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**RE: Docket No. 2004D-0228;**  
**Comments on the "Draft Guidance for Industry: Fixed-Dose Combination and Co-Packaged Drug Products for Treatment of HIV", *Federal Register*, Volume 69, No. 97, pages 28931-28932, May 19, 2004.**

Dear Sir or Madam:

Reference is made to the notice, as published by the Food and Drug Administration in the *Federal Register* on May 19, 2004, to invite written comments on a new draft guidance for industry ("Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV") (1). The purpose of this letter is to provide comments on this new draft guidance.

GlaxoSmithKline is a research-based pharmaceutical and biotechnology company. Our company is dedicated to the discovery, development, manufacturing, and distribution of medicines and vaccines that enable people to lead longer, happier, healthier, and more productive lives. GlaxoSmithKline has a long history of productive research and development of products for the treatment of HIV and other viral infections. In these efforts, we have worked constructively for almost two decades with the Division of Antiviral Drug Products and other groups within FDA, with our first approved antiretroviral drug product entering US distribution in 1987. GlaxoSmithKline holds FDA-approved New Drug Applications for Retrovir (zidovudine) products, Epivir (lamivudine) products, Ziagen (abacavir sulfate) products, Agenerase (amprenavir) products, and Lexiva (fosamprenavir calcium) Tablets. In addition, we have specific expertise in pharmaceutical and clinical development of fixed-dose combination antiretroviral drug products (FDCs). GlaxoSmithKline successfully developed the first 2 FDCs in the United States; these products are Combivir Tablets (a 2-drug combination of 150mg lamivudine plus 300mg zidovudine, approved on September 26, 1997) and Trizivir Tablets (a 3-drug combination of 150mg lamivudine plus 300mg zidovudine plus 300mg abacavir sulfate, approved on November 14, 2000). In addition, we have ongoing activities to develop new FDCs and co-packaged antiretroviral drug products. In view of our longstanding work in this field and our substantial interest in the topics in this new draft guidance, we welcome this opportunity to provide comments for FDA's consideration.

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In the following sections, we provide comments on the draft guidance. We have provided comments on each major section of the draft guidance. The focal point of each comment is identified by line numbers in the draft guidance. We trust that this approach will facilitate your review and consideration of these comments.

### **I. Introduction (pages 1-2)**

**Lines 19-21:** FDA states on lines 19-21 that this draft guidance is ". . . intended to encourage sponsors to submit applications to the Food and Drug Administration (FDA) for approval of fixed dose combination (FDC) and co-packaged versions of previously approved antiretroviral therapies . . .". GlaxoSmithKline applauds this intent and supports FDA's effort to provide clarification of the usual regulatory requirements for such applications. We support the views, as summarized in the draft guidance, that FDCs 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.

Importantly, FDA's encouragement of development of new antiretroviral FDCs is entirely consistent with and builds on multiple historical examples of fixed-dose combination products that have made clinically meaningful contributions to the infectious diseases armamentarium. Examples of such products are Augmentin<sup>®</sup> (amoxicillin/clavulanate potassium), Kaletra<sup>®</sup> (lopinavir/ritonavir), Malarone<sup>®</sup> (atovaquone/proguanil), Rifamate<sup>®</sup> (rifampin/isoniazid), Rifater<sup>®</sup> (rifampin/isoniazid/pyrazinamide), Septra<sup>®</sup> (trimethoprim/sulfamethoxazole), Timentin<sup>®</sup> (ticarcillin/clavulanate potassium), Unasyn<sup>®</sup> (ampicillin/sulbactam), and Zosyn<sup>®</sup> (piperacillin/tazobactam). In each example, each component of the FDC contributes to the effects of the product. The intent of this new draft guidance is fully consistent with these historical precedents for FDCs for products to combat infectious diseases.

