Combination Products Coalition

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VIA ELECTRONIC SUBMISSION

Jerry Moore, NIH Regulations Officer
Office of Management Assessment
6011 Executive Boulevard, Suite 601, MSC
7669, Rockville, MD 20852–7669

RE: Docket No. NIH-2011-0003: The National Institutes of Health (NIH) Proposed Rule – Clinical Trials Registration and Results Submission

Dear Mr. Moore,

The Combination Product Coalition ("CPC") is pleased to offer its comments on NIH's Proposed Rule – Clinical Trials Registration and Results Submission.

By way of background, the CPC is a diverse group of drug, biological product, and medical device manufacturers with substantial experience and interest in the policy issues affecting combination products. Our members range in size from small start-ups to multi-billion dollar manufacturers and it is this diverse, cross-industry membership which allows the CPC to bring a broad and unique perspective to the various policy issues affecting combination products. For more information on the CPC, please visit our website: http://www.combinationproducts.com.

On November 21, 2014, the National Institute of Health ("NIH") published a notice of proposed rulemaking regarding requirements for clinical trial registration and the reporting of results (alternatively, the "Notice" or the "Proposed Rule"). Given the CPC's focus on combination products, our comments relate solely to the aspects of the Proposed Rule that directly and uniquely impact combination products. In that regard, we request that NIH update the Proposed Rule to ensure that clinical trial reporting obligations applicable to combination products are consistent with FDA regulation of combination products. Our specific requests are outlined below.

1) **Applicable clinical trials involving combination products with a device primary mode of action should be considered "applicable device clinical trials" not "applicable drug clinical trials."**

NIH's proposal that the term "applicable drug clinical trial" encompass all applicable clinical trials involving combination products is an improper expansion of the statutory definition of this term and is inconsistent with FDA regulation of combination products. Section 282(j) of title 42 of the United States Code defines "applicable drug clinical trial" to mean "a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 355 of title 21 or to section 262 of [title 42]."

Although all combination products may contain drugs, as defined by section 321 of title 21 or biological products, as defined by section 262(i) of title 42, not all combination products are subject to the requirements of either section 355 of title 21 or section 262 of title 42. Rather, some combination products, i.e., those with a device primary mode of action, may be legally marketed under premarket notification, pursuant to 360(k) of title 21, or premarket approval, pursuant to 360e of title 21. Both premarket notifications and premarket approvals are reviewed by FDA's Center for Devices and Radiological Health ("CDRH") rather than the Center for Drug Evaluation and Research ("CDER"). Further, many of the clinical trials of such products are conducted under investigational device exemptions ("IDE").

However, under NIH's proposed definition, a clinical trial of a combination product with a device primary mode of action being conducted under an IDE would be considered a *drug* clinical trial. This not only fails to align with FDA's regulatory requirements for these products, but also imposes more burdensome obligations on these combination products than for other products that FDA regulates as devices.

Specifically, as a result of being considered an applicable drug clinical trial, the registration information for such a combination product will be published within 30 days after it is submitted, regardless of whether the combination product has been previously approved. This process diverges from applicable device trials for previously unapproved or uncleared products for which registration information is not made available to the public until after approval or clearance of the device. Thus, NIH's Proposed Rule actually subjects combination products with a device primary mode of action to a higher level of regulation than other regulated devices. This inconsistency with FDA regulations could lead to negative unintended consequences when NIH attempts to enforce the Proposed Rule.

For example, the Notice indicates that NIH is proposing a method to determine whether a clinical trial is an "applicable clinical trial" based on a subset of the data elements required for clinical trial registration. A clinical trial must meet at least one of the following, among other requirements, to be deemed an applicable clinical trial: "(A) At least one Facility Location for the clinical trial is within the U.S. or one of its territories; (B) A drug under investigation is a Product Manufactured in the U.S. or one of its territories and exported for study to another country; or the clinical trial has [an FDA] IND Number." Since NIH has determined that all combination product clinical trials are drug clinical trials, such a trial may not be considered an "applicable drug clinical trial" if the study is conducted under an IDE, all sites are located outside of the United States, and the combination product is not manufactured in the United States.

We thus recommend that NIH differentiate between combination products that have a device primary mode of action versus those with a drug primary mode of action and not lump all applicable clinical trials involving combination products in the definition of "applicable drug clinical trial."

