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Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
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Re: Draft "Guidance for Industry: Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays: Special Controls";
***Federal Register* 66 (No. 168): 45682-45683 (August 29, 2001);**
[Docket No. 01D-0286];
Comments for Consideration

Dear Sir or Madam:

Reference is made to FDA's issuance of a draft guidance for industry entitled *Draft Guidance for Industry: Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays: Special Controls*. The purpose of this letter is to provide written comments on this draft guidance.

GlaxoSmithKline, a research-based pharmaceutical company, has been an industry leader in the development of new drugs to treat HIV infection. We currently have six approved drugs on the market for treatment of HIV infection: Retrovir® (zidovudine), Epivir® (lamivudine), Combivir® (lamivudine/zidovudine), Ziagen® (abacavir sulfate), Agenerase® (amprenavir), and Trizivir® (abacavir sulfate, lamivudine, and zidovudine).

GlaxoSmithKline is committed to continuing research and development of new drugs in the fight against human immunodeficiency virus infection (HIV). In addition, we are committed to optimal utilization of currently available antiretroviral agents. In this regard, GlaxoSmithKline, through our Virology Department and outside collaborations, has committed significant resources to the study of resistance profiles of drugs for the treatment of HIV infection. We have drawn on our experience in this area to prepare these comments. Our comments are grouped according to section headings appearing in the draft guidance.

General Comments

GlaxoSmithKline supports use of resistance testing to optimize antiretroviral treatment of HIV infection. Data from the GART (Baxter et al., AIDS; 2000; 14: F83-93) and Viradapt (Durant et al., Lancet; 1999; 353: 2195-9) studies demonstrated the value of genotypic testing over standard of care in optimizing virologic outcomes for patients. Moreover, at the

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November 2-3, 1999 Antiviral Drugs Advisory Committee meeting, it was concluded that resistance testing can make an important contribution to the drug development process.

We applaud the Agency's direction in moving toward standardization of analysis and interpretation of genotypic resistance assays. As reported by Dr. Carlos Salama at the Fifth International Workshop on HIV Drug Resistance and Treatment Strategies (June 4-8, 2001, abstract #123), significant confusion exists among treating physicians regarding interpretation of genotypic resistance assays. Standardization of genotypic assay testing and interpretation will help alleviate this confusion and will assist physicians in appropriately utilizing available antiretrovirals to optimize patient outcomes.

We noted that this draft guidance was issued in the event that HIV genotype assays are re-classified from Class III to Class II. We understand that Class III devices require premarket approval by FDA, while Class II devices may be distributed pursuant to a 510(k) with a demonstration of substantial equivalence to a predicate device. In GSK, we believe that, at present, HIV drug resistance genotype assays are consistent with the definition of Class III devices since such a device can be life-sustaining (when used properly) and has the potential for substantial harm to human health (when used improperly). Further, we support categorization of these assays as Class III devices because these devices are still in their relative infancy of testing and clinical use; once substantial experience in the conduct, interpretation, and clinical application of these assay results is accumulated and reported to FDA and other stakeholders, it may be reasonable to then re-consider categorization as a Class II device.

Section I.A: Purpose and Section VI: Labeling

Section I.A states that "You will help ensure the production of standardized, reliable, and reproducible tests for detecting HIV mutations known to be associated with HIV drug resistance if you follow the recommendations in this document." In addition, in Section VI, the stated intended use is "...for use in detecting HIV genomic mutations that confer resistance to specific types of anti-retroviral drugs, as an aid in monitoring and treating HIV infection." The scope of the draft guidance and intended use of approved kits appear to extend beyond the stated purpose of this document since the guidance appears to include inferences on genotypic data and prediction of phenotypic results, as well as information on potential associations between genotypic assay results, clinical trial data, and patient outcomes. We suggest that the stated purpose and intended use be clarified to assure internal consistency within the guidance.

Section I.C. Background

The International AIDS Society (IAS)-USA Panel is a recognized body with expertise in many aspects of the management of HIV infection, including resistance testing. This consensus panel's recommendations can be used to guide clinical utilization of resistance testing. In Section I.C of the draft guidance, resistance mutations in Tables A-E are referenced from the IAS-USA Panel consensus statement, as published by Dr. Martin Hirsch

and colleagues in JAMA 2000; 283: 2417-26. More recently (April 2001), the Resistance Mutations Project Panel of the IAS updated the reference information on mutations, depicting mutations in the reverse transcriptase and protease genes associated with reduced susceptibility to antiretroviral drugs (D'Aquila et al., Topics in HIV Medicine 2001; 9(2): 31-2, and HIV Clinical Trials 2001; 2(4): 346-55). As knowledge continues to evolve regarding genotypic resistance to HIV drugs, the IAS will provide updated mutations figures and other resistance information on its website, www.iasusa.org. Several references are made to Tables A and B throughout the guidance document, indicating that the mutations located in these tables are to be used as standards in the analysis, interpretation, and reporting of genotypic resistance assay results. However, some of this information is outdated, so we strongly recommend the utilization of the revised IAS-USA mutation figures.

As new drugs are introduced and more resistance data become available for drugs or classes of drugs, the need exists to provide a mechanism for ensuring that algorithms used to interpret FDA-approved resistance tests are continuously updated. It is stated in this Section that "As advances are made in science and technology, we will amend the guidance as appropriate". Alternative ways of referencing current mutations should be considered. We do not anticipate that FDA would have the resources to sustain timely, periodic updates to this guidance to reflect evolving changes in resistance data. We suggest that, rather than amending the guidance or having specific mutations listed in the guidance, the guidance could reference the IAS-USA website, which will contain the most up-to-date information on resistance testing, including data on new drugs, from a consensus panel of experts. This approach would be similar to the determination of antibiotic susceptibility breakpoints (MICs) that are recommended by National Committee on Clinical Laboratory Standards (NCCLS), updated quarterly, with methodology referenced in the labeling of antibiotics and susceptibility testing kits. We suggest that the role of IAS for antiviral drugs could be analogous to the role of NCCLS for anti-infective drugs. By taking this approach, the Agency would ensure that current information from a panel of experts is used to interpret genotypic resistance tests and guide patient care.

In Section I.C, the guidance states "We recognize that the mutations listed in Tables A and B are associated with HIV drug resistance. Other mutations, including those in Tables C-E, are suspected of being associated with HIV drug resistance, but their significance has not been widely accepted." This is a confusing and contradictory statement, as the same mutations listed in Tables A and B are also listed in Tables C-E. We encourage you to revise to avoid this confusion.

Section II: Scientific and Clinical Background

In this section, it is stated that "We are willing to work with you to determine the correlation between use of the assay and benefit to the patient for mutations that are currently not generally recognized as being associated with HIV resistance to anti-retroviral drugs". We would recommend that CBER work not only with sponsors, but also with the Division of

Antiviral Drug Products in CDER, as well as a scientific panel of experts through the IAS-USA to make such determinations.

Section III.B: Performance of the Assay in Determining Genotype

In subsection (b) under Analytic Sensitivity, it is stated that "You should test each of these clones at least ten times, using three different lots of the assay, at clinically relevant viral loads". The term "clinically-relevant viral load" should be defined in this setting. Based on our experience, we suggest that 2,000 copies/mL would be an appropriate definition of clinically relevant viral load since most laboratories are able to routinely obtain genotypes on samples with such a viral load.

We did note with interest the relatively large number of assays to be performed to conform with this draft guidance. By our reading, in order to comply with the recommendation of this draft guidance, 40 mutations must be assayed 10 times each, using 10 subclones and 3 different lots of the assay (Section III.B 1a). In addition, common multiple mutations should be tested 10 times using 3 different lots of the assay (Section III.B 1b). Further, specific mutations should be tested over the entire range of the assay using different proportions of each mutation (Section III.B 2). Using minimal proportions of mutant species, assay performance should be measured at two-log intervals above the minimal viral levels and at half-log intervals below the minimal viral levels of detection (Section III.B 2a). Taken together, the assays required for registration of a drug resistance genotype assay could number between 10,000 and 50,000; we wonder whether this large number of total assays was indeed intended.

Table F: Requirements for Different Tracks

The requirements for the two different approval tracks in this table (and throughout the document) are confusing and require clarification and, perhaps, simplification. For example, in Table F itself, it is unclear what clinical trial data will usually be required in the "Clinical Trial Track". Additionally, it is unclear whether the manufacturer is free to identify the mutations that will be subjected to stringent analytical studies, or if such mutations are to be identified by the agency.

Section V: Product Modification

This section states that "Specific examples of when a new 510(k) should be filed include, but are not limited to, new labeling for genotypic prediction of phenotypic resistance for new anti-viral drugs, new labeling for newly discovered mutations or mutations with newly documented phenotypes, or material changes in the interpretation algorithm". If the tables of mutations remain part of the guidance, we are concerned with delays in updating the mutations via a new 510(k) to reflect currently available data. We would recommend that the NCCLS model be considered to provide an expert panel for designating relevant mutations. The IAS-USA consensus panel has indicated that their updates will be available quickly on their Internet web site after a periodic review.

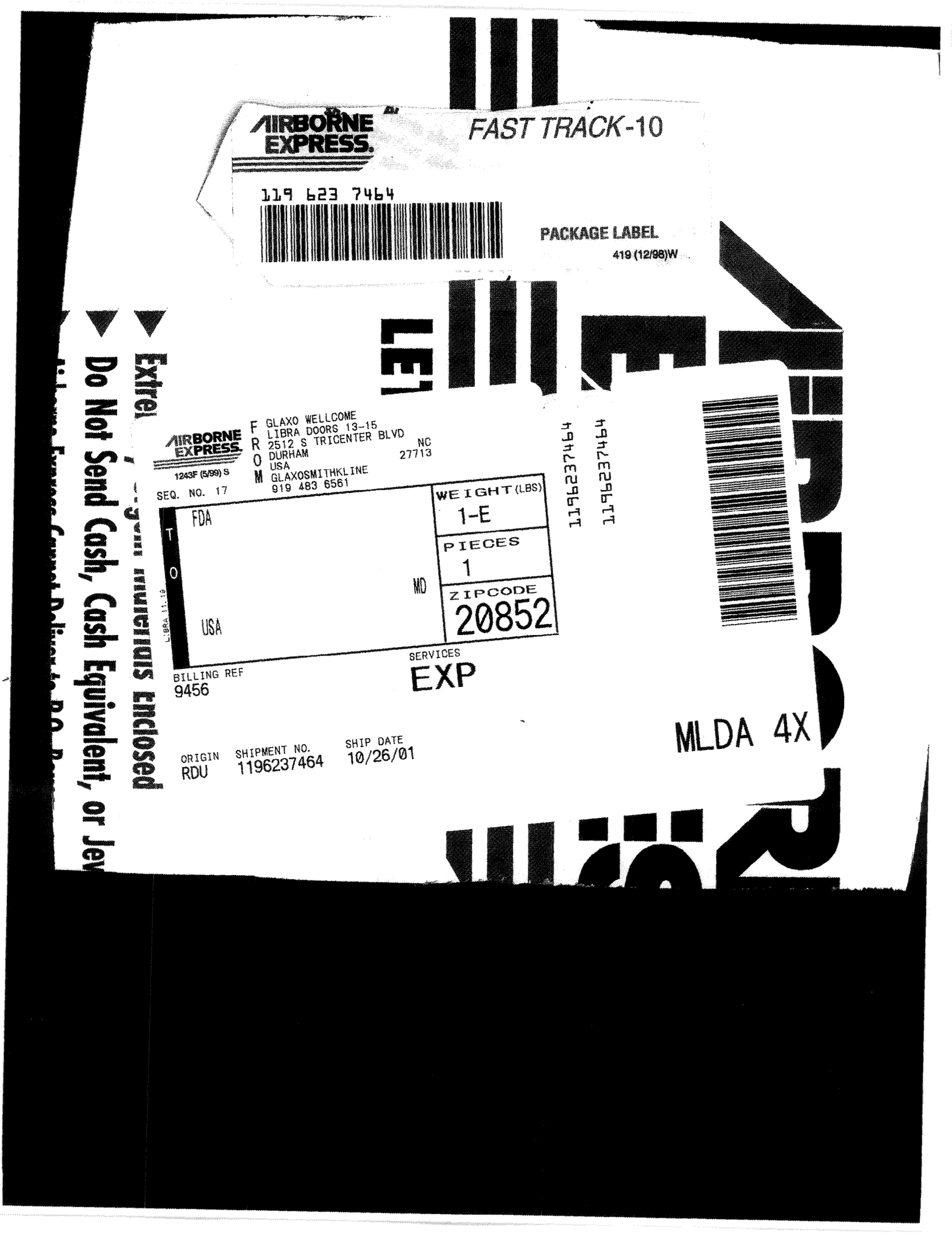
As this draft guidance describes the requirements for validation of assay interpretation algorithms, does this suggest that an interpretative algorithm not linked to a specific company's genotypic assay could be approved for use in conjunction with another company's kits?

This submission is provided in duplicate. We hope that you find these comments constructive. Please contact me at (919)-483-5127 if you want to discuss any of these comments. Thank you for the opportunity to provide comments.

Sincerely,

David M. Cocchetto

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