**Lines 19-27:** FDA's clarification of regulatory requirements, as well as clear and strong encouragement to sponsors to submit such applications, are essential precursors to stimulating the desired increase in development and registration of such FDCs and co-packaged products. This clarification of requirements and strong encouragement to sponsors is important for antiretroviral co-packaged products, in part due to some discouraging precedents in some other therapeutic areas that illustrate non-streamlined development and registration of co-packaged products. FDA is wise to emphasize their encouragement of development of FDCs and co-packaged antiretroviral products in order to be clear that the Agency actively supports such endeavors.

### **II. Background (pages 2-3)**

**Lines 52-54:** The draft guidance states that there are several preferred regimens in the HHS treatment guidelines, yet reference # 3 cites both the HHS and IAS treatment guidelines.

We support explicit recognition of both the HHS and IAS treatment guidelines. Further, part of the motivation for this new draft guidance is to help FDA and HHS respond to the President's Emergency Plan for AIDS Relief (PEPFAR, 2) and WHO's 3-by-5 initiative (3), both of which strive to deliver first-line antiretroviral combination therapy in a patient-friendly manner that facilitates adherence. GSK urges FDA and HHS to explicitly acknowledge that the highest priority now, and for the foreseeable future for the developing world, is to focus on delivering the four first-line HAART regimens recommended by WHO. These four first-line regimens are (1) lamivudine + zidovudine + efavirenz, (2) lamivudine + zidovudine + nevirapine, (3) lamivudine + stavudine + efavirenz, and (4) lamivudine + stavudine + nevirapine. It is inconsistent with public health priorities for FDA to embrace and accelerate applications for FDCs or co-packs for second-line and third-line regimens to the exclusion of the four first-line HAART regimens.

**Lines 55-57:** The draft guidance states that triple FDCs or co-packaged products are "probably most useful for treatment-naive patients". We believe that the utility of triple FDCs or 3-drug co-packs is not necessarily limited to therapy-naive patients; the utility of any given FDC or co-pack in patients with various degrees of prior exposure to antiretroviral therapy will depend largely on the specific individual drugs included in that FDC or co-pack. We trust that FDA will continue to review the proposed uses of each new FDC or co-pack on its own merits in view of the evidence submitted in the application.

**Lines 64-65:** The draft guidance states that it is important to evaluate the safety and efficacy of possible combinations in various populations. GlaxoSmithKline believes that it is essential in this draft guidance to be absolutely clear and explicit that the current statutory and regulatory requirements for each NDA apply in full to FDCs and co-packs of antiretroviral products. Specifically, each FDC or co-pack 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. We encourage FDA to make this information explicit within the draft guidance, as well as include an explicit reference for sponsors to FDA's guidance of May 1998 on various alternative means of demonstrating evidence of effectiveness (4). Absent such explicit statements, some readers will wrongly assume that lower standards are being applied to these FDCs and co-packaged products.

### **III. HIV Therapy and Resource Poor Settings (pages 3-4)**

**Lines 113-114:** The draft guidance states that a draft of a document (entitled "Principles for Fixed-Dose Combination Drug Products") was posted on the Internet on April 22, 2004 and comments were solicited (5). If it is FDA's intent to rely upon this Principles document as a basis for scientific and regulatory decision making in the United States, we recommend that FDA publish a notice in the *Federal Register* and invite comments from stakeholders. Absent such a notification by FDA, it remains unclear whether FDA intends to rely upon this Principles document or whether FDA considers this Principles document to capture its current best thinking on this important topic.

**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. We respectfully disagree since the Federal Food, Drug and Cosmetic Act is clear and explicit that "substantial evidence" of effectiveness must be provided from adequate and well-controlled trials as part of the requirements for approval of an application for a prescription drug product (6). There is no legal or regulatory basis to modify the current standards governing safety, efficacy, and quality of FDCs and co-packaged products.

