. We are sure that the current board would not want future board members and staff to enforce this rule under the misunderstandings that we and others took great pains to point out at this moment in time. We are concerned that Board staff's previous response to this concern did not demonstrate their understanding of our concern. **Recommendation:** (d) "Essentially a copy" of a commercially available drug product means a preparation that includes the same active pharmaceutical ingredient(s) (API(s)) as the commercially available drug product, **the API(s) have the same, similar, or an easily substitutable dosage strength; and the commercially available drug product can be used by the same route of administration as prescribed for the compounded drug** except that it does not include any preparation in which there has been a change made for an identified individual patient that produces for that patient a clinically significant difference, as **verified and documented** by the **pharmacist**, between that compounded preparation and the comparable commercially available drug product.	
3	1736.1(b)	CSHP	We would like to continue our objections to this proposed regulation for the reasons that we and others have pointed out both in writing and written comments up to this point.	Board staff have reviewed the comment and do not recommend any changes to the proposed text based on the comments received.

			As stated before, we object to the proposed regulation since it would severely limit pharmacies' ability to utilize the immediate-use provision to only those limited situations where the failure to administer such CSP could result in loss of life or intense suffering of an identifiable patient. This continues to narrow the scope of application of the immediate use provisions of USP to a point where it is practically unusable. We and others continue to point out the unintended consequences that this rule has been responsible for in the past, such as shifting compounding to disciplines that do not fall under the jurisdiction of the board. We are concerned that the board's response to stated concerns negates the complexity of health system operations by implying our practices are inefficient and potentially in accurate. . The Board's responses, at times, fails to provide evidence for the continued support of the proposed regulations that have been identified by the regulated entities as potentially harmful to the patients we serve. We thank the board for clarifying our questions regarding the expectations for reporting utilization of the proposed immediate use during instances when the appropriate compounding environment is not available at the time. A review of the ISOR does not address the increase in direct and indirect costs to licensees and the board of the proposed rules associated with the expected increase in reporting. The changed text makes clear the expectations that every single instance of initiation of immediate-use in this context be reported to the board, even in cases where routine maintenance of the engineering controls is scheduled and there is an emergent need for an immediate use compounded medication. We once more reiterate our concern that the board will not have adequate resources to manage the onslaught of additional reports that will be received from licensees. The subsequent increase in staffing	Board staff note that the comment is outside the scope of the fourth modified text. The Board notes that it has previously responded to this comment and respectfully refers the commenter to the Board's prior response. The Board also notes that the commenter appears to be speculating on unintended consequences. The Board has also previously responded to this speculation about shifting compounding to disciplines that do not fall under the Board's jurisdiction. The Board notes that its regulations cover a variety of different practices, and its regulations must address processes and use cases beyond health systems. The Board notes that it's approach to immediate use provisions is consistent with its consumer protection mandate, focused on reducing the opportunity for compromise of the CSP. Immediate use compounding is inherently at higher risk for potential contamination. The Board notes that the commenter suggests potential cost impacts to the proposed requirements. Staff note that in existing regulation, immediate use preparations require administration to begin no later than one hour following the start of the compounding process. USP and the Board's proposed regulations allow for use of immediate use provisions for up to 4 hours with expanded opportunities for use. Staff note that current regulations do not allow for immediate use compounding in the event of equipment or environment failure. Under the proposed regulation text, reporting to the Board would be required when compounding equipment or environment fail, and the facility elects to use the expanded provisions for immediate use as allowed in the proposed regulation text. **Note**: The Board did not include the strikethrough words (appears to be track changes) in a sentence in the CSHP comment in this area.

