



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

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RE: 2004D-0431

Draft Guidance for Industry and the Food and Drug Administration;  
Current Good Manufacturing Practices for Combination Products

These comments are submitted by Cambrex Bio Science Walkersville, Inc. (CBSW). The CBSW facility is located at 8830 Biggs Ford Road in Walkersville, Maryland.

**Background: Introduction to and Product Types Produced at CBSW.**

CBSW is a leading global provider of biology based solutions to the biotechnology, biopharmaceutical, and Life Sciences communities. CBSW has been a supplier of liquid and powdered media since 1976. The current product line is represented by over 1,000 catalog (made to stock) products, along with custom production. CBSW's standard catalog products are designated as Class 1 Medical Devices by the FDA and are required to be manufactured and distributed under FDA's Quality System regulation (QSR). Title 21 Part 820 of the Code of Federal Regulations. Some products, for which use in *in vitro* diagnostic or clinical use have not been established, are labeled for research, laboratory, or further manufacturing use.

In addition, some CBSW media are planned for use in investigational and approved cell and tissue therapy products that in final form may be a combination product regulated as a biological product, such as a treatment for failure of the heart or organ system. Therefore, the media may become a device constituent part of a combination product regulated as a biological product. Also, some of these media are planned for use in products that may contain bioactive components while being regulated as a device, such as a wound healing cell therapy product on a matrix. CBSW manufactures these various regulated products under a single facility quality system and subject to the same quality procedures and programs.

**GMP/OSR Requirements**

It is important to note that requirements for current good manufacturing practice (cGMP) apply in addition to adulteration and misbranding. Regulated products still demonstrate safety and effectiveness under drug provisions, proper clearance under device provisions, and safety, purity, and potency under biologics provisions. This requirement exists independently of manufacturing conditions and procedures. Federal Food, Drug, and Cosmetic Act (FFDCA) §§ 505, 510, 515 (21 USC §§355, 360, and 360e, and PHS Act § 362 (42 USC § 262). Regulated products also must be free from adulteration, *e.g.*, cross contamination, super- or sub-potency, and unsanitary conditions. FFDCA § 501, 21 USC § 351. Regulated products also must be free from misbranding, which may occur not only when unsupported claims are made but when adulterating ingredients are not included on the label. FFDCA § 502, 21 USC § 352.

Cambrex Bio Science Walkersville, Inc. | 8830 Biggs Ford Road | Walkersville, MD 21793  
Phone: 301.898.7025 | Fax: 301.845.6099 | www.cambrex.com

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As such, if there is an adverse effect on a regulated product from a manufacturing process, then the product will be adulterated or misbranded by the process. The product must not be distributed, and criminal and civil penalties apply if distribution occurs. GMP requirements are in addition to the requirements listed above.

### **Comments**

CBSW appreciates FDA's effort to clarify the application of cGMP and QSR to combination products in the guidance. Nevertheless, we have important comments for FDA's consideration in the finalization of this document, and we seek FDA's response. In sum, CBSW requests that FDA clarify its position so that either cGMP or QSR will apply to the final product, related to the application that is the basis for the product approval.

We expect that FDA inspectors will rely on this guidance during inspections, as will customers who perform audits required by their own manufacturing program. In the application of this guidance, its provisions will be applied in an uneven, unpredictable and arbitrary manner. Not only will the different provisions in the guidance table be applied to some manufacturers and not to others, to some combinations and not others, and to some product classes and not others, but also to products where compliance with the particular provisions is not possible. We believe this potential inconsistency needs to be addressed through a more formal process.

### **Concurrence with the Draft Guidance**

The guidance provides relief for combination product stakeholders in that FDA clarifies that before combination or co-packaging, the manufacture of each constituent part is subject only to the current good manufacturing practice (cGMP) regulations associated with each constituent part. Therefore, a cell therapy manufacturer using cell culture media and other device supplies will satisfy its regulatory obligation by obtaining these materials from a supplier that complies with QSR. We agree with this result, and appreciate FDA's clarification.

Generally, CBSW does not contest the importance of ensuring product stability. In fact, a product with an expiration date unsupported by stability data is probably mislabeled regardless of how its manufacturing process is regulated. FDA approves the labeling of the final product, and can require during the review process that the final product expiry on the label be supported by competent, reliable evidence (or additional evidence, depending on the regulatory review standard of the products, regardless of manufacturing procedures. Therefore, this specific provision in the guidance arguably does not impose new requirements. Also, CBSW does not contest the value of corrective and preventative actions (CAPAs) and this is an important part of continuous improvement, and the information is valuable for process analysis and risk analysis.