**Lines 135-138:** The draft guidance summarizes FDA's intent to utilize fast track designation, Priority review, and Subpart E procedures in order to expedite development and review of applications for FDCs and co-packaged products. We suggest that FDA may wish to explicitly encourage sponsors to also utilize the existing regulatory procedures for meeting with FDA (particularly for End-of-Phase 2 and Pre-NDA meetings) in order to reach shared understandings about the development plan for FDCs and co-packaged products, as well as for the proposed format and content of a New Drug Application for such a product (7-9). In our experience, such milestone meetings are key opportunities to facilitate the future review of the application by assuring that the sponsor provides application contents that addresses FDA's needs.

**Lines 164-170:** This part of the draft guidance lists desirable and important characteristics of FDCs and co-packaged products. In the case of FDCs, it is important to add the following additional characteristic to this list:

- Contains two or more drugs that can be administered with compatible food and fluid requirements

This characteristic is intended to avoid creation of a two-drug FDC, for example, where one drug must be administered with a fat-containing meal to achieve the desired exposure and the second drug must be administered in the fasted state to achieve the desired exposure. We understand that this concept is captured in text in one of the paragraphs, but we think this key item merits the prominence of a bullet point.

**Lines 186-188:** We request that you delete the statement about the one triple-nucleoside FDC since guidance documents typically do not provide product-specific comments. In addition, this product-specific comment will become outdated if this information changes in future HHS treatment guidelines.

**Lines 199-202:** The draft guidance states that FDA created the list of examples in Attachment B based on information in either (1) FDA-approved labeling or (2) peer reviewed literature. We understand (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. Nonetheless, we have two specific comments on this matter.

- First, there are a number of HAART regimens that are in FDA-approved labeling or peer reviewed literature, yet they are not included as examples in Attachment B (e.g., lamivudine + zidovudine + atazanavir). We recommend, at a minimum, that regimens in FDA-approved labeling (including lamivudine + zidovudine + atazanavir) be incorporated into Attachment B.
- Second, it appears that some regimens in Attachment B are not based on either FDA-approved labeling or peer reviewed literature. Rather, it appears that the basis for some regimens was clinical judgement or extrapolation from existing information on various drug products. For example, the regimen "tenofovir + emtricitabine + efavirenz" is not described in FDA-approved labeling, nor has an adequate and well-controlled trial been reported in peer-reviewed literature, yet this regimen is included in Attachment B. There are other similar examples. We recommend that Attachment B be restricted to combinations and regimens based on either (1) FDA-approved labeling or (2) peer reviewed publications of adequate and well-controlled clinical trials.

**Lines 226-231:** This paragraph points out that specific antiretroviral drugs should not be combined if there is (1) pharmacologic antagonism, (2) overlapping toxicities, or (3) poor virologic efficacy. We recommend that FDA expand this list of 3 reasons to 5 reasons by including the following additional reasons: (4) physicochemical incompatibility between the drugs and (5) instability of one or more of the drugs in the drug product, particularly in climatic zones III and IV.

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

**Lines 257-258:** This statement in the draft guidance pertains to situations where the applicant may provide information on clinical safety and efficacy by relying on FDA's prior findings of safety and effectiveness for an approved drug product. We recommend that FDA make explicit the facts that (1) this provision applies only to Abbreviated New Drug Applications submitted to FDA pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and (2) each such ANDA must contain the required patent certification statements with prompt notification by the applicant of each patent holder, as well as the holder of the NDA for the Reference Listed Drug. Absent such explicit statements in this guidance document, some applicants may mistakenly assume that the law has been changed for FDCs and co-packaged antiretroviral drugs.

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

**Lines 366-378:** This paragraph pertains to stability data for co-packaged products. 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."

**Lines 395-397:** This section (possibly intended for drug product only) does not clearly discriminate requirements by ICH guidance for synthesis-related impurities and potential degradation products for drug substance and potential degradation products only for the drug product. Please consider inclusion of the following statement: "Validated analytical methods for the drug product should be capable of distinguishing each active ingredient and potential degradation products (reference: ICH Q6A)."

**Lines 397-398:** 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, 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 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) and is not for the United States. The guidance of reference describing stress storage conditions (DS only) for the US (relevant ICH regions) is Q1AR.

