AdvaMedDx
Vital Insights | Transforming Care

January 12, 2015

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

Re: Docket No. FDA-2014-D-1351; Draft Guidance for Industry and FDA Staff on Flow Cytometric Devices

Dear Sir or Madam:

On behalf of AdvaMedDx, a Division of the Advanced Medical Technology Association (AdvaMed), we provide these comments on the Food and Drug Administration (FDA) "Draft Guidance for Industry and FDA Staff on Flow Cytometric Devices (hereinafter "guidance").

AdvaMedDx member companies produce advanced, *in vitro* diagnostic (IVD) tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health care costs. Functioning as an association within AdvaMed, AdvaMedDx is the only multi-faceted, policy organization that deals exclusively with issues facing *in vitro* diagnostic companies in the United States and abroad. Our membership includes manufacturers engaged in the development of innovative diagnostics, including flow cytometric devices.

GENERAL COMMENTS

AdvaMedDx appreciates FDA (or "Agency") efforts to develop this guidance, which provides FDA current thinking on considerations related to premarket submissions for flow cytometric devices for leukocyte immunophenotyping. Considering the maturity of flow technology and its longstanding record of safety and effectiveness, our comments are intended to enhance clarity, improve flexibility, and support a least burdensome approach.

AdvaMedDx greatly appreciates the opportunity to provide comments. All efforts were made to provide detailed recommendations to assist FDA as it works to develop final guidance on these technologies of importance to the public health.

Sincerely,

/s/

Khatereh Calleja
Vice President
Technology and Regulatory Affairs

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ADVAMEDDX SPECIFIC COMMENTS

AdvaMedDx Comments on Draft Guidance for Industry and FDA Staff—
Flow Cytometric Devices

Edit No. – Comment number

Section –Section of the guidance

Line No. – Guidance line number

Change – Proposed change to the guidance

Comment/Rationale – Reason for proposed change

Edit No.	Section	Line No.	Change	Comment/Rationale
1	General	N/A	Guidance does not reference use of scientific literature in addition to performance studies using clinical samples. Submission requirements should be commensurate with information available for the test.	Since flow cytometry is a 30-year proven technology, many published papers and studies have been performed using clinical samples. Such literature should supplement testing burden.
2	General	N/A	Guidance does not consistently refer to the use of recognized standards.	Many standards exist to outline the needs for analytical performance testing and should be referenced and integrated into the guidance.

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3	General	N/A	Guidance does not reflect the applicability of the Instrument Family/Reagent Replacement Policy (IFFR) and Assay Migration Studies for *In Vitro* Diagnostic Devices guidance.	For many line extensions and often use of the same markers, the IFRR policy should be utilized to reduce submissions necessary for FDA review. For new instrument platforms, since the flow cytometer technology is essentially the same, many assays, if not all, cleared on existing platforms can be migrated to the new platforms following the assay migration guidance.
4	I. Intro IV. Device Description	87-90 157-158	Further detail and emphasis should be placed on the re-positioning of existing devices (e.g., Lytic reagents) as part of a greater system with a new product code and classification.	Without further clarification and discussion, there exists the potential to introduce confusion around the inconsistencies between this guidance and the current product code database/CFR. As drafted, this is a fairly wide move from the longstanding point of view that an accessory is effectively regulated at the highest level classification of the associated devices to the treating other stand-alone, already classified devices in the same way. Accessories are usually not otherwise regulated or classified.
5	II. Background	113	Additional focus should be included for qualitative and semi-quantitative methods.	Guidance only focuses on quantitative methods of flow cytometry.

