October 18, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD
20852 U.S.A.

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Subject: Docket No. 01D-0286 – Comments regarding Draft "Guidance for Industry: Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays: Special Controls"

Dear sir/madam:

Further to your request for comment following publication in the August 29, 2001 Federal Register of Draft Guidance Document "Guidance for Industry: Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays: Special Controls", docket number 01D-0286, attached please find our suggestions. There are three main comments regarding the guidance document, as summarized below and detailed in the attached pages.

1) The guidance should emphasize the importance of integration of the system, including chemistry. Genotyping is accomplished through a system that is comprised of chemistry, validated software run on hardware made in compliance with the Quality System Regulations, and a physicians report from a scientifically valid algorithm. The first pathway emphasizes chemistry and lacks emphasis on the potential role/interplay of this chemistry with hardware and software-or the analysis of the data generated by the chemistry. Additionally, analytically correct chemistry could render the device unsafe and ineffective if it is run on instruments and with software that are incompatible, unreliable, or inconsistent, and not subject to the same rigorous review and scrutiny as the chemistry.
2) The Software Algorithm presented in Tables A through E is not useful in practice, as is, and may potentially be harmful.
3) The two pathways described end with two different "products".

At your request, suggestions for improvement have been offered below. The format of the suggestions follows the titles outlined in the Guidance Document. Please call me if you require any additional information or clarification, (office phone 650-654-3844, or cell phone 650-704-5778).

Sincerely,
Dean Winslow
Dean L. Winslow, MD, VP of Clinical and Regulatory Affairs

cc: Dr. Andrew Dayton, Medical Officer

Visible Genetics Inc.
700 Bay Street
Suite 1000
Toronto, Ontario
M5G 1Z6

T 416.813.3240
F 416.813.3250
E info@visgen.com
www.visgen.com

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Guidance for Industry: Premarket Notifications [510(k)s] for In Vitro HIV Drug Resistance Genotype Assays: Special Controls

I. Introduction – C. Background

Two pathways for clearance are discussed. The first pathway, "demonstrating rigorously the analytical sensitivity of your test for mutations in Tables A through E" emphasizes the kit chemistry only. Part of the requirement should also be that the kit is assayed on all different hardware combinations available in the market place to assure the same or comparable performance characteristics, regardless of hardware or software used. The requirement should be to have the instrumentation combinations compatible with the kit (chemistry) reviewed and approved as either part of the Genotyping Assay 510(k) submission, or as a separate submission under this classification. Alternatively, if this pathway is followed, the use of the kit is restricted in labelling to the specific hardware with which the kit performance characteristics were determined. If the hardware changes (through upgrades) 510(k) applications would be needed to keep the kit on the market, to show that the hardware upgrades have not impacted kit performance. This clearance would then be for a HIV genotype assay that meets the requirements of the stated purpose on page 1 of the guidance document: "to ensure the production of standardized, reliable and reproducible tests for detecting HIV mutations known to be associated with HIV drug resistance". This pathway, as described in the Guidance Document, does NOT take into consideration the "interpretation" of the mutations detected by the kit. As explained in **III. Data Considerations** "you need only to provide analytical data demonstrating the ability of your test to detect mutations". Note: NO claim of clinical efficacy.

The second pathway discussed, which allows for "a less rigorous demonstration of the analytical sensitivity of the test for the mutations in Tables A through E, provided that clinical studies give evidence that use of the test will provide a medical benefit" assumes the use of hardware and software with an interpretation of the mutations. The "clinical benefit" comes from a combination of the ability of the kit to detect mutations and the interpretation of those mutations into prescribing information. Note the first pathway, as written does not require the interpretation of the mutations to be tested at all. This second pathway may become difficult to follow, as banked or stored plasma samples (such as the GART samples) are used up. The alternative for the sponsor would be to conduct prospective clinical efficacy studies. These studies may be impossible to run since the proposed study design (with and without the investigational assay) either means a no-genotype control arm that probably would be difficult to recruit for, or a genotype test would be incorporated into "standard of care" in both arms and you may be looking for an incremental improvement, or no change, over an existing test which could present statistical difficulties.

III. Data Considerations

Under the bullet points of "You should submit", please also add the interpretation algorithm used to generate the data output of the assay.

