

**AMGEN**

Amgen Inc.  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799  
805.447.1000

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

**Ref: [Docket No. 2004D-0431]**

Draft Guidance for Industry and FDA: Current Good Manufacturing practice for Combination Products

Dear Sir/Madam:

Amgen Inc. is please to provide these comments on the Draft Guidance for Industry and FDA: Current Good Manufacturing practice for Combination Products. Amgen Inc. is a global biotechnology and pharmaceuticals products company based in Thousand Oaks, CA.

**Comments:**

**Point #1**

**What is a combination product? (Line 37-60)**

A combination product is defined under 21 CFR 3.2(e).

- There is no discussion or definition here to describe if tissue-derived products (e.g., tissue from patient, cultured, and shipped to hospital) that are combined with devices will be included under the category biologic/device?

**Point #2**

**How are combination products regulated? (Line 76-93)**

Under section 503(g)(1) of the Act, assignment to a center with primary jurisdiction, or a lead center, is based on a determination of the primary mode of action (PMOA) of the combination product.

- When would a drug manufacturer use the new 510k (pre-market notification) paradigm to demonstrate substantial equivalence for a new drug product delivery or administration system?
- If a combination product's device component's design execute and control the ergonomics for the patient-user interface, can it also qualify as the "primary mode

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of action” for the combination product? This is not discussed under the combination products regulation section.

**Point #3**

**Implementation of CGMP and the QS regulations (Line 124-125)**

FDA considers the CGMP and the QS regulations to be similar, and they are meant to achieve the same goals.

- We recommend FDA elaborate inspectional approach and requirements for PAI as a criterion for approval or non-approval for the combination product manufacturer vs. constituent part manufacturer.

**Point #4**

**Stability and Design Validation (Line 134-139)**

FDA has suggested that under the QS regulation, for a combination product with a drug constituent part, yield and stability requirements would be incorporated more generally as part of the design validation provisions (21 CFR 820.30(g)).

- There should be elaboration on design validation instead of a very general statement that stability requirements fall under design validation. There are instances that shelf life of the device components is carried out by the supplier. Additionally, not every device will come in direct contact with drug product.

We recommend that FDA detail their expectations on design validation of the device manufacture vs. the combination product manufacture.

**Point #5**

**Key Current Good manufacturing Practice Provision to Consider (Lines 186-194)**

FDA recommends manufacturers of combination products carefully consider specific QS requirements such as Sec. 820.30 Design Controls, Sec. 820.50 Purchasing Controls, and Sec. 820.100 Corrective and Preventative Actions during and after joining the constituent parts, if the operating manufacturing control system is Part 210/211 to ensure compliance with both the CGMP and QS regulations.

- A combination product may also be manufactured using components that are designed and manufactured by a device component supplier. In other cases, manufacturers of combination products may only provide user requirements inputs and confirm that design conforms to the intended use of the device, including the needs of the users and patients. We recommend that FDA provide guidance on how the QS regulations should be applied to Design Controls in such cases.
- What would be the expectations of FDA on supplier qualification and monitoring program of the combination product manufacturer?

- The Guidance does not reference specific QS requirements on risk management, or post-market surveillance of complaints and adverse event. What would be FDA's expectation on them?

**Point #6**

**Present information to FDA when the product is being developed (Line 205-210)**

FDA recommends that manufacturers of the four types of combination products, defined under 21 CFR 3.2(e), present information to the Agency when the product is being developed about how they intended to achieve compliance with each set of regulations during and after joining the product together?

- Should there be more guidance on how a sponsor can use Office of Combination Products to determine Center jurisdiction for novel combination products?

**Point #7**

**Compliance with both CGMP and QS regulations (Lines 228-238)**

Before combination or co-packaging, the manufacture of each constituent part is subject only to the current good manufacturing practice regulations associated with each constituent part. Once the product is combined into a single entity or co-packaged, both sets of regulations apply to the combination.

- We recommend that FDA expand discussions on the application of CGMP and/or QS regulations by correlating to manufacturing process or activities.

**Point #8**

**CGMP for Combination Products (Line 168-174; 235-238)**

Guidance says, "It should generally not be necessary for manufacturers who make combination products that are produced as a single entity or are co-packaged to maintain two separate manufacturing systems to ensure compliance with both sets of regulations during and after joining the components together. FDA believes that compliance with both sets of regulations during or after joining these types of combination products can generally be achieved by using either the cGMP or QS regulations..."

It also says, "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 to achieve compliance with all applicable good manufacturing practices regulations."

- They seem inconsistent.

**Point #9**

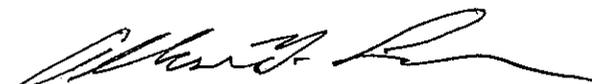
**When does FDA recommend discussing CGMP issues with the Agency? (Line 254-272)**

“Manufacturers are encouraged to seek FDA comment on their implementation of current good manufacturing practice during pre-investigational (pre-IND/IDE) meetings and throughout combination product development.”

- It focuses only on investigational new drugs/devices and not on marketed products.
- No discussion re: drug product(s) that are combined with a device(s) that may be individually approved but together are not approved as a combination product (e.g. a new or novel method of drug administration) What strategy should a sponsor use to apply and communicate with the Office of Combination Products to request a designation in order to identify the Center for primary jurisdiction?

If you have any questions regarding our comments, or how we may assist with further development of the Guidance, please contact me.

Sincerely,



Allan Y. Lin  
Project Manager, Corporate Quality Compliance  
Phone (805) 313-1618  
e-mail: alin@amgen.com