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6	II. Background	114	Should read "…based on Laser Light Scattering and determination of cellular antigen…."	Light scatter is mentioned as a parameter in the principles of the test but not in the first reference to analyze parameters.
7	II. Background	125	Should include a reference to PMA or *de novo* pathways.	PMA and *de novo* pathways referred in lines 195 and 844.
8	IV. Intended Use	173-179	Remove the suggestion that a specific software version be included in a statement of either indications for use or intended use.	The guidance inappropriately suggests that the specific version of software used in the system be explicitly included in the intended use statement. While we agree that the software is an important component of the system, including the specific software version in the intended use or indications for use would unreasonably and arbitrarily restrict the basis for 510(k) clearance by calling out one very specific system component. Many device software modifications that result in new version numbers (i.e., revision levels) do not rise to the level of requiring a new premarket notification under the standards set forth in 21 CFR 807.81 as many such software changes and upgrades would not "significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy

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				source, or manufacturing process." The guidance suggestion would thus likely result in numerous, otherwise unnecessary new 510(k) submissions, contrary to the clear standard established in Part 807 and other longstanding FDA guidance.
9	IV. Reagent Characterization	204	We do not understand why a submitter must show why reagent combinations were selected.	This is part of design control. Markers and concentrations are fully tested through analytical performance and clinical performance testing.
10	IV. Reagent Characterization	215	Clarification needed.	Providing dilution curves for each component does not control for median fluorescence intensity (MFI).
11	IV. Quality Control	235-239	General comment	This alludes to the possibility that the plan for development and validation of control material will be part of the regulatory filing and not necessarily its actual use.
12	IV. Quality Control	240-260	We do not understand why guidance provides technical solutions.	This is covered by manufacturer's design control process.

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13	IV. Instrumentation and Software	265	Version number is not appropriate in the intended use and will result in unnecessary submissions and labeling changes.	Software versions change for many different reasons and not all require submission. If the intended use includes the specific software version, however, the intended use needs to be changed every time the software version is changed. Further, when the intended use is changed, a new submission is triggered. See comment #8.
14	IV. Instrumentation and Software	284-285	Unclear what the intended use would be in this example.	Based on this example, it is unclear what anticipated intended use would be expected by FDA.
15	IV. Instrumentation and Software	293-294	Remove IVD software.	RUO (Research Use Only) aspects of a device can be successfully integrated to the device while maintaining all expectations laid out in lines 288-289. Software will physically contain RUO and IVD diagnostics capabilities. Although segregated in functionality, the RUO is physically connected to the IVD, so it would be more correct to state "software."

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16	IV. Analytical Performance Studies	335-336	Guidance is inappropriately prescriptive as to where clinical performance trials take place. If the in-house site is in the U.S., does it count as one U.S. site?	EU has similar demographics as U.S., so requiring a U.S. site based on demographics is not valid. In addition, in instances of diseases that are not prevalent in the U.S. or have very rare populations, the one U.S. site requirement is too burdensome to comply with. Also, in the event that an in-house clinical site is available, that should meet the U.S. site requirement.
17	IV. Specimen Types and Matrices	367-373	Clarification needed.	When to use manipulated samples, cell-lines, or transfected cells in development and testing? Under what condition is it acceptable to use? How rare is rare?
18	IV. Specimen Types and Matrices	371	"Scientific validity" should be replaced with "scientific rationale."	Validity does not appear to correctly capture intent.
19	IV. Specimen Types and Matrices	372-373	Inconsistent statement with previous comments in guidance.	Some manipulated samples have traditionally been allowed to fill all bins in testing. Studies not allowing manipulated sample may never fill the binning requirements and could delay treatment options to the patient.

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20	IV. Specimen Types and Matrices	372-373	Remove restriction on manipulated specimens.	There are a number of performance studies that can and have previously used contrived samples as part of pre-market notifications. Additionally, use of these materials will be especially important for those conditions that are rare, or patient populations that do not lend themselves to three-site, high N studies (e.g., high-risk pediatric patients)
21	IV. Analytical Specificity	427	Recommend changing "therapeutic agents" to "interfering substances."	It would be very difficult and burdensome to test for every possible therapeutic agent. Manufacturers should test substances known (through literature or technical experience) to interfere and possibly affect the flow cytometric result.
22	IV. Analytical Specificity-Reagents	437-447	Testing would be excessive if this is to be done with all products under development.	As written, the implication is that MFI should be the same. However, it really should focus on the % positive as that is a suitable comparator. Only % positive implies the analytic outcome.
23	IV. Analytical Specificity-Reagents	437-454	Clarification needed.	This should not apply to single color as the example is only speaking to multicolor.

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24	IV. Analytical Specificity-Reagents-Specimen and Data Analysis	471-487	Clarification needed.	In inherent normal population, the use of the specific reagent in an iso-type control will define the dim, moderate, and bright cell populations. The use of an iso-type control will identify non-specific bound reagent allowing elimination from the analysis (in addition to software controls).
25	IV. Analytical Specificity-Reagents-Specimen and Data Analysis	471-487	Clarification needed.	Guidance mentioned FMO (fluorescence minus one) as comp control, but it is not clear why it is appropriate (individual blocking reagent).
26	IV. Analytical Specificity-Reagents-Specimen and Data Analysis	472, 484	Quantitative method specific.	Gating strategies may be sample-dependent in qualitative and semi-quantitative methods.
27	IV. Analytical Specificity-Reagents-Specimen and Data Analysis	483-487	Clarification needed.	It is vague to know how to meet these suggestions and more detail on the instructions for use should be provided.

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28	IV. Analytical Specificity-Reagents-Specimen and Data Analysis	484	Clarify meaning of "atlas."	Meaning is unclear.
29	IV. Analytical Specificity-Reagents-Interfering Substances	490-495	Removal of interfering substances may not be appropriate for all tests.	Demonstration of cell washing to remove interfering substances (e.g., drugs, RBC, bilirubin, triglyceride, etc.) may be appropriate for some assays (fusion protein) but not others.
30	IV. Analytical Specificity-Reagents-Interfering Substances	495	Add a reference to CLSI EP07 for study design information.	
31	IV. Analytical Specificity-Reagents-Interfering Substances	501	Ref. 15 should be changed to carryover study within CLSI H26.	Current reference is not relevant for proposed testing.
32	IV. Analytical Specificity-Reagents- Interfering Substances	501 - 506	Not clear on how to test reagent (only) carryover.	Cell carryover is measured with a Clinical Laboratory and Standards Institute (CLSI) protocol, but no method exists for reagent carryover. Cell carryover (if there is residual reagent) would automatically show the reagent

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				carryover. In addition, with the fluidic layout and the subsequent testing (through verification and validation), the ability of the instrument is tested to show that reagent carryover is not present due to the instrument's design.
33	IV. Analytical Sensitivity-Signal Detection Sensitivity	526	May not be needed with other scientific rationale.	Each analyte in the reagent combinations is excessive.
34	IV. Analytical Sensitivity-Signal Detection Sensitivity	527	Focuses on quantitative methods.	Range for qualitative and semi-quantitative methods may have huge variability.
35	IV. Analytical Sensitivity-Signal Detection Sensitivity	530-536	Clarification needed.	Does each marker require an effective delta (ED)? Can alternative measurement be used (e.g., stain index)? Does ED apply to qualitative and semi-quantitative marker? Surrogate to optical/instrument performance?
36	IV. Analytical Sensitivity-Signal Detection Sensitivity	543-623	Remove detailed instructions. Replace with broad language describing requirement to assess for non-specific binding.	This is a highly prescriptive specific approach which is uncertain to perform in all instances.

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37	IV. Analytical Sensitivity-Signal Detection Sensitivity	583-589	Guidance should emphasize that it is an example as it may not be applicable to rare sample types.	Guidance calls out specific number of samples.
38	IV. Analytical Sensitivity-Signal Detection Sensitivity	583-623	Need a non-binding curve specific example.	Provide a specific example for the use of non-specific binding curve.
39	IV. Analytical Sensitivity-Signal Detection Sensitivity	583-623	Clarification needed.	Even when there is a smear between negative and positive populations (e.g., CD38), these populations can still be defined. A stain index measurement should be sufficient in situations where the negative versus positive population separation is unambiguous.
40	IV. Analytical Sensitivity-Signal Detection Sensitivity	613-619	Clarification needed.	Section is unclear as to what FDA suggests to meet requirement.
41	IV. Analytical Sensitivity-Enumeration of Rare Events	626	Change title to “Measurement Capability.”	This revised title would provide a more clear description of required testing.