### **CBSW requests for clarification and reconsideration**

In sum, CBSW requests that FDA provide clarification and consideration of the following issues:

- that FDA identify the authority by which GMP and QSR may be imposed on a product regulated under a single drug, device, or biological product application, and address why rulemaking is not appropriate or necessary;

- that FDA assure that the principles in this guidance are consistent and appropriate postmarket regulation of like products subject to the same statutory requirements;
- that FDA assure that the principles in this guidance meet the “least burdensome” test in the device provisions of the FFDCA;
- that FDA assure that biological products are not subject to unnecessary layers of regulation;
- that FDA identify not only GMP and QSR principles that might apply across product lines but also GMP and QSR principles that might not apply across product lines; and
- that FDA coordinate with other regulatory initiatives, including PAT, Risk-Based initiatives, and international harmonization.

We have not suggested replacement wording because we believe we have identified complex matters that have not been addressed in this draft. To include these issues requires a reconsideration and redraft, and more likely, rulemaking.

#### FDA authority

The guidance does not discuss under what authority FDA may subject products approved under device provisions to the drug GMP requirements in 21 CFR parts 210 and 211. 21 CFR Part 210 applies to “Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs;” 21 CFR Part 211 applies to “Current good manufacturing practice for finished pharmaceuticals.” Nothing in the regulation suggests that this applies to products with a device primary mode of action.

Likewise, the guidance does not discuss under what authority FDA may subject products approved under drug or biologics applications to the QSRs on devices in 21 CFR Part 820. The scope of this regulation states, “The requirements in this part govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all *finished devices* intended for human use.” 21 CFR § 820.1 (emphasis supplied). Nothing in Part 820 suggests that this applies to products with a drug primary mode of action.

This fact that these conditions would be imposed by guidance is particularly troubling for two reasons: (1) the enabling statute requires notice and comment rulemaking; and (2) because this is a new position for the Agency.

First, the FFDCA provision on General Provisions Respecting Control of Devices Intended for Human Use, states at that FDA:

... may, in accordance with subparagraph (B), prescribe regulations requiring that the methods used in, and the facilities and controls used for, the manufacture, pre-production design validation (including a process to assess the performance of a device but not including an evaluation of the safety or effectiveness of a device), packing, storage, and installation of a device conform to current good manufacturing practice, as prescribed in such regulations, to assure that the device will be safe and effective and otherwise in compliance with this Act.

(B) Before the [Commissioner] may promulgate any regulation under subparagraph (A) he shall --

- (i) afford the advisory committee established under paragraph (3) an opportunity to submit recommendations to him with respect to the regulation proposed to be promulgated,
- (ii) afford opportunity for an oral hearing; and
- (iii) ensure that such regulation conforms, to the extent practicable, with internationally recognized standards defining quality systems, or parts of the standards, for medical devices.

[FDA] shall provide the advisory committee a reasonable time to make its recommendation with respect to proposed regulations under subparagraph (A).

FFDCA § 520(f)(1)(A). No such procedural steps have been afforded here.

Regardless of whether FDA proceeds with rulemaking, we note there is no evaluation of the economic impact of requiring multiple Quality regulations for a single final product. This impact may be especially burdensome when evaluated against the risk: no showing or indication is suggested that there may be any adverse effect on any product by a single program to oversee manufacturing. It is important to emphasize that if there is such an effect on the product from a process, then FDA has a remedy because the product will be adulterated or misbranded.

*Ensure consistency and appropriateness of regulation*

Under the Medical Device User Fee and Modernization Act (MDUFMA) the Office of Combination Products “shall ensure the consistency and appropriateness of postmarket regulation of like products subject to the same statutory requirements.” FFDCA 503(g), 21 USC § 353(g). The guidance does not address how this assures consistency. For example, a wound healing product that is a combination would be subject to postmarket GMP requirements that are inconsistent with those that would be applied to a product for the same indication that is not a combination. To comply with this provision, the guidance (or proposed rule if FDA proceeds with rulemaking) should address this inconsistency and seek comments on the necessity of inconsistent GMP oversight.