III. Data Considerations – A. Performance of the Interpretation Algorithm

Using Tables A through E as minimal algorithms (page 4) is not clinically practical. Tables A through E have not been tested in clinical studies and would likely be confusing to a prescribing physician. The tables deal with single point mutations, rather than the system of complex combination(s) of mutations that were tested in GART and VIRADAPT. A sponsor that selected the first pathway for approval, that supplied Tables A and B as the

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"clinical interpretation algorithm" would more likely cause medical harm, due to vagueness, than benefit a patient.

As an example, for mutation L90M:
In **Table B**, this states "more strongly associated with SQV or NFV but in combination with other mutations may confer resistance to all PI".

In GART: "L90M + 48V SQV, possible RTV, INV, NFV and 90M or 48V + 63P, 71T/V SQV, possible NFV".

In VIRADAPT: G48V or L90M SQV, G48V or L90M and any two of the following mutations L10I/R/V, I54V, A71V/T, G73S, I84V SQV, possible RTV, INV and D30N or any three of the following mutations M36I, M46I/L, A71V/T, V77I, I84V, N88D, L90M NFV.

In the GuideLines™ Rules (version 4.0):

Rule #	PI Rules Comment 7 will appear when a rule is fired for saquinavir, indinavir or amprenavir.	Effect	Drug	Evidence Basis
37	Any of: D30N I84V L90M	RESISTANCE	Nelfinavir	II
38	Any of: G48V L90M	RESISTANCE	Saquinavir	II
39	G48V + any of: V82A/F/T I84V L90M	RESISTANCE	Saquinavir Nelfinavir Indinavir Ritonavir	II II II II
40	G48V + any of: V82A/F/T L90M	POSSIBLE RESISTANCE	Lopinavir with ritonavir	III
41	G48V + any of V82A/F/T I84V L90M + 2 or more of: L10I/R/V K20M/R M36I I54L/M/V A71V/T	RESISTANCE	Amprenavir	II
42	G48V + any of: V82A/F/T I84V L90M	POSSIBLE RESISTANCE	Amprenavir	II
47	M46I/L + any of: V82A/F/T I84V L90M	RESISTANCE	Indinavir Ritonavir Nelfinavir	I I II
48	M46I/L + any of: V82A/F/T L90M	POSSIBLE RESISTANCE	Lopinavir with ritonavir	III
49	M46I/L + L90M	RESISTANCE	Saquinavir	I
52	I54L/M + any of V32I M46I/L I47V L90M	POSSIBLE RESISTANCE	Amprenavir	II
54	V82A/F/T + any of: M46I/L G48V I84V L90M	RESISTANCE	Indinavir Ritonavir Nelfinavir	I I I
55	V82A/F/T + any of: M46I/L G48V L90M	POSSIBLE	Lopinavir with	III

		RESISTANCE	ritonavir	
56	V82A/F/T + any of: G48V L90M	RESISTANCE	Saquinavir	I
60	I84V + any of: M46I/L G48V V82A/F/T L90M	RESISTANCE	Indinavir Ritonavir Nelfinavir Amprenavir Saquinavir	III II III III III
63	L90M	POSSIBLE RESISTANCE	Indinavir Ritonavir	I II
64	L90M + any of M46I/L V82A/F/T I84V	RESISTANCE	Indinavir Ritonavir Saquinavir Nelfinavir Amprenavir	II II I II III
65	L90M + any of M46I/L V82A/F/T	POSSIBLE RESISTANCE	Lopinavir with ritonavir	III
68	Any 1 of M46I/L V82A/F/T I84V L90M + any 5 of L10I/R/V K20M/R L24I/V M46I/L F53L I54L/M/V L63P A71T/V V82A/F/T I84V L90M	POSSIBLE RESISTANCE	Lopinavir with ritonavir	II
69	Any 1 of M46I/L V82A/F/T I84V L90M + any 7 of L10I/R/V K20M/R L24I/V M46I/L F53L I54L/M/V L63P A71T/V V82A/F/T I84V L90M	RESISTANCE	Lopinavir with ritonavir	II

Comment 7. When used in combination with low-dose ritonavir, increased levels of saquinavir, amprenavir or indinavir may result in enough antiviral activity to at least partially suppress some protease inhibitor resistant viral mutants. Data do not yet allow reliable prediction of which sets of multiple protease gene mutations can mediate resistance to *in vivo* suppressive effects of ritonavir-boosted saquinavir, amprenavir or indinavir.

