U.S. FOOD & DRUG ADMINISTRATION

Update on OIR Review Policy for Flow Cytometry:

Reagent Replacement Policy, Class II Exemption of Flow Cytometers

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AMDM: April 11, 2019

Agenda

1. Replacement Reagent Policy (RRP), applied to flow cytometry
   - Definition
   - Flowchart
2. Proposed Flow Cytometer Instrument Exemption
   - Limitations

Replacement Reagent Policy: RRP

What is RRP?

- IVD test systems
- regulated by CDRH
- previously cleared assay
- previously cleared automated laboratory instrument
- an instrument family for which another member has been cleared

What is an Instrument Family Member?

- group of one or more instruments
- same manufacturer
- same general architecture, design, tolerance limits, and capabilities, such as detection methods, signal range and intensity, and reaction conditions

Basic Outline of the Replacement Reagent Policy (RRP)

