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

RE: Docket No. 2004D-0228; Guidance for Industry on Fixed-Dose Combination and Co-Packaged Drug Products for Treatment of HIV, 69 Federal Register 28931-28932, May 19, 2004.

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. Investing over \$32 billion in 2003 to discover and develop new medicines, our member companies are leading the way in the search for cures.

PhRMA applauds the intent and supports the Food and Drug Administration's (FDA) effort to provide clarification of the regulatory requirements for fixed dose combination (FDC) and co-packaged versions of medicines to treat human immunodeficiency virus (HIV). We support the views, as summarized in the draft guidance, that FDC and co-packaged products should facilitate provision of complete regimens through health care distribution channels, should simplify HIV regimens, may improve patient adherence, and may help minimize development of viral resistance. We also share the FDA's goals of facilitating distribution of combination therapies and improving patient compliance and, thus, appreciate the agency's encouragement of sponsors to submit such applications that will allow for achievement of these goals.

### **General Comments**

Our member companies are committed to helping make affordable HIV drugs available in sub-Saharan Africa and the Caribbean. At the same time, we appreciate and support the FDA's acknowledgement in this Guidance of innovators' patent and other proprietary rights within the United States that support continued innovation in this area. Our comments on specific aspects of the Draft Guidance are set forth below (the focal point of each comment is identified by line numbers in the Guidance).

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*Pharmaceutical Research and Manufacturers of America*

## **Specific Comments**

PhRMA notes that, while specific recommendations are provided with respect to clinical considerations, clinical pharmacology and biopharmaceutics information, and information regarding chemistry, manufacturing, and controls, the draft guidance does not address principles that might apply to labeling. For co-packaged products particularly, it would be useful to include FDA's current thinking with regard to the professional labeling for the co-packaged product, more specifically under what conditions it might be acceptable to enclose separate package inserts for each product contained in the co-package.

### **Section II. Background (page 2-3)**

**Lines 52-57 and 186-187:** The draft guidance makes repeated reference to the treatment guidelines published by the Department of Health and Human Services (HHS) Panel on Clinical Practice for the Treatment of HIV Infection (*Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents*). This creates an implication that recommendations in these (and, perhaps, other) guidelines might provide a sufficient basis for approval for a fixed dose combination or co-packaged product. PhRMA requests the guidance provide further clarification on the role of treatment guidelines in the approval of such products to avoid confusion created by reference to them in this context.

**Lines 64-65:** The draft guidance states that it is important to evaluate the safety and efficacy of possible combinations in various populations. PhRMA recommends that the draft guidance reiterate that the current statutory and regulatory requirements for each new drug application (NDA) apply in full to FDCs and co-packages of antiretroviral products. Specifically, each FDC or co-package must meet all current statutory and regulatory standards governing product quality and safety, as well as have substantial evidence of efficacy for the proposed therapeutic use. Absent such explicit statements, some readers may wrongly assume that lower standards are being applied to these FDCs and co-packaged products.

**Lines 81-86:** The draft guidance states "that FDC and co-packaged products may also be valuable in the treatment of other serious infectious diseases such as tuberculosis and malaria." While it goes on to note that this guidance is being written to address issues in HIV therapy, many of the principles relied upon are more generally applicable. It concludes this point by suggesting that sponsors "with potential products for other serious infections such as those just mentioned are invited to contact the Division of Anti-Viral Drug Products to discuss these proposals." Is the intent of this statement to make the Division of Anti-viral drug products the contact point for information regarding FDCs or co-packaged products for all infections regardless of whether they are viral in origin?

### **Section IV. General Considerations (pages 4-7)**

**Line 128:** The draft guidance states that FDA's guidance applies to certain products for which "adequate evidence" of safety and efficacy in combination already exists. To ensure consistency Section 505 of the Federal Food, Drug and Cosmetic Act (FFDCA), we request the guidance be revised to use the term "substantial evidence," at least when referring to effectiveness.

**Lines 199-202:** Attachment B of the guidance contains a list of examples based on information in either (1) FDA-approved labeling or (2) peer reviewed literature. PhRMA understands (per lines 220-221) that the list in Attachment B is not meant to be comprehensive and it will evolve over time, and we support such evolution. Thus, we recommend that Attachment B be restricted to combinations and regimens based on either (1) FDA-approved labeling, (2) peer reviewed publications of adequate and well-controlled clinical trials and (3) consistent with DHHS guidelines.