			will then be passed to licensees via increases in license fees. We are concerned that the board may underestimate the seriousness of challenges that many hospitals that are not designated critical access hospitals will experience in the state. Especially those that serve rural communities. We maintain our position that the board's proposal for immediate use in instances where there may be equipment and engineering control failures is egregiously inadequate. It does not account for both catastrophic failures of the equipment and environment or for catastrophes like natural disasters. We once more reiterate our stance that the additional allowance for critical access hospitals only addresses the problem partially. We object to this partial addressing of this problem and again recommend that the board recognize that there are many rural hospitals that are not designated as critical access hospitals. These hospitals can run into the exact same problems with equipment and engineering controls as critical access hospitals with equally devastating consequences. There are even standalone, single owner hospitals in metropolitan areas without the benefit of belonging to a health system that can be impacted. While we highly recommend that subsection (b) be changed to our recommendation below under the bolded heading of 'Recommendation", absent an acceptance of this recommendation, we recommend that the allowances of subsection (3) be changed to: 3) If the sterile compounding equipment or environment fail(s) to meet any required specification in a critical access hospital **that are not within 40 road miles of a hospital of the same corporate ownership** , ~~as defined in the Social Security Act 42 U.S.C. 1395i-4 section (c)(2)(B)~~, after attempts to remediate pursuant to the facility's SOPs are unsuccessful, an immediate use CSP may be compounded without the requirement for there to	

			be loss of life or intense suffering or an identifiable patient. This provision may be used for 120 hours after such failure(s). All such failures shall be documented in accordance with facility's SOPs and shall be reported to the Board within 72 hours. To continue with the proposed requirement, in essence, means California pharmacists will be the only licensed professionals in the USA banned from utilizing the USP immediate-use allowance. It is concerning that other than stating that "this is existing language at section 1751.8(e)…" there are no reasons provided in the ISOR for the requirement that CSPs used for immediate administration be limited to situations where the failure to administer could result in loss of life or intense suffering. This requirement was created based on the old USP standards when there was limited understanding of the applicable microbiological principles and the wide clinical barriers it creates as it relates to immediate use. It is important that the board consider the negative impact on patient care that this antiquated rule creates. Since the ISOR does not address the objective and scientific reasons for the limitation on immediate use, we recommend that the regulation be deleted. We are concerned that the board has not demonstrated their understanding of our concern regarding this issue. The expectation of an emergency plan to provide compounding services when the hospital's sterile compounding operations are down are ideal and hospitals are required by federal regulations to have emergency plans. However, the proposed regulations are implying the hospital must have a backup cleanroom. This is a multi-million dollar investment which is not possible for most hospitals and especially for rural and stand alone hospitals. . The impact of the proposed regulations will have significant impact on hospitals financial solvency with unintended consequences to patient care. Elimination of low complexity immediate use	

			provision creates additional hurdles to acquiring the medication that might be insurmountable and therefore jeopardize patient safety. We wish to provide the following realistic example: when a rural non-critical access hospital pharmacy has a sterile compounding airflow hood malfunction, and the replacement hood must be ordered and shipped, they can use immediate use compounding for two days. After this they must stop compounding. What is a pharmacy supposed to do then? Think about it, a licensee has the drugs in their hands, but they cannot go through the simple process of mixing it together in a few seconds to treat a patient. . In the absence of a workable solution, we recommend that the immediate use regulation be deleted. We are concerned that the board has not demonstrated their understanding of our concern regarding this issue that has the potential to shut down rural hospitals to the significant detriment of patients and communities. We continue to object to the boards business impact numbers. The immediate use regulation alone will cause a loss in income totaling millions of dollars if a hospital must close their doors and ship patients out to a hospital with a working cleanroom. The Board failed to capture the economic impact to health systems in their ISOR. The board's response to the question of "Business Impact" in ISOR states; "the board anticipates minimal ongoing costs ranging from approximately $5,700 to $15,000 per year related to administrative and maintenance workload." This statement applies to the multiple proposed regulations requiring the addition of new administrative procedures, reporting requirements, and enhanced testing. The amount stated is a gross underestimation of the true cost to health systems. Understandably the Board lacks the internal expertise to accurately reflect those anticipated costs associated with development of policies and procedures, monitoring implementation of those	