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42	IV. Analytical Sensitivity- Enumeration of Rare Events	628-631	Remove Bethesda reference or modify the language to indicate this is only an example.	Very specific suggestion based on particular disease area. Does not apply to wide range of applications.
43	IV. Analytical Sensitivity- Enumeration of Rare Events	638	Update reference to CLSI EP17-A2.	There is a new revision.
44	IV. Analytical Sensitivity- Enumeration of Rare Events	635-643	Clarification needed.	What is the role of LOB, LOD, and LOQ in qualitative and semi-quantitative assays? Is the LOx application based solely on the output results and not MFI (e.g., % output would use % and not MFI to define the LOx)?
45	IV. Precision- Repeatability	672	Replace specific requirements with reference to CLSI standards. This can be accomplished through replacing the paragraph with a reference to CLSI EP5-A3 for study design guidance.	In instances where this is a product line extension or known makers, a subset (8 data points) should be acceptable for repeatability rather than 20.
46	IV. Precision- Repeatability	682	Suggest rewording in considering that not all markers have clear clinical cutoff.	This is applicable to CD4/ CD34/ CD3 where the clinical cutoff is known. There are other markers, however, that this type of testing is not feasible.

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				[e.g., multicolor assays for leukemia & lymphoma (or L&L)].
47	IV. Precision-Repeatability	690	Update reference to CLSI EP5-A3.	There is a new revision.
48	IV. Precision-Reproducibility	704	Replace the requirement to use specimens for reproducibility testing with the use of cell lines, controls and/or stabilized cells.	Specimens are not stable for the duration required for reproducibility studies.
49	IV. Precision-Reproducibility	707-712	Remove this section and refer to CLSI EP 5-A3 for guidance on study design.	This content is overly prescriptive and discrepant with CLSI EP5-A3.
50	IV. Precision-Reproducibility	712-714	Change “these three lots should be unique in formulation in that the monoclonal source material should be distinct for each of the three lots” to “these three lots should be unique in formulation in that the monoclonal source material should be distinct for each of the three lots only unless justification can be provided showing minimal variation in monoclonal source material.”	With 3 lots requirement, the conjugation and manufacturing variations are more extensive than the monoclonal source variation. In-house data often exist showing lot-to-lot monoclonal consistency, demonstrating minimum. Therefore, asking for 3 lots of distinct monoclonal source material is unnecessary. Rarely are 3 lots of distinct monoclonal source material manufactured in 1-2 years.

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51	V. Precision-Reproducibility	717	Change “and provide the protocol” to “and provide the protocol description.”	Description and reports will properly encompass the testing design and results performed to meet analytical performance.
52	V. Precision-Reproducibility	735	Update reference to CLSI EP5-A3.	There is a new revision.
53	V. Precision-Reproducibility	744	Revise from 18-22 to room temperature. Revised from 6 hours to 8 hours.	Guidance should allow for increased flexibility.
54	V. Stability	758	Add a reference to CLSI EP-25 guideline for reagent stability.	
55	IV. Performance Studies	761	Change section title to “Evaluation of Clinical Performance.”	Need to clarify the applicable studies since clinical samples can also be used in analytical performance studies (e.g., precision study).
56	IV. Performance Studies- Study Population	764	Revise to indicate to provide information as needed for specific study type.	Combines requirements of method comparison to predicate and clinical evaluation to clinical condition. Requirements should be separated or left broader for sponsor’s determination of what information should be provided.