**Line 219:** Please clarify whether the bullet "Recommended as preferred or alternate regimens for initiating antiretroviral therapy" refers to the DHHS guidelines.

#### **Section V. Clinical Considerations (pages 7-8)**

**Lines 257-258:** PhRMA recommends revision of the statement, "Relying on FDA's finding of safety and effectiveness for approved drug products, subject to U.S. intellectual property rights" by replacing "approved drug products" with "approved combination drug products." This would clarify that reliance on an FDA finding of safety and effectiveness applies only to Abbreviated New Drug Applications seeking approval of a copy of an approved drug product and submitted to FDA pursuant to Section 505(j) of the FFDCA.

**Lines 269-271:** PhRMA recommends that the agency address drug-drug interactions in the context of the clinical characterization in this section of the guidance.

#### **Section VI. Clinical Pharmacology (page 8)**

**Line 286:** With respect to considerations related to relative bioavailability and bioequivalence PhRMA recommends recognition that requests for a waiver of the requirement for a bioequivalence study ("biowaiver") for lower potencies of individual products in co-packages or FDCs should be considered based on proportional similarity and/or BCS classification if applicable.

**Line 342:** With respect to dissolution testing, we recommend adding a recognition that, although, a single dissolution medium is desirable for a fixed dose combination product, it may not always be achievable. For these cases, the use of a second medium should be allowed. (See comment on Line 407.)

#### **Section VII. Chemistry, Manufacturing, and Controls (pages 9-12)**

**Line 360-361:** PhRMA requests that it should also be recognized that co-packages should not be limited to blisters. Please consider inclusion of the following: "Co-

packages are not limited to blisters. Other packaging may be appropriate and should be discussed with the agency."

**Line 366:** This paragraph pertains to stability data for co-packaged products. We recommend approval flexibility when the sponsor(s) is proposing a more protective blister co-package than is approved for one of the individual products. For example, sponsor A (product A) has FDA approval for Aclar blister package and sponsor B (products B & C) has approval for a more protective aluminum foil blister package. In this situation, available data suggests that actual stability data is not necessary on the aluminum foil dispensing package to support approval of the aluminum foil co-package for products A, B & C. A commitment could be made to provide stability data post approval.

Additionally, we recommend inclusion of a general statement regarding planned blister co-packs which are equivalent to the FDA-approved blister pack for the single drug products. In these cases, no new stability data may be necessary as stability is supported by individual blister cavity data. Please consider inclusion of the following statement: "Where the individual products are being co-packaged into identical packages as approved under the individual NDAs respectively, it may be possible to submit with no new stability data on the co-packaged product."

There should also be some allowance for blisters of similar composition to show equivalency (i.e., comparative MVTR, contact materials) to the planned market packs. In this case, a commitment to place material on stability may be all that is needed for submission/approval. Please consider inclusion of the following statement: "Where the individual products are co-packaged into similar blister packs as approved under the individual NDAs respectively, it may be possible to use comparative data (USP MVTR, etc.) to support absence of stability data in the co-packaged application with a commitment to place co-packaged product on stability and report data in the Annual Report."

PhRMA also recommends that the FDA clarify the expectations of child resistance testing/requirements that support approval for packaging that will be used exclusively outside the United States (i.e., in Africa). The standards should be based on the WHO Annex 9 "Guidelines on packaging for pharmaceutical products", and not on the U.S. Consumer Products Safety Commission protocol for child resistant packaging.

**Lines 397-398:** The need for control of solid-state particle size and polymorphic form will depend on the final formulation. In the case of a traditional solid oral table dosage form, this could be relevant depending on what is known regarding the relationship of changes in these properties and the corresponding impact on bioavailability. For many poorly soluble compounds, however, a traditional tablet formulation may not be feasible. In many instances, a more sophisticated drug delivery technology may be required to achieve bioavailability. In some cases, the properties of the API in the final

formation may be very different than the properties of the original API raw materials. We believe this is an issue that needs to be addressed on a case-by-case basis.