*Ensure consistency with previous statements*

Secondly, FDA staff has advised regulated industry that one manufacturing oversight program is acceptable. This concern has been raised as part of the review of combination products early in the history of the Product Jurisdiction Officer, and that Office advised industry to use the program relevant to the application under which the product is approved. There is no suggestion that products approved to date have been subject to both programs. Moreover, there is no suggestion that this has been inadequate since all statutory requirements related to safety, efficacy, premarket approval, labeling, and inspections remain in place.

In sum, this draft reverses FDA’s previous position that one Quality program is acceptable. FDA should use notice and comment rulemaking and cite statutory authority for this change.

### Least Burdensome

The concept of “least burdensome” applies to all devices and device components of combination products regulated by FDA under the device provisions (including *in vitro* diagnostics (IVDs)). In sum, this policy provides additional support to the contention that FDA consider what effect the implementation of this combination product guidance will have, including its effect on similar but non-combination products.

FDA has explained that the “least burdensome” concept should be integrated into all premarket activities, as well as postmarket activities as they relate to the premarket arena. [www.fda.gov/cdrh/ode/guidance/1332.html](http://www.fda.gov/cdrh/ode/guidance/1332.html). This includes guidance document development and application. CBSW urges that its principles be included in considering inspections and manufacturing operations.

Despite this policy, its principles are not evident in the draft guidance. FDA does not evaluate the affect of duplicate manufacturing oversight programs of the same product, while not being imposed on similar products and products for the same indication. CBSW requests this evaluation and specifically proposes that to accomplish this, “least burdensome” principles require that FDA evaluate this burden and less burdensome alternatives before FDA identifies more than one regulatory manufacturing oversight program that applies to a regulated product; that is, before FDA applies a manufacturing oversight in addition to those triggered by the application that is the basis for approval. The inclusion of this evaluation should generate another draft guidance to allow for notice and comment on this matter, since this evaluation is absent from this document.

Alternatively, in order to achieve the “least burdensome” way to accomplish this goal of manufacturing oversight, FDA should identify not only the sections of GMP that will apply to products also regulated under QSR, but the sections of GMP that will not apply.

### Biological Products

FDA also states in the guidance that combinations with biological components are subject to multiple layers of regulation. Specifically, the guidance states:

The biological product regulations, *21 CFR Parts 600-680*, may also apply to the manufacture of drugs that are also biological products *along with the drug CGMP* provisions. They also may apply *along with the QS regulations* to the manufacture of devices that are also biological products (footnotes omitted).

CBSW specifically requests that FDA remove this statement from any final guidance. While our objections are the same as described above, it seems particularly troubling here to cite additional requirements over and above Part 210, 211 and 820 to include the 600s. Moreover, biological establishments are subject to licensure, and much of the manufacturing testing and equipment is independently licensed. FDA should demonstrate the need for additional standards for manufacturing before they are applied.

### Need for exemptions

The draft document states that, "once the product is combined into a single entity or co-packaged, both sets of regulations apply to the combination. FDA recommends manufacturers follow the guidance described in section III.B above (cross referencing particular provisions of the applicable GMP regulation to the inapplicable QSR provision, and vice versa) to achieve compliance with all applicable current good manufacturing practice regulations." The guidance states these requirements differ in specificity.

As mentioned above, CBSW does not object to the suggestion that the expiry be supported by stability data or to the suggestion for CAPAs and related investigations where applicable. However, the suggestions to apply provisions of unrelated manufacturing oversight programs to some classes of products are unmanageable.

We expect that FDA inspectors will rely on this guidance during inspections, as will customers who perform audits required by their own manufacturing program. In the application of this guidance, its provisions will be applied in an uneven, unpredictable and arbitrary manner. Not only will the different provisions in the guidance table be applied to some manufacturers and not to others, to some combinations and not others, and to some product classes and not others, but also to products where compliance with the particular provisions is not possible. We believe this potential inconsistency needs to be addressed through a more formal process.

Products manufactured by CBSW are cell therapies, and the combinations are most often in a housing or matrix to protect or direct the cell products. While CBSW does not object to the performance of the calculation of yield where possible, this is not possible for cell therapy combinations and other biotechnological products that make up a significant part of FDA's combination product class. These products grow, often in protected containers through transport, so yield calculation may not be possible. More importantly, the guidance would impose design controls on combination products after the products are combined. Cell therapies are unlike devices in that they are not designed, and CBSW asks FDA to recognize that they cannot and should not be subject to design controls.

