August 14, 2018

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

Re: Docket No. FDA–2018–N–2065: Alternative or Streamlined Mechanisms for Complying with the Current Good Manufacturing Practice Requirements for Combination Products; Proposed List Under the 21st Century Cures Act

Dear Sir or Madame:

The Advanced Medical Technology Association (“AdvaMed”) appreciates the opportunity to provide comments on the Food and Drug Administration’s (“FDA” or “Agency”) proposed list of alternative or streamlined mechanisms for complying with the current good manufacturing practice (“CGMP”) requirements for combination products.

AdvaMed is the world’s largest association representing manufacturers of medical devices, diagnostic products, and medical technology. AdvaMed’s member companies range from the largest to the smallest medical product innovators and manufacturers, with nearly 70 percent of our members generating less than $100 million in annual sales. AdvaMed’s member companies produce innovations that transform health care through earlier disease detection, less invasive procedures, and more effective treatments.

AdvaMed commends FDA for meeting the requirement in Section 3038(c) of the Cures Act to publish a list identifying types of combination products and manufacturing processes for which good manufacturing processes may be adopted that vary from the requirements set forth in 21 CFR § 4.4, or that can satisfy § 4.4 through alternative or streamlined mechanisms. We believe that publication and regular review, revision, and supplementation of this list will help combination product sponsors meet CGMP requirements while avoiding unnecessary or inefficient practices that slow or prevent patient access to medical products.

To that end, we enclose with this letter comments on the proposed list of alternative or streamlined mechanisms. These comments focus on stability expectations for combination products and providing relevant examples of bracketing and matrixing approaches as applied to reserve samples. Our comments also encourage FDA to highlight combination product types and manufacturing processes for which good manufacturing processes vary from standard combination product CGMP requirements, as well as to describe alternative or streamlined approaches to meet CGMP requirements. We believe that this description will help sponsors understand varying, alternative, or streamlined mechanisms and processes and apply such mechanisms and processes to their products.
AdvaMed thanks FDA for its consideration of its comments. Please do not hesitate to contact me at 202-434-7243 or ssilverman@advamed.org if you have any questions.

Respectfully Submitted,

/s/

Steve Silverman
Vice President
Technology & Regulatory Affairs
AdvaMed

Attachment
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<tr>
<th>#</th>
<th>Section</th>
<th>Comment</th>
<th>Rationale/Justification</th>
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<td>1</td>
<td>II.B.1-II.B.3</td>
<td>Clarify that the references in these sections to “do not affect” or “do not impact” the drug constituent part mean that any effect or impact on the drug constituent part does not cause the part to fail to meet final specifications. For example, in connection with section II.B.1, the manufacturer would need to establish that differences in the manufacturing process for product samples that are not finished combination products would not compromise the finished product’s compliance with final specifications. Or, in connection with section II.B.3, a manufacturer could define a “batch” as the drug constituent part of a combination product provided that any subsequent manufacturing processes would not cause the finished product to fail to meet final specifications.</td>
<td>“Affect” and “impact” are broad terms that go beyond what is required to assure product safety and effectiveness. The relevant consideration is whether alternate approaches compromise a product’s compliance with final specifications. Consequently, this consideration should govern use of the terms “affect” and “impact.”</td>
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Add a section on annual stability expectations for combination products, as follows: “Companies seeking to comply with stability study requirements may, after approval, monitor the stability of combination products according to a continuous program to detect stability issues associated with the product (e.g., changes in levels of impurities or dissolution profile) in its marketed container closure system or in the constituent part if the primary container merely holds the drug until use. The stability program should monitor the combination product over its shelf life and determine that it remains, and will remain, within specifications under labeled storage conditions. The protocol for the stability program can differ from initial long-term stability studies in the marketing authorization dossier if this is justified and documented in the protocol. The number of batches and the frequency of testing should provide sufficient data to permit trend analysis. Unless the combination product is not produced during the year, or unless otherwise justified, at least one batch per year of extremes – in both product dimensions and total drug load – for each product design should be included in the stability program.

In some cases, additional batches should be included in the continuous stability program. For example, after any significant change or significant deviation to a process or in the container closure system, an ongoing stability study should be conducted. The sponsor should document and maintain a summary of the data generated, including any interim conclusions, and this summary should be subjected to periodic review and updated as appropriate.”

This addition is offered as a proposed alternative mechanism to meet applicable cGMP requirements for stability studies for combination products that include drug constituent parts. FDA’s and other regulators’ guidance documents promote such studies. For example, FDA’s Inspection Technical Guidance, “Expiration Dating and Stability Testing for Human Drug Products,” (“Expiration Dating Guidance”) provides, “it is imperative that stability studies are not limited only to initial production batches[,] but a portion of annual production batches be the subject of an ongoing stability program.” Expiration Dating Guidance, Stability Testing, B.1. Similarly, the European Union directs that, “[u]nless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year).” EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, 6.32.
Revise to, “Using samples from representative lots of a larger batch for retention of reserve samples. To meet the requirements of § 211.170, CP manufacturers may be able to use bracketing and matrixing approaches to retain reserve samples from certain lots to adequately represent the broadly defined batch of the combination product. For example, CP manufacturers might be able to retain reserve samples of appropriately varied sizes of a drug coated combination product from a single-batch formulation used to coat multiple lots of different-sized device constituent parts. This mechanism would be available if the lot-release testing and specifications are the same for the product matrix and there is no impact on the drug constituent part from subsequent or different manufacturing processes, including when constituent parts are combined to produce the finished combination product.

This revision offers a relevant example of matrixing by highlighting use of a single-batch formulation for diverse constituent part sizes. As important, the example clarifies that the mechanism applies only if there is no impact from the manufacturing process on the drug constituent parts.
List examples of combination product types and manufacturing processes for which good manufacturing processes vary from standard combination product CGMP requirements or for which alternative or streamlined approaches satisfy CGMP requirements.

This information would allow sponsors to better understand the varying and alternative or streamlined mechanisms available to meet combination product CGMP requirements. In turn, this information would position sponsors to apply these mechanisms or propose new mechanisms.