2) <u>NIH should update the definitions of "FDA-regulated drug" and "FDA-regulated device" to include combination products with the appropriate primary modes of action.</u>

NIH's Proposed Rule requires several additional data elements that are purportedly necessary during clinical trial registration to "allow the effective implementation of, [and] compliance with" other requirements of Section 402(j) of the PHS Act.

The additional data elements include:

- whether the product was manufactured in the United States or one of its territories;
- any other current or former names of the interventions being studied in the clinical trial;
- an "intervention description" that includes additional information beyond the intervention name, which can help distinguish the intervention being studied in the clinical trial from other interventions being used in the control arms or in other clinical trials;
- **whether the product being studied in the clinical trial is an FDA-regulated device or FDA-regulated drug; and**
- the scientific and ethical review status of the clinical trials listed in the database.

With respect to the bolded requirement in the list above, it is unclear whether NIH expects a sponsor of a clinical trial involving a combination product to designate the product being investigated as a FDA-regulated drug or an FDA-regulated device. Indeed, given NIH's position that all combination products are considered drugs for the purpose of applicable clinical trials, which is inconsistent with FDA regulations, manufacturers of combination products would not know how to submit this data element.

Therefore, we recommend that NIH update the definitions of "FDA-regulated drug" and "FDA-regulated device" to be consistent with FDA regulations. To this end, the definition of "FDA-regulated drug" should include combination products with a drug or biological product primary mode of action, and the definition of "FDA-regulated device" should include combination products with a device primary mode of action. These changes will allow sponsors to classify their products appropriately within NIH's proposed data elements and based on FDA regulations.

Specifically, we recommend the definitions of "FDA-regulated drug" and "FDA-regulated device," as proposed in 42 C.F.R. § 11.10, be modified as follows (recommended changes are in ***bold italics***):

> <u>FDA-regulated device</u> means, for purposes of this part, a device subject to section 510(k), 515, 520(m), or 522 of the Federal Food, Drug, and Cosmetic Act ***or a***

combination product subject to section 503(g) of the Federal Food, Drug and Cosmetic Act with a device primary mode of action.

FDA-regulated drug means, for purposes of this part, a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act***, ~~or~~*** a biological product subject to section 351 of the Public Health Service Act***, or a combination product subject to section 503(g) of the Federal Food, Drug and Cosmetic Act with a drug or biological product primary mode of action***.

3) NIH should confirm that even if one constituent part of a combination product is approved, licensed or cleared independently, a combination product as a whole will be considered unapproved, unlicensed or uncleared by the FDA so long as any constituent part remains unapproved, unlicensed or uncleared.

Exercising the authority granted by Section 402(j)(3)(D)(ii)(II) of the PHS Act, NIH proposes to require responsible parties to submit results of applicable clinical trials involving unapproved, unlicensed, or uncleared products, a significant expansion of the current requirements under the PHS Act. In addition, NIH's Proposed Rule does not extend the results submission timeline to 18 months and is instead proposing that clinical trial results data for all applicable clinical trials be submitted by the earlier of: (1) one year after the completion date of the primary outcome measure; (2) 30 calendar days after initial FDA approval, licensure or clearance of the drug or device for any indication studied in the applicable clinical trial.

Without an appropriate exception for combination products, these new and accelerated reporting requirements would require that sponsors immediately publish clinical trial data for a combination product that has an already approved drug constituent or a cleared or approved device constituent, even if FDA has not approved, licensed or cleared the combination product as a whole. For example, an uncleared injection device pre-filled with an FDA-approved drug is a combination product that must be separately approved by FDA. However, without clarification, the manufacturer of the product may be prevented from delaying publication of any clinical data because the drug constituent is already FDA-approved. Thus, a combination products manufacturer is at a significant competitive disadvantage because it cannot use the delayed publication timeline unless all constituents of a combination product are unapproved, unlicensed, or uncleared. Additionally, in the event NIH ultimately decides to extend the results submission timeline to the full 18 months, the manufacturer of such a product would still not be able to take advantage of the extension.

Therefore, we request NIH specify that a combination product that has not been approved, licensed, or cleared, shall not be considered an approved, cleared or licensed product even if one of its constituent parts has been separately approved, licensed, or cleared. This approach would eliminate the discrepancy in submission requirements for combination product manufacturers versus manufacturers of drug, biologic, and device

products, and is consistent with NIH's stated goal of aligning the Proposed Rule with current FDA regulations.

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The CPC urges NIH to incorporate our suggested changes so that the final rule provides the needed clarity on the registration and results submission requirements applicable to clinical trials involving combination products.

Kindest regards,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition