VIRCO

Mechelen, October 26, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852, USA
Tel 301 827 6210

Re:
Docket No. 01D-0286
Comments on Draft "Guidance for Industry: Premarket Notifications 510(k)s for In Vitro HIV Drug Resistance Genotype Assays" (August 29, 2001)

Dear Sir/Madam,

Please find enclosed a document containing comments on the draft guideline referred to above.

One of our special concerns is the inclusion of the statement regarding Analyte Specific Reagents (ASRs) in HIV drug resistance assays. As detailed in our comments, we believe that ASRs used in HIV drug resistance assays are classified as Class I ASRs and, therefore, they are governed by regulations applicable to Class I ASRs.

This document contains comments as well as a number of questions we have concerning drug resistance genotype assays. We would like to emphasize the complexity of the assay, especially the complexity of establishing the drug resistance profile of the patient's virus based on the determination of a genetic sequence. Characterization of drug resistance profiles requires highly flexible prediction systems, which need to undergo frequent updates as new antiviral drugs are being licensed and as new mutational patterns associated with drug resistance emerge.

If you have any questions regarding our comments, please do not hesitate to contact us for additional information.

Respectfully submitted

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Page 1.

I. INTRODUCTION

A. Purpose

"....production of standardized, reliable, and reproducible tests for detecting HIV mutations known be associated with HIV drug resistance...."

Comments: The intention of FDA is to ensure standardized, reliable and reproducible detection of resistance-associated mutations in HIV. Reliable and reproducible detection of resistance-associated mutations in HIV as such represents a first and necessary step to generate a drug resistance profile of a patient's viral isolate. However, the second and equally important, but probably more complicated task is to predict the drug resistance profile which can be used by physicians to make therapy decisions. The prediction of the phenotype from the genotype is complex issue because of the multitude of possible resistance-associated mutations, the effect of which on the phenotype must be accurately predicted. This involves taking into consideration *the effect of mutations themselves*, *mutation interactions*, *assay variation*, *biological variation* and the *magnitude of the effect of the mutations on the resistance profile*. A good drug resistance assay must also consider the *clinical relevance of the degree of resistance* of a viral isolate to a drug. Therefore, the guidelines should also address the issues concerned with this second step of the generating of a drug resistance profile. How will FDA ensure that if a manufacturer chooses the analytical-pathway only approach, the resistance assay meets the definition sub I.B.: end of sentence: "...as an aid in monitoring and treating HIV infection."?

B. Definition

Comment: see above

C. Background

§1 of section C: " ..... the mutations listed in Tables A and B ....., including those listed in Tables C-E....."

Comments

- What evidence does FDA need to consider a mutation as being associated with drug resistance?
- Lists of mutations in tables is not exhaustive: some published mutations are not

§3 of section C: "two pathways"

Comments

- "Two possible alternative pathways towards approval of resistance testing assay systems is confusing and may to lead to a two-tier system:

1. One system that meets rigorous analytical standards for detection of mutations, but that does not necessarily provide an *accurate resistance profile* of the patient's viral isolate.
2. One system that needs to meet less rigorous analytical standards for detection of mutations, but that can provide evidence of medical benefit.

Both systems will be considered under one label, i.e., "In vitro HIV drug resistance genotype assay". So they should be comparable in producing comparable results usable by physicians and patients. How will FDA ascertain that the first pathway provides equally good evidence of medical benefit if no clinical studies are needed? How could equivalency of both devices be established?

§3 of section C "….. additional mutations may become widely recognized as clinically significant.":
Comments:
How will FDA determine the clinical usefulness of these mutations?
Will clinical studies by applicants be needed in order to demonstrate medical benefit?
How will the guidelines be amended?

Page 2.
D. Regulatory Jurisdiction

Analyte Specific Reagents

Comments:
ASR regulations as detailed in 21 CFR Parts 809 and 864 define the conditions for assigning analytes to either Class I, II or III devices. All ASRs, except those that meet the definitions of Class II or Class III ASRs, are exempt from premarket notification requirements. The regulations define an analyte as belonging to Class II "when the analyte is used in blood banking tests that have been classified as Class II devices" (21 CFR §864.4020(b)(2). Furthermore, the regulations define an analyte as belonging to Class III "when (i) The analyte is intended as a component in a test intended for use in the diagnosis of a contagious condition that is highly likely to result in a fatal outcome and, prompt, accurate diagnosis offers the opportunity to mitigate the public health impact of the condition (e.g., human immunodeficiency virus (HIV/AIDS) or tuberculosis (TB)); or (ii) The analyte is intended as a component in a test intended for use in donor screening for conditions for which FDA has recommended or required testing on order to safeguard the blood supply or establish the safe use of blood and blood products (e.g., tests for hepatitis or tests for identifying blood groups)." (21 CFR §864.4020(b)(3).

ASRs used in HIV drug resistance genotype assays do not meet the definition of Class II ASRs: they are not used in a blood banking test. Likewise, ASRs used in HIV drug resistance genotype assays do not meet the definition of Class III ASRs: they are not used for the diagnosis of a contagious condition or for donor screening. The presence of HIV in the samples used in the genotyping assay has already been established and confirmed in earlier tests, carried out prior to initiation of the genotyping assay and independent of the genotyping assay. According to the regulations and definitions reviewed above, ASRs that are used in HIV drug resistance assays are considered to be Class I ASRs. Therefore, it is recommended that the statement on ASRs in this guidance document be amended to reflect their status as Class I ASRs.

Page 3.
II. SCIENTIFIC AND CLINICAL BACKGROUND

§1 of section II: "Absolute IC50 or IC90 levels ....."
Comments:
This statement should be removed from the present guidelines as it does not pertain to assays they are attempting to regulate.

§2 of section II: "Correlation between the use of the assay and benefit to the patient for mutations that are currently not recognized as being associated with HIV resistance."
Comments
How does FDA intend to structure this cooperation? Will these newly recognized mutations also be considered as Class II? If clinical trials were to be required for proving medical benefit of the assay when new mutations are identified and are used in the assay, this could be a lengthy process and the cleared assays would always lag behind by a fair number of months (years).
This aspect of the guidelines should be kept very flexible as new mutations associated with resistance to already approved drugs may develop, and new mutations will appear as a result of treatment with drugs that may or may not belong to the existing classes of drugs. It should remain an open-ended system.

Page 3.
III. DATA CONSIDERATIONS

§1 of section III: "types of data and analysis"
Comments
Will the definitive guidelines spell out exactly what type of data and analysis are to be furnished to FDA?
If there is no legally marketed medical device with the same intended use, what type of studies would be required to determine the operating characteristics of the device?

Page 4.

Comments:
Separate lists of mutations: if a mutation appears in clinical isolates and can be shown in vitro that it can impart resistance and is not a polymorphism, then we think it should be accounted for in any algorithm. As mutation numbers increase and become more complex, it will be more difficult to design minimum algorithms and to show that specific mutations can impart resistance.
Interpretation algorithms of tables A and B are vague and actually not defined. They are listings of mutations, but the interpretation columns of these lists do not explicitly state nor indicate what the exact relationship is between these mutations and combinations of mutations with drug resistance profiles of those sequences. How will FDA ascertain that

the rules used by an applicant lead to a clinically meaningful result when no clinical studies are required (cfr analytical-data-only track does not require clinical trials)? How will FDA evaluate intended use and medical benefit of those assays? What criteria will FDA use to compare assays and to decide on equivalency of devices?
How will FDA deal with applications, each having their own interpretation systems, which provide different results starting from the same mutational configuration?
The concern is that the user may not be able to choose the correct one.
The way the guidelines are formulated here could lead to multiple Class II genotyping assays that may be very unequal in their ability to provide clinically meaningful results. The less adequate tests could be incorrectly granted a better status than they deserve, and the better ones will not be differentiated from the lesser ones. This may be harmful to the patient. The way the guidelines are written here provide no incentive for the development of the best test possible.

A. Performance of the Interpretation Algorithm

1. Validation of Phenotypes predicted by Genotyping: In Vitro Studies

Comments on heading of section A.1.

The title of this section must be changed: genotype will never be able to fully predict phenotype because it cannot predict interaction of all mutations whether known, unknown, primary, secondary, associated with resistance or not. Some resistance-associated mutations cause reversal of resistance to other drugs, etc.

§1 of section A.1.:

Comments

As mentioned above, in the comment on page 4 §3 of section III of the guidance documents, the lists A and B are too vague to serve as starting point to use in validation studies.
The concern is that there is great heterogeneity in results generated by rules-based interpretation algorithms.

Page 5.

2. Verification of Phenotypes Predicted by Genotyping: Clinical Studies

§1 of section A.2.:

Comments

clinical benefit, suggesting that controlled prospective trials followed by (independent?) retrospective looks at datasets are the acceptable and standard way of doing this. If there is no demonstrable clinical benefit, then the assay should not be approved.

B. Performance of the Assay in Determining Genotype

1. Analytic Sensitivity

a.

b.

page 7.

c. "….. demonstrate the detectibility of "Secondary mutations…."
Comments
All mutations should be detectable with equal precision, since the distinction in importance and effect between "primary" and "secondary" mutations can frequently not be made. Some are compensatory mutations that may have an effect on fitness and not necessarily on binding to the inhibitor.

d. "…. assays should correctly identify the amino acids at all codons in PR and RT known or suspected to be involved in conferring drug resistance.
Comments
It is strongly urged that a category be set up entitled "**Genome Coverage**"
In order to ensure a correct determination of resistance profiles it is necessary to sequence the entire length over which such resistance-associated mutations may occur in the viral genome. Otherwise, the phenotypic prediction will prove to be inaccurate. Examples: recently discovered 318 and 333 mutations in RT. If these, and other mutations that are not detected because of incomplete sequencing and because of gaps due to primers, cannot be detected, the utility of the resistance testing assay is seriously compromised. All assays should be prepared to pick up new as well as existing known mutations and be able to identify new mutations as the use and approval of new drugs will lead to selection of other (and in some cases new) mutations. Most existing genotyping methods already miss some RT mutations that have appeared in clinical isolates.
Adequate sequencing includes taking into account the following:
- Adequate length of sequencing of the viral genome in order to cover all codons where changes associated with drug resistance are known to occur.
- Acceptable amount of single stranded sequence (single stranded regions can affect accuracy of base calling)
- Gaps (gaps are not acceptable and are easily avoided with proper primer sets)

2. Range of Detectability
3. Precision
4. Reproducibility
5. Lot
6. Specificity
7. Assay Interference
8. Reagent

9. Sample Collection

C. Stability

D. Assay Performance on Clinical Samples

Page 11.

E. Clinical Trial Data Supporting Efficacy

Comments

Not needed to submit clinical trial data supporting efficacy of assays is when the analytical data is complete: in what way will this approach ensure that the assay results are usable in the clinic by the physician? If no clinical benefit of algorithm can be demonstrated then what use can be made of an assay that is technically sound, but whose clinical significance is not demonstrated? The only way to ensure that is to have -clinical data to confirm the correctness of the algorithm.

Not all mutations from the lists may be encountered in subjects participating in a clinical trial. In what way would submitting data from a clinical trial rather than submitting analytical data, need to limit the claims made if the clinical trial demonstrates that performing the assay is clinically relevant?

F. Modifications of Criteria for Special Purpose Assays

Page 12.

Comments

Add New Category: G. Frequency of algorithm updates Since new mutations will be found and new drugs will trigger the selection of different sets of mutations, interpretation algorithms need to be updated frequently. How will FDA monitor the frequency of such updating, the frequency of distribution to end-users, the mode of distribution (CD-ROM, web-site, diskette, etc.)?

Add New Category: Minimum standards for reports. What are the minimum for requirements for the test reports that are issued? Listing of all resistance-associated codons sequenced?

IV. OTHER CONSIDERATIONS

A. Design controls

B. Statistical Methods

C. Devices

D. Instruments

E. Pre-submission

Page 17.
Table F
Comments
Analytical-track-only: may yield an assay that meets all analytical requirements, but the question still is how the physician will use the result.

Page 19.
V. PRODUCT MODIFICATION
Comments
See above.

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