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57	IV. Performance Studies- Study Population	770	Indication of who made diagnosis may not be available.	Many studies are performed with leftover and pooled samples and diagnoses are not available or applicable.
58	IV. Performance Studies- Expected Phenotypes	778	In some tests, patient-to-patient variation is too high.	Expected phenotype, for example in L&L, the patient-to-patient variation is too high to name all the possible phenotypes.
59	IV. Performance Studies- Expected Phenotypes	778-784	Need to make this an optional section based on the specific assay.	Does not apply to all assays.
60	IV. Performance Studies- Normal/ Reference Range	793	Guidance focuses on quantitative methods.	For qualitative and semi-quantitative methods, normal ranges are not established or not applicable (i.e., L&L).
61	IV. Performance Studies- Normal/ Reference Range	793-810	Description of normal/reference range is too prescriptive.	Does not take into account bio-statistical variability and may be excessive.
62	IV. Performance Studies- Normal/ Reference Range	794-795	Remove “minimum of 50 normal donors from each of the three geographically diverse sites” and replace with a reference to CLSI C28 for guidance on study design.	Guidance should allow for increased flexibility.

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63	I IV. Performance Studies- Normal/ Reference Range	796-800	Ranges are not always well established, especially in situations where a single, known disease state is being evaluated. Remove starting "with 50 samples…" and refer to CLSI C28 for guidance on study design.	For qualitative and semi-quantitative methods, cutoff/normal range is not established or not applicable (i.e., L&L). This is overly prescriptive. Guidance should allow for increased flexibility.
64	IV. Performance Studies- Normal/ Reference Range	805	Change reference range to reference intervals for consistency with CLSI guideline. Incorporate reference to CLSI EP28-A3c.	This reference is shown in the Appendix section, but it is not cited in the text. In addition, this section does not distinguish between establishing (community at large – literature and KOLs) and transferring (application of the established) reference intervals. By following CLSI EP28-A3c, it is much clearer.
65	IV. Performance Studies- Normal/ Reference Range	813-822	Remove specific reference to the number of samples and refer to CLSI EP28 for guidance on study design.	This is overly prescriptive. Guidance should allow for increased flexibility. Abnormal ranges (e.g., MRD) are not as definitive as this document suggests. As it does not take into account bio-statistical variability, sample rarity and may be excessive, sample size should be statistically meaningful (using the CLSI EP28).

Edit No.	Section	Line No.	Change	Comment/Rationale
66	IV. Performance Studies- Normal/ Reference Range	842-844	Change "clinical studies to support a premarket approval (PMA) may be involved" to "clinical studies to support a premarket approval (PMA) may be involved, unless justification can be made for the *de novo* process."	Some testing does not have an FDA-recognized standard of care, but it may be appropriate for the *de novo* process. A PMA should not be presumed.
67	IV. Performance Studies- Normal/ Reference Range	859-860	Please clarify: "The comparison samples should be the same for all instruments."	It is unclear if this is meant as the same sample across all instruments within the study or just from test to predicate device.
68	IV. Performance Studies- Normal/ Reference Range	860	Change "[y]ou should submit a detailed protocol describing…" to "[y]ou should submit a detailed description of …"	Description and reports will properly encompass the testing and results performed to meet analytical performance.
69	IV. Performance Studies- Normal/ Reference Range	870	Clarification needed of "reference range."	There is discrepancy between this section and a previous section regarding the normal reference range.
70	IV. Performance Studies- Normal/ Reference Range	870	Need clarification of "cutoff."	Need to include EP24A2e reference that addresses the analysis for clinical relevant cutoff. Also can include EP9A3 and AP12A2, which address quantitative and qualitative analysis methods.

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71	Appendix	917-981	Consider replacing the listing of CLSI standards to "CLSI standards recognized by FDA."	CLSI standards are updated on a regular basis. Referencing particular ones/versions in the guidance document will require timely update of the guidance when the standards are changed. Besides, not all relevant CLSI standards are listed (e.g., EP25, EP9A3, etc.).
72	Appendix	960	Update reference to CLSI EP17-A2 or CLSI EP17.	There is a new revision. See comment #71.
73	Appendix	968	Update reference to CLSI EP05-A3 or CLSI EP05.	There is a new revision. See comment #71.
74	Appendix	980-981	Remove reference 15 and substitute with CLSI H26.	This does not appear relevant.