Furthermore, the need for a particle size control is described by ICH Q6A guidance (decision tree # 3) and cannot be generalized to all poorly soluble drugs. Please consider inclusion of the following statement: "If the active ingredients are poorly soluble and are present in the dosage form as discrete particles, consideration for particle size control on drug substance should be given, according to the criteria described under ICH Q6A guidance."

**Line 398:** The need for a polymorphic forms control is described by ICH Q6A guidance (decision tree # 4) and cannot be generalized to all poorly soluble drugs. Please consider inclusion of the following statement: "If these active ingredients can exist in different solid-state polymorphic forms, additional controls may be needed according to criteria described under ICH Q6A guidance."

**Lines 399-401:** Acceptance criteria for impurities should be established as described in the relevant ICH guidance. Please consider inclusion of the following statement: "Acceptance criteria for process impurities and degradants should be based on manufacturing experience and toxicological considerations, as described by relevant ICH guidance on drug substance and drug product (reference: ICH Q3B(R))."

**Line 407:** Although a single dissolution medium is desirable for a fixed dose combination product, it may not always be achievable. For these cases, the use of a second medium should be allowed. (See comment on line 342.)

**Line 418:** The ICH guidance Q1F describes stress storage conditions needed to support marketing in Climatic Zones III & IV (e.g., 50°C and 25°C/80%RH); this testing requirement is not for the United States. The guidance of reference describing stress storage conditions for the US (relevant ICH regions) is Q1A(R2).

**Line 448:** FDA should continue to exercise its role of the guardian of public health and therefore ensure that products that do not obtain approval or tentative approval under the process described in this guidance can not be imported or distributed within the US. Also, product that has only a tentative approval is not legally authorized to be distributed in the US and thus, FDA should not allow such product to be distributed within US.

## **Section X. Other Regulatory Considerations (pages 13-15)**

**Lines 507-508:** Please clarify the necessity of the statement "patents and exclusivity should not be a bar to the review and approval of such products." We recommend that the guidance instead state: "If these FDC and co-packaged products are to be developed by sponsors who either own or can obtain a right of reference to the underlying data, the regulations that govern these submissions should apply. If these

products are not developed by the innovator, applicants who neither own nor can obtain a right of reference to the underlying data should file under the regulations that govern the submission and approval of 505(j) and 505(b)(2)."

**Lines 541-553:** The draft guidance provides information on pediatric studies. From PhRMA's perspective, FDA should expect sponsors to routinely seek a waiver for assessment of pediatric patients below a certain age for whom the doses in a fixed-dose combination product are not medically appropriate. We encourage FDA to state explicitly that the Agency expects to grant a waiver in such situations.

Co-packaged antiretroviral products, in our view, should not be subject to the provisions of the Pediatric Research Equity Act (PREA) because an application for a co-packaged product does not provide a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Therefore, in our view, this guidance should state explicitly that FDA's interpretation of PREA is that the pediatric assessment requirements of PREA do not apply to co-packaged antiretroviral drug products.

**Attachment A Scenarios for Approval of FDA/Co-Packaged Combinations for Treatment of HIV (pages 16-18)**

Please provide clarification on the following concern. Scenario 1 in Attachment A outlines the regulatory requirements for innovative companies filing an NDA for a fixed-dose combination product. Scenario 2-4 outlines the requirements for non-innovator applicants. PhRMA is concerned that the CMC standards specified in the guidance for Scenario 2-4 appear to be lower than for Scenario 1. Specifically, innovative companies are advised on line 363 of the draft Guidance to cross-reference another application or a drug master file. Non-innovator applicants should be guided to specific quality standards that will be required. Since non-innovative companies do not have access to current CMC documents, the quality standards for their manufacturing should be explicitly described.

**Line 615:** PhRMA understands that "tentative approval" means that the application meets the technical and scientific requirements for approval, but that "approval" can not be issued until governing patents and exclusivity expire. It will be helpful if FDA can clarify whether "tentative approval" also means that the proposed manufacturing facilities have been inspected for this application and comply with FDA's current requirements.

PhRMA member companies appreciate this opportunity to provide comments on this important topic.

Sincerely,