			procedures, correctly reporting to the Board as proposed by this regulation and others, cost of monitoring visits by the Board, enhanced environmental and personnel testing requirements, purchase of additional inventory for PPE, implementation of technology to support the deployment of the policies and procedures and hiring of additional staff to support compliance with the proposed regulation. The Board further states in the ISOR under the header of "Business Impact" as it relates to the issue of cost the following: "This initial determination is based on the absence of testimony to that effect during the public discussion and development of the proposed regulation." The public meetings mandate testimony be limited to a few minutes and attendees tend to focus their input on the specific wording of the proposed regulation and not the cost. It is incumbent on the Board to actively pursue input from those that can accurately project the cost to health system of the proposed regulation. The Board should, during public meetings, or by other means seek input from experts who can inform the Board's ISOR development as it relates to both "Business Impact" and Economic Impact Assessment" to ensure the ISOR is an accurate reflection of the impact to health systems on cost and health care access. We continue to ~~wish to further~~ point out that the board has not responded to our comments regarding the economic impact of this proposed rule since they have not approached senior health system leaders who are best situated to assess and assist them with economic impact of this rule. Neither has the board shared their assessment of how this rule will increase their cost of enforcement of the proposed rule. USP 797 provides sufficient guidance in their improved and updated standards for immediate-use compounding, and we once more recommend that the board to require USP's standards and not	

			engage in additional regulations that are not based on an articulated and proven evidence that such proposed regulations will enhance patient safety efforts beyond the national standards. We appreciate the complexities of regulating sterile compounding across the diversity of health system procedures and processes and we would like to invite board members and staff to consider doing site visits to gain a greater appreciation for how health systems promote patient safety and quality of compounded drug preparations. We would be happy to set up those site visits with our members. Specifically, we are inviting board members with limited background and experience in compounding. We once more are signaling our agreement that the routine utilization of immediate use in a hospital is an inappropriate practice. CSHP and our members have the same goals for patient safety as the board. It is unfortunate that some have engaged in this practice and now the majority of law-abiding facilities and pharmacy licensees must suffer the consequences. To account for the unfortunate choices of the few, whilst not punishing the majority we would recommend a more measured approach by limiting the time that an immediate use sterile compound can be used for up to 12 hours maximum from the time that compounding starts. This way the concerns for patient safety is addressed while it is also not so restrictive to the vast majority of ethical and law-abiding licensees. It also has the added benefit that it will not lock both licensees and board staff in a burden of reporting and administrative duties. Additionally, this problem does not have to be solved with multiple layers of regulation that attempts to solve for endless 'what-if' scenarios. As we have taken pains to point out in the aforementioned, these regulations will be creating insurmountable obstacles to patient care, which	

			could in practice only be overcome by licensees making immediate use sterile compounds which would be a violation of the regulations if enacted. Please see our recommendation below. **Recommendation:** Remove the requirement limiting the use of immediate-use CSP's to situations where failure to administer could result in loss of life or intense suffering due to this being deleted from the new USP 797 standards and the profound negative impact on patients. This will subsequently remove the need for reporting to the board. **Recommended Text:** (b) CSPs for direct and immediate administration shall only be compounded in such quantity as is necessary to meet the immediate need of the patient. A compound made for immediate use shall have a maximum beyond use date of 4 hours and shall expire after 12 hours. Note: We note that the board did not show understanding of this recommendation in their response. We therefore wish to clarify that our recommendation is aligned with USP in that it copies the requirement of a beyond use date of 4 hours for immediate use. It must be noted that USP does not assign expiration dates to compounds. Contrary to board staff's assertion that we expand immediate use provisions, we actually limit the life span of an immediate use compound. Board staff's previous comment relayed their concern for patient safety where it is observed that some licensees engaged in preparing epidural and intrathecal compounds that stays on the patient for 24 hours or longer. We mimic the boards approach of adding additional rules to limit USP standards by addressing the stated concern of the board. With this recommendation, we place an expiration date on the compound, implying that a drip or infusion may be started within 4 hours of compounding and use on the patient must then be discontinued by the 12-hour expiration date.	