**Line 448:** FDA is well aware of the public health implications of illegal diversion of pharmaceutical products from another country into the United States. FDA is also well

aware of a number of antiretroviral drug products (including some FDCs) that are not approved for use in the United States and not manufactured in facilities with records of compliance with FDA's requirements for Good Manufacturing Practices. In view of these considerations, it is important for FDA to explicitly state its continued vigilance in protecting the public health of US patients from counterfeit drug products, as well as diverted drug products. Therefore, we recommend that FDA extend the statement on line 448 to say that "FDA will work with applicants on rapid evaluation of anti-counterfeit technologies<sup>22</sup> and approaches to minimize product diversion."

#### **VIII. Microbiology/Virology (pages 12-13)**

**Line 466:** This statement in the draft guidance pertains to situations where the applicant may provide information on virology by relying on FDA's prior findings of safety and effectiveness for an approved drug product. We recommend that FDA make explicit the facts that (1) this provision applies only to Abbreviated New Drug Applications submitted to FDA pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act and (2) each such ANDA must contain the required patent certification statements with prompt notification by the applicant of each patent holder, as well as the holder of the NDA for the Reference Listed Drug. Absent such explicit statements in this guidance document, some Applicants may mistakenly assume that the law has been changed for FDCs and co-packaged antiretroviral drugs.

**Lines 486-488:** This statement describes situations where a high failure rate was observed in some clinical studies with "triple-nucleoside regimens". We suggest that it is more precise to say that "In clinical studies, some regimens consisting of three reverse transcriptase inhibitors have been shown to have high virologic failure rates associated with high rates of drug resistance (see Attachment C)."

#### **IX. Adverse Event Reporting (page 13)**

**Lines 497-500:** We understand FDA's desire for collection and reporting of clinical safety data, regardless of the location of patients and prescribers. However, neither the Federal Food, Drug and Cosmetic Act nor the regulations in 21 CFR 314.80 and 314.81 give FDA the statutory or regulatory authority to require an applicant to create a "system of collecting and reporting adverse drug reactions". We agree that it is desirable for the local governmental health agency or NGO distributing the product to have such a system, but it is beyond the scope of the applicant and FDA's authority.

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

**Lines 515-537:** We support FDA's effort to explicitly address the topic of user fees for FDCs and co-packaged antiretroviral products because clarity on this topic is an important aspect of encouraging sponsors to develop products and submit applications. We understand

FDA's description of the considerations and the statement on lines 532-533 that FDA is evaluating the circumstances under which conventional user fee requirements will not apply.

We believe that the substantial public health challenges from HIV infection merit a simple and clear approach, namely, that FDA will waive the application, product, and establishment fees for all FDCs and co-packaged antiretroviral drug products. This approach comprises a clear and strong source of encouragement to sponsors to develop these products and submit applications to FDA. The approach is fully justified, in our view, by the frank HIV crisis in many countries around the world, certainly including the countries in PEPFAR. The approach is also supported by the fact that, in virtually all cases, the Agency will already have collected application, product, and establishment fees from the applicants for prior applications for the single-entity antiretroviral products; importantly, these prior applications for the single-entity products contain the clinical data that was previously reviewed to support use of the drug in combination antiretroviral therapy; few NDAs for an FDC or co-packaged product will contain new clinical data requiring medical review and, in turn, meriting a user fee. Finally, in our view, waiver of user fees is also justified for FDCs and co-packaged products for use in the United States, as well as other countries, due to the continued public health challenge of HIV in the US, the need in the US for products that facilitate adherence, and the need for constructive steps in the US to leverage approaches that may delay emergence of viral resistance and thereby prolong the useful lifespans of our existing antiretroviral drugs. In the latter regard, poignant lessons have been learned in infectious disease about the critical importance of combatting emergence of bacterial resistance and prolonging the useful lifespans of existing antibacterial drugs (10); FDA has collaborated with IDSA, ISAP, and PhRMA to foster two public workshops on this topic in an effort, in part, to stimulate investment in discovery and development of new drug products to address the challenges of infections due to drug-resistant bacterial pathogens (11, 12). The recognized potential of FDCs and co-packaged antiretroviral products as important tools that may delay emergence of viral resistance is sufficient, in our view, to merit a waiver of user fees in view of the long-term public health importance of prolonging the useful lifespans of our existing antiretroviral drugs.