As the QSR and GMP impose different procedures, including design control and yield calculation, the programs differ more than merely in specificity. These new provisions go beyond the scope of the other program, and in fact anticipate different pathways through research, discovery or design, and manufacture. As such, CBSW requests that FDA remove suggestions for other oversight that might be inappropriate to identifiable classes and types of manufacturing programs for regulated products. Alternatively, if FDA determines there is authority to impose both QSR and GMPs on these products, FDA should include in the guidance not only when suggested GMP or QSR programs should borrow provisions from each, but should also clarify when such borrowing would be inappropriate or unnecessary. Because this document can be expected to be used for inspections, the need for exclusions is especially important to achieve consistency in implementation.

**Explain Any Coordination with and Affect of Other Documents and Initiatives on this Guidance**

On the surface, this document imposes requirements that seem at odds with the new Process Analytical Technologies (PAT) initiative, because that new PAT initiative would eliminate procedural manufacturing requirements that are subject to process analysis where risks can be minimized. This guidance would add more regulatory requirements regardless of the risks identified after analysis of the particular manufacturing process. CBSW requests this evaluation and specifically proposes that to accomplish consideration of PAT, FDA should identify why additional requirements can be eliminated where processes may instead be subject to PAT analysis. The inclusion of this evaluation should generate another draft guidance to allow for notice and comment on this matter, since evaluation of this issue is absent from this document.

The approach in the guidance to apply GMP and QSRs across classes of products regardless of risk or product type also seems inconsistent with the Risk-Based Approach that is being taken by CDER. <[www.fda.gov/cder/gmp/](http://www.fda.gov/cder/gmp/)>. CBSW likewise requests this evaluation. Further, CBSW specifically proposes that to accomplish the implementation of a risk-based approach, FDA should identify risks that cannot be addressed by a single manufacturing oversight program. Again, the inclusion of this evaluation should generate another draft guidance to allow for notice and comment on this matter, since evaluation of this issue is absent from this document.

FDA also recently announced a "Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations." The draft guidance illustrates where FDA can harmonize across agency centers and with other non-U.S. quality management requirements. This draft guidance was developed by the quality systems group formed as part of the CGMP for the 21st Century initiative. Docket No. 2004D-0443; <[www.fda.gov/OHRMS/DOCKETS/98fr/04-22206.htm](http://www.fda.gov/OHRMS/DOCKETS/98fr/04-22206.htm)>. To the extent FDA will coordinate these quality systems in this related effort, manufacturing of combination products should be incorporated into that approach rather than treated differently from other products.

CBSW requests that the final guidance, or more formal procedure if undertaken, include an explanation of how this guidance is to be applied in light of these documents and initiatives.

In addition, FDA is harmonizing its manufacturing requirements with international organizations and agencies such as the EU. This draft does not discuss the effect of these requirements on those initiatives, particularly whether this proposal exceeds the requirements of those initiatives.

**Conclusion.**

CBSW appreciates the opportunity to provide comments on FDA's guidance document. In sum, we request"

- that FDA identify the authority by which GMP and QSR may be imposed on a product regulated under a single drug, device, or biological product application, and address why rulemaking is not appropriate or necessary;

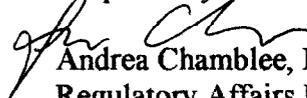
- that FDA assure that the principles in this guidance are consistent and appropriate postmarket regulation of like products subject to the same statutory requirements;
- that FDA assure that the principles in this guidance meet the “least burdensome” test in the device provisions of the FFDCA;
- that FDA assure that biological products are not subject to unnecessary layers of regulation;
- that FDA identify not only GMP and QSR principles that might apply across product lines but also GMP and QSR principles that might not apply across product lines; and
- that FDA coordinate with other regulatory initiatives, including PAT, Risk-Based initiatives, and international harmonization.

Because the inclusion of this evaluation would be new, and regulated persons can provide important on these issues, CBSW believes this discussion justifies reissuing the document as a draft if FDA pursues this position.

We urge FDA especially to revise the draft document to identify instances where GMP does not apply to combinations that include devices, and where QSR does not apply to combinations that include drugs. Because this document can be expected to be used for inspections, this is especially important to achieve consistency in implementation.

Should you have any questions regarding our comments, please do not hesitate to contact us. Thank you for the opportunity to submit our comments.

Respectfully submitted,

  
Andrea Chamblee, Esq., RAC  
Regulatory Affairs Manager  
Cambrex BioScience Walkersville, Inc  
8830 Biggs Ford Road  
Walkersville, MD 21793-0127  
fax 301-845-6452  
voice 301-898-7025 ext 2288  
andrea.chamblee@cambrex.com