Ortho-Clinical Diagnostics
a Johnson-Johnson company

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

Subject: **Docket No. 2003D-0120**
Comments on the Draft Guidance for Industry on Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns

Dear Sir or Madam:

Thank you for the opportunity to provide comments on the *Draft Guidance for Industry on Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns,* dated April 21,2003. Listed below are the comments of Advanced Diagnostic Systems', a division on Ortho-Clinical Diagnostics, for your consideration.

1. **Introduction (III. Genetics vs. Expression)**
Sponsor of these tests should consider array physical design strategies . . ..

We request further definition of the phrase " array physical design strategies" and if this 'strategy' is used by the Sponsor, what the Agency could expect to see submitted in an application.

2. **Intended Use of a Test or Device**
Some tests may have multiple intended uses. The FDA has recommended a separate application for each intended use that requires unique and separate supporting studies.

We recommend that the least burdensome and beneficial approach would be to submit multiple intended uses in a single application where there is: a common use of the device, the test analysis can be done in a simultaneous instructions-for-use procedure, and there are associated analytical and clinical studies. Unique and separate supporting studies would be identified and delineated within the application. Further, the application could also then include an assessment of any chemistry interactions that may occur within the assay.

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3. **Analytical Validation**

- **Design and Manufacturing**

Specifically, the following elements of arrays and multiplex platforms should be well-characterized: design, internal controls used, oligonucleotides, primer, probes, or other capture elements, conditions (e.g., temperature, length of time), methods used to attach the target material to the matrix. Composition and spatial layout of arrays or other spatially fixed platforms, specificity of markers or targets, and stability of the platform.

The Agency has provided a general list of the components of the arrays and multiplex platforms that should be well characterized. We request that what the Agency would want to see in terms of characterization of probes should be further defined. For example, probe lengths on *in-situ* synthesized platforms will be a mixture of the final length (n), n-1, n-2, etc. due to average stepwise yields of 95-98%, resulting in failure sequences present at each feature. It will be extremely difficult to determine the population at each length for every feature on the chip. We suggest a solution would be to have the Manufacturer define their process and the resulting expected performance from this process. Manufacturers would provide data on why the specific probe sequences were chosen, why the specified number of probes were chosen, and data validating the performance of these probes in a prototype assay/product.

We request what the Agency would want to see in terms of characterization of the specificity for markers or targets should be further defined. These are potential concerns on what kinds of data (*in silico* or experimental) would be acceptable? If experimental data would be desirable, would complex messages from a number of tissues or synthetic *in vitro* transcripts be required? Additionally, would we have to generate data for each probe on the array or a sampling of the probes? We suggest a solution would be to have the manufacturer provide data on the expected specificity of probes, given the probe length and manufacturing process. For example, manufacturers would provide *in silico* data on these probes, as obtained from a BLAST or Smith-Waterman homology search. Ultimately, the specificity will manifest itself in the performance (sensitivity and specificity of prognosis) of the product.

Lastly, we believe that the following list of elements should be well-characterized and represent an appropriate level of characterization: array design, internal controls used, oligonucleotide sequences, array fabrication methods, and general data on specificity and stability (see above).

- **Validation of Specific Performance Characteristics: Analytical Laboratory Studies**

We recommend that the following should represent an appropriate level of validation: data on sensitivity and specificity of the assay, data justifying the cut-off or reference range(s) used for each of the markers in the gene signature and the range of possible expression levels for each marker, independent validation of the prognostic value of the pattern, and required amount of RNA (to address the effect of excess or limiting sample). Depending on the product application, Manufacturers would also provide data on expression levels of the markers comprising the gene signature in cells which may contaminate the original biopsy or bodily fluid or could validate the signature using laser capture micro-dissected samples. However, we do not believe extensive testing of interfering sources, beyond what may be present in a typical patients' regime, will be beneficial.

- **Validation of instrumentation (addition of Software Validation)**

We recommend the addition of a statement regarding instrument and data management software validation, with reference to FDA recognized standards, regulations, and guidance documents.

We believe that overall the draft guidance will be helpful in providing information on the content of applications for this new technology. Advanced Diagnostic Systems appreciates this opportunity to comment on the Draft Guidance for Industry on Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns. Please contact me at (908) 704-3942 should you have any questions regarding this letter.

Cordially,

Debra J Rasmussen

Debra J. Rasmussen
Director
Regulatory Affairs