**Lines 541-553:** The draft guidance provides information on pediatric studies. From our 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 it does not apply to co-packaged antiretroviral drug products.

**Additional Topic (page 15):** We urge FDA to add a new section, "D. Certificate of a Pharmaceutical Product" to the draft guidance. As you know, a Certificate of a Pharmaceutical Product (CPP) provides important regulatory documentation to facilitate prompt and reliable registration of a product in many countries in the developing world (including the target countries in the PEPFAR initiative). FDA provides CPPs via the Export Certificate Program in CDER in accordance with a standard procedure (13). Under this program, after FDA renders an approval or tentative approval action for a New Drug Application or Abbreviated New Drug Application for an antiretroviral FDC or co-pack (pursuant to the scenarios in Attachment A of the draft guidance), achievement of the objectives of PEPFAR and other US-supported AIDS relief efforts depend on the applicant's ability to proceed in an expedited and efficient manner from FDA's approval or tentative approval of the application to FDA's issuance of CPPs for the product. Such CPPs are key documents to facilitate product registration in the countries of the developing world where emergency relief is needed; absence of a CPP will be an obstacle to product approvals in the developing world and jeopardize the good intent of this initiative. FDCs and co-packs subject to applications in accordance with this draft guidance may be manufactured at a variety of production facilities in the United States and other countries. Regardless of the country where the product is manufactured, we urge FDA to add text to the draft guidance to explicitly state that (1) FDA recognizes the important role of its CPP to efforts to expeditiously register the product in other countries and (2) FDA fully intends to work with applicants to expeditiously issue CPPs for antiretroviral FDCs and co-packs (regardless of the country of manufacture of the product). In this regard, we emphasize the importance of FDA proactively supporting expeditious and parallel issuance of CPPs for these products, regardless of the country of manufacture of the product. An arbitrary, unnecessary, and burdensome restriction of CPPs to US-based manufacturers will delay achievement of the objectives of the AIDS relief effort by requiring otherwise unnecessary manufacturing site changes for some products. Finally, FDA should plan for expeditious post-approval processing of multiple, parallel requests from the applicant for a CPP for use in documents to be submitted to each of the target countries in PEPFAR. From our perspective, all of these topics on CPPs could be efficiently and readily addressed in a new section, "D. Certificate of a Pharmaceutical Product", for addition to the draft guidance.

**Attachment A (pages 16-18)**

**Line 615:** We understand 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.

**Attachment C (page 21)**

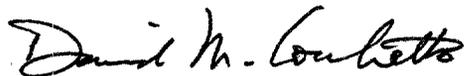
Lines 728-729: The display of two product names as "lamivudine (or emtricitabine)" is a format that is often used to display two alternative names for the same drug. Obviously, lamivudine and emtricitabine are two different drugs. In the interest of clear communication and avoiding potential confusion, we suggest that the regimens on lines 728-729 be listed as follows:

abacavir + lamivudine + tenofovir  
abacavir + emtricitabine + tenofovir  
didanosine + lamivudine + tenofovir  
didanosine + emtricitabine + tenofovir

Again, thank you for this opportunity to provide comments on this important topic.

This submission is provided in duplicate. Please contact David M. Cocchetto at (919)-483-5127 for any matters regarding this submission. Thank you.

Sincerely,



David M. Cocchetto, Ph.D.  
Vice President, Antiviral/Antibacterial Regulatory Affairs

### References

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5. Scientific and Technical Principles for Fixed Dose Combination Drug Products. April 22, 2004.
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