Rules based algorithms need to take into consideration the complexity of mutation interactions. In addition, each rule should be supported by various levels of scientific evidence with *in vivo* virologic response data having the greatest weight on a hierarchical scale of evidence support. In the example provided above (GuideLines Rules version 4.0), evidence basis "I" means that the "rule is based upon 2 or more large, independent virological response studies and supporting *in vitro* data. In those instances where phenotypic data does not agree with virological response data, virological response data provides the basis for the rule." While evidence basis "III" means that the rule "is based upon *in vitro* data (includes phenotypic data and/or *in vitro* demonstration of mutation selection). No virological response data was available at the time this Rule was devised." The GuideLines Rules are revised regularly allowing for the incorporation of new data once it becomes available.

Device manufacturers need to incorporate appropriately rigorous design controls and internal SOP's that incorporate procedures for both internal and external validation of resistance rules. Companies or device manufacturers must also agree to assuring that their resistance interpretation algorithms are kept current incorporating recent clinical response data, *in vitro* phenotypic data (when clinical response data are not available), and as much

relevant unpublished data as can be gleaned from various sources including pharmaceutical manufacturer's virology data made available to the device manufacturer. One of the key concerns of the Blood Products Advisory Committee which met on Sept 17, 1999 was the ease of interpretation. As Dr. Chamberland summarizes on page 138-140 of the manuscript - how is the information going to be presented to clinicians in a way that they can use on a day to day basis that is interpretable? It does not appear to us that a minimal algorithm based upon Tables A to E would address this legitimate concern.

III. Data Considerations – B. Performance of the Assay in Determining Genotype

1. Analytic Sensitivity

Under 1C, the reference to "we may require precautionary labeling in the Limitations for Use section of the package insert indicating which mutations have been incompletely tested and verified" and the reference to limiting claims of intended use if limited analytical data are presented are a bit confusing to the reader. If the analytical/clinical testing of the system demonstrated adequate sensitivity of detection of the mutations concerned under a range of different testing parameters and protocols to satisfy FDA, then it is cleared. The fact that there are few entries in the fully verified performance list is confusing to the lay reader and potentially to the end user who will wonder - what does the regulatory clearance actually mean? Some guidance needs to be given on the differential in the agency's mind of a device cleared on limited analytical data and a device cleared with fully verified performance.

2. Range of Detectability

In order to determine assay performance, how many times should each sample be processed? Is it correct to assume that these tests can be conducted with a single lot of the device?

3. Precision

As described, the study requires greater than 600 samples, unless more than one mutation can be tested/represented per sample set, though this study may be overlapped with the "Range of Detectability" study.

4. Reproducibility

As written, the guidance is unclear as to whether each sample needs to be run in triplicate over the whole study or whether in triplicate at each site, in triplicate on each day, in triplicate with each investigator and in triplicate with each lot.

5. Lot Acceptance Testing

This is an extensive and excessively rigorous degree of testing required post-approval, for lot release, considering that the product is developed under Design Control and is being manufactured under Quality System Regulations, with process validation in place. An approved kit detects mutations under all circumstances demonstrated in the studies used to support the approval, including at the lowest levels/proportions in the range of detectability. VGI would propose instead, that a known molecular sequence at a concentration near the lower limit of detection of the assay be used for lot acceptance.