4	1736.1(b)	Kaiser	At this juncture, we have nothing new to say about this regulation; however, we do not want to risk our silence on the matter being misconstrued as agreement. We continue to believe that this regulation is not necessary because the USP standard on immediate use compounding strikes the appropriate balance between patient safety and timely access to compounded medications. This regulation will have a chilling effect on pharmacy personnel performing immediate use compounding, including in critical situations like Code Blue events in hospitals, and is likely to promote immediate use compounding by non-pharmacy personnel. ~~(b) (1) Except as allowed in paragraph (2), CSPs for direct and immediate administration as provided in USP Chapter 797 shall only be compounded in those limited situations where the failure to administer such CSP could result in loss of life or intense suffering of an identifiable patient. Any such compounding shall be only in such quantity as is necessary to meet the immediate need of the patient. If not already documented in the patient's medical record, documentation for each such CSP shall also include the compounded date and time, the patient's name and patient's unique identifier and the circumstance causing the immediate need of the patient. Such documentation need not be redocumented by the compounding staff if already available.~~ ~~(2) If the sterile compounding equipment or environment fail(s) to meet any required specification, after attempts to remediate pursuant to the facility's SOPs are unsuccessful, an immediate use CSP may be compounded without the requirement for there to be loss of life or intense suffering of an identifiable patient. This provision may only be used for 48 hours after such failure(s). All such failures must be documented in accordance with facility's SOP and shall be reported to the Board within 72 hours.~~	Board staff have reviewed the comment and do not recommend a change in the proposed text. The Board has previously considered this comment. The Board respectfully refers the commenter to the Board's prior responses. Staff note that in existing regulation, immediate use preparations require administration to begin no later than one hour following the start of the compounding process. USP and the Board's proposed regulations allow for use of immediate use provisions for up to 4 hours with expanded opportunities for use. Staff note that current regulations do not allow for immediate use compounding in the event of equipment or environment failure. Under the proposed regulation text, reporting to the Board would be required when compounding equipment or environment fail, and the facility elects to use the expanded provisions for immediate use as allowed in the proposed regulation text.

5	1736.1(e)(1)	Novo Nordisk	**Comment:** We reiterate our request that the Board update Section 1736.1(e)(1) to state only the prohibition on compounding of "essentially a copy of one or more commercially available drug products," as defined at Section 1736(e), for the same reasons as described above in our comments regarding Section 1735.1(e)(1). Specifically, the provisions relating to the ASHP Drug Shortage List and compounding when a health care facility cannot obtain a drug from the manufacturer or wholesaler are inconsistent with federal law and policy, create risks for patient safety and health, and undermine a key check on compounding unapproved drugs. **Recommended language revision:** "(e) In addition to prohibitions and requirements for compounding established in federal law, no CSP shall be prepared that: (1) Is essentially a copy of one or more commercially available drug products, as defined at Section 1736(e) of this article. Documentation by the pharmacist that the compounded drug product produces a clinically significant difference for the medical need of an identified individual patient, as provided for at Section 1736(e) of this Article, must be maintained in a readily retrievable format."	Board staff have reviewed the comment and do not recommend a change to the proposed text. Board staff note that the comment is outside the scope of the proposed changes in the fourth modified text. The Board has previously considered this comment. The Board respectfully refers the commenter to the Board's prior response.
6	1736.1(e)(1)(B)	CA Medical Association	**Requirement to Verify a Preparation Produces a Clinically Significant Difference Interferes with Exercise of Professional Judgment and Exceeds Federal Law (§§ 1735(d), 1735.1(e)(1)(B), 1736(d), 1736.1(e)(1)(B))** CMA reiterates its concern regarding the Board's proposed requirement for pharmacists to "verify" that a compounded drug produces a clinically significant difference for a patient. This proposed requirement creates an undue burden and restricts the professional judgment the Board intended to preserve. Mandating verification for every instance of compounding a commercially available drug that is not on a shortage list establishes a rigid,	Board staff have reviewed the comment and do not recommend a change in the proposed text. Board staff note that the comment is outside the scope of the proposed changes in the fourth modified text. Board staff note that the comment has been previously considered and a response provided. Board staff respectfully refer the commenter to the Board's prior response.

			prescriptive standard. This contradicts the Board's stated goal of maintaining flexibility, and, as such, the language violates the clarity standard because it conflicts with the Board's description of the effect of the regulations in its formal response to members of the public regarding this issue. We refer you to our comment letters dated January 27 and February 21, 2025, for detailed discussions of this issue. To enhance clarity and ensure patients maintain timely access to medications, CMA reiterates its request from our prior comment letter, dated January 27, 2025, to remove "verify and" from proposed sections 1735(d), 1735.1(e)(1)(B), 1736(d), and 1736.1(e)(1)(B) of the third modified text.	
7	1736.1(e)(2)	Wedgewood	We appreciate that the Board addressed our earlier concerns about the ambiguous reference to AMDUCA, but we continue to remain concerned about a direct reference to a Guidance Document that could be eliminated tomorrow by the current administration. What will compliance look like if the Agency rescinds or edits the guidance document making this reference irrelevant? We again make the following Recommendation: This compound shall be in compliance with current industry guidance. ~~the Center for Veterinary Medicine Guidance for Industry #256 – Compounding Animal Drugs from Bulk Drug Substances issued August 2022~~.	Board staff have reviewed the comment and do not recommend a change in the proposed text. Board staff note that the comment is outside the scope of the proposed changes in the fourth modified text. The Board has previously considered these comments. The Board respectfully refers the commenter to the Board's responses.
8	1736.9(e)	Novo Nordisk	We write to alert the Board to a new critical patient safety issue raised by the most recent changes to the Proposed Rule, notably by allowing compounding of untested fixed-dose combinations of a Category 1 bulk drug substance with a component of an FDA-approved drug. In addition, while we acknowledge the Staff Responses to NNI's comments to the Third Modified Text, we urge the Board to further consider the legal considerations raised in our prior comments and update the Proposed Rule to account for these important issues.	Board staff have reviewed the comment and do not recommend a change to the proposed text. Board staff appreciate the commenter raising patient safety concerns and agree with the potential for patient harm when using category 1 bulk drug substances. The Board has made a determination following significant public comment, that the Board's approach to allow for compounding using bulk drug substances included on the published 503A Category 1 bulk drug substances may be performed consistent with federal law, federal guidance and national standards, including for example that the component must be found suitable

			Comment: The Proposed Rule's bulks provisions should be further revised to protect patients against harmful combinations of compounded drugs that have not been assessed for safety or effectiveness. The Board states that it intends to "provide a legal pathway in California to compounding using bulk drug substances included on the FDA Category 1 bulk drug substances list that meet the requirements of federal law, federal guidance and national standards." The Fourth Modified Text, however, goes far beyond the Board's stated intent by proposing to allow untested and unsafe compounding of Category 1 substances in combination with components of an FDA-approved drug. We strongly urge the Board to add our recommended text below to limit the scope of this allowance and protect patients from unknown harms associated with compounded combination products. As written, the Board's Fourth Modified Text would permit compounding of "semaglutide" with co-active ingredients. Combining ingredients that have not been studied with "semaglutide" heightens the complexity of compounded "semaglutide" formulations and introduces some known risks and, critically, a myriad of unknown risks. Developing a fixed-dose combination product is an extremely complex process and requires a careful assessment of the individual drugs alone and when used in combination. This is particularly true when the co-active ingredient is a Category 1 bulk drug substance that has not been evaluated by FDA for its own safety and effectiveness. FDA itself states that a fixed-dose combination "may present greater risk compared to clinical development of an individual drug" and "should ordinarily be reserved" for circumstances where there is a (a) combination intended to treat a serious disease or condition, (b) strong biological rationale for use of the combination, (c) full nonclinical characterization of the activity of both	for the sterile drug preparation consistent with the requirements of the national standards. Board staff note that Section 503A requires compounding to be patient-specific prescription.