7. Assay Interference

This list appears to be identical to the CBER guidance document, "Guidance for Industry in the Manufacture and Clinical Evaluation of In Vitro Tests to Detect Nucleic Acid Sequences of Human Immunodeficiency Viruses Types 1 and 2", December 1999 for HIV detection. Some of the items included in the assay interference section may be unnecessary and may not apply to the patient population for which a genotyping assay is designed, since the assay is not designed for the detection of HIV. The following (using the numbering system in the Guidance Document) should be excluded from the list:

a) Other infections – yeast infections, pneumocystis, *M. tuberculosis*, *M. avium M. intracellulare* (There is nothing to suggest that sequence homology to HIV exists, nor evidence from other molecular tests to detect or quantitate HIV that these interfere).
c) Bacterially contaminated samples (probably unnecessary for reason given in (a) above) Hemolyzed samples (examination of the effects of hemoglobin and/or bilirubin should suffice as surrogates for hemolyzed samples).
d) Heated and detergent treated samples (molecular diagnostic tests are generally not designed to use these types of samples)
f) Plasma pool (This requirement would apply to a device designed for blood screening, not clinical management of individual infected patients)
g) Samples from patients with autoimmune diseases including Systemic Lupus Erythematosus (SLE), other patients with diseases associated with Anti-Nuclear Antibodies (ANA), Rheumatoid Arthritis, and mixed cryoglobulinemia. (Again, no evidence that these autoantibodies interfere with any other molecular tests—these would be of potential concern to immunoassays for either antigen or antibody, not molecular tests)

Mainly, interfering pathogens/substances with significant sequence homology with the target ligands should be included, and as you have detailed, substances that are likely to be found in the target patient population.

III. Data Considerations – D. Assay Performance on Clinical Samples

1. Sensitivity on Clinical Samples and 4. Reproducibility on Clinical Samples

Are the reproducibility studies required for a subset of the repository samples? If so, then how many times does each sample not included in these studies need to be run (i.e. for clinical sample sensitivity studies alone)? The proposed studies for 1 and 4 will, in combination require a large amount of plasma to be taken from patients. If the plasma from these studies is added onto the plasma required for the reference standard determination (sub-cloning), and stored back-up panels, then collection by plasmapheresis methods from the 50 plasma donors may be required.

Table B – (Ref. 3)

In the footnote, rit**ona**vir is mis-spelled as rit**oan**vir.

Other

IDEs have not been requested for this Class II device. The guidance recommends only a pre-submission meeting. Is this your intention if a sponsor chooses to take the analytical/clinical route to clearance?

Proposed Alternative
It may be easier for FDA to regulate genotyping devices as two distinct products through the routes proposed in this guidance, as detailed further below.

- A sponsor wishes to manufacture and register a kit ONLY. Regulate the kits to make sure they detect what they say they detect and with the degree of reliability etc claimed. NO clinical claims associated, purely an analytical procedure. Because the sponsor is choosing only one part of a system and has potentially little to no control over the other parts of the system, this route would require the extensive analytical testing on a variety of systems (if compatible) and would be subject to 510(k) submissions when hardware changes are made to ensure continuing compatibility and performance. Users would then be obliged to select to use this kit with a system that includes software that has been cleared by FDA and is subject to ongoing FDA scrutiny per the route below. Thus, the sponsor would be limited by labelling to promote an analytical kit, presumably to clinical laboratories. The user would be responsible to identify a clinically useful interpretation software package, FDA cleared.
- Regulate full systems which include complex software interpretation algorithms that have been subjected to FDA scrutiny and are fully defensible by clinical and / or laboratory studies. Clinical claims allowed, based upon the algorithm. This route would be subject to 510(k) submissions for the algorithm but as the system is integrated and under the control of one sponsor, hardware changes would be managed through design control and annual 510(k) updates. The whole system is integrated and the use of the kit and software will be restricted through labelling to the specific integrated device. With reference to the FDA statement in the background section, these systems should only require validation to the degree necessary to characterize the scientific basis of the assay. The validation should be of the analytical performance of the system and the software algorithm. FDA can reserve the right to reduce the degree of analytical testing required for an integrated system because of the increased degree of control exercised by a sponsor over the design and development of a whole system. Clearly there must be some minimum performance levels below which a system is unacceptable. These can be defined.

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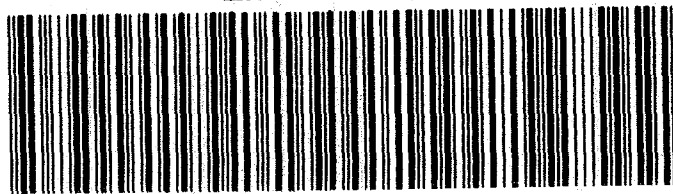

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