			the combination and the individual drugs, or a short-term clinical study on an established biomarker that suggests the combination may provide a significant therapeutic advantage over an available therapy and is superior to the individual agents, and (d) compelling reason why the new drugs cannot be developed independently. These circumstances do not exist for the compounded fixed-dose combination products purporting to contain "semaglutide." Because fixed-dose combination products are more complicated than individually formulated drugs, extensive testing, which compounders do not conduct, is essential to ensure that all ingredients in the drug product work together to provide the expected safety and efficacy profile. Co-active ingredients in compounded "semaglutide" drugs that are not present in FDA-approved semaglutide products include Body Protection Compound-157 (BPC-157), L-Carnitine (levocarnitine), vitamin B-12 (cyanocobalamin or methylcobalamin), glycine, pyridoxine, chromium PIC, tirzepatide, and nicotinamide adenine dinucleotide (NAD+). Testing conducted on some of these compounded samples with multiple APIs revealed impurities and degradants caused by the interactions between the semaglutide and the co-active ingredient, underscoring how complex it is to create such a formulation. For instance, testing revealed safety and efficacy concerns involving a compounded drug containing semaglutide and NAD+, an oxidized form of NAD. NAD and NAD+ "substantially degrade when exposed to light, moisture, alkaline pH, or standard room temperatures; therefore, [they] will not be stable under ordinary storage conditions." Testing results for the sample showed extremely high levels of oxidations and di-oxidations, likely due to the NAD+ reacting with the semaglutide peptide. These testing results indicated that the stability of semaglutide was compromised, which may	

			adversely impact its effectiveness. In addition, the oxidation may result in the formation of aggregates with the potential to induce or enhance immune responses. Novo Nordisk received a complaint from a patient who took compounded "semaglutide" and NAD, was hospitalized, and was diagnosed with liver cirrhosis. The FDA Adverse Event Reporting System (FAERS) also includes one report associated with "semaglutide" and NAD+ where a patient suffered a liver injury, was hospitalized, and ultimately died. These adverse event reports (although limited in number and information) suggest that combinations of "semaglutide" with Category 1 substances may be dangerous. Compounders attempt to justify their compounding of "semaglutide" products based on supposed clinical needs of patients. No clinical justification supports the serious risks associated with compounding "semaglutide" with Category 1 co-actives. The FDA-approved semaglutide medicines come in a variety of strengths and dosage forms to meet the needs of many patients, and if an individual patient has a medical need for a compounded Category 1 substance, the physician can prescribe that drug for the patient. Instead of using this approach, some compounding pharmacies offer prescribers options like the ability to "add Vitamin B6 or Vitamin B12 to semaglutide to prevent nausea or . . . request a formulation of the drug that is delivered under the tongue, . . . which is different from the injectables marketed by [Novo Nordisk] . . . ." However, in those cases where a prescriber determines that a patient needs another drug to complement their therapy, such as vitamin B-6 or B-12, the patient could easily be separately prescribed that vitamin B-6 or B-12 medication alongside an FDA-approved semaglutide medicine, rather than be prescribed an unapproved compounded "semaglutide" product in which the "semaglutide" is mixed with vitamin B-6 or B-12. There	

			is no clinical evidence that using these products in a fixed-dose combination will improve patient outcomes; to the contrary, there are significant unknown risks to patient safety from patients taking such unapproved compounded fixed-dose combination products. FDA expressed some of these unknown risks at an Advisory Committee meeting on methylcobalamin. FDA recommended against adding methylcobalamin to the list of 503A Category 1 substances partly because the Agency had "a concern regarding lack of available safety data with methylcobalamin, particularly for intravenous injections and infusions." An Advisory Committee member raised a specific concern that a published study "found cobalt levels following Vitamin B12 injections were significantly high" and multiple Advisory Committee members voted against adding methylcobalamin to Category 1 due to its unknown safety and effectiveness profile. As we note above, these unknown risks are amplified when methylcobalamin and other co-actives are compounded with "semaglutide." For these reasons, we urge the Board to expressly state that a Category 1 substance should not be permitted to be used as a co-active in a fixed-dose combination product. **Recommended language revision**: "(f)(1) A component included in the published 503A Category 1 bulk drug substances list shall not be used as a co-active in a fixed-dose combination product." **Comment**: We also suggest that the Board reinsert the requirement that a compounded drug is dispensed pursuant to a patient-specific prescription that documents the clinical circumstances that require the use of a bulk drug substance currently on the 503A Category 1 bulk drug substance list. This requirement is consistent with the Federal Food, Drug, and Cosmetic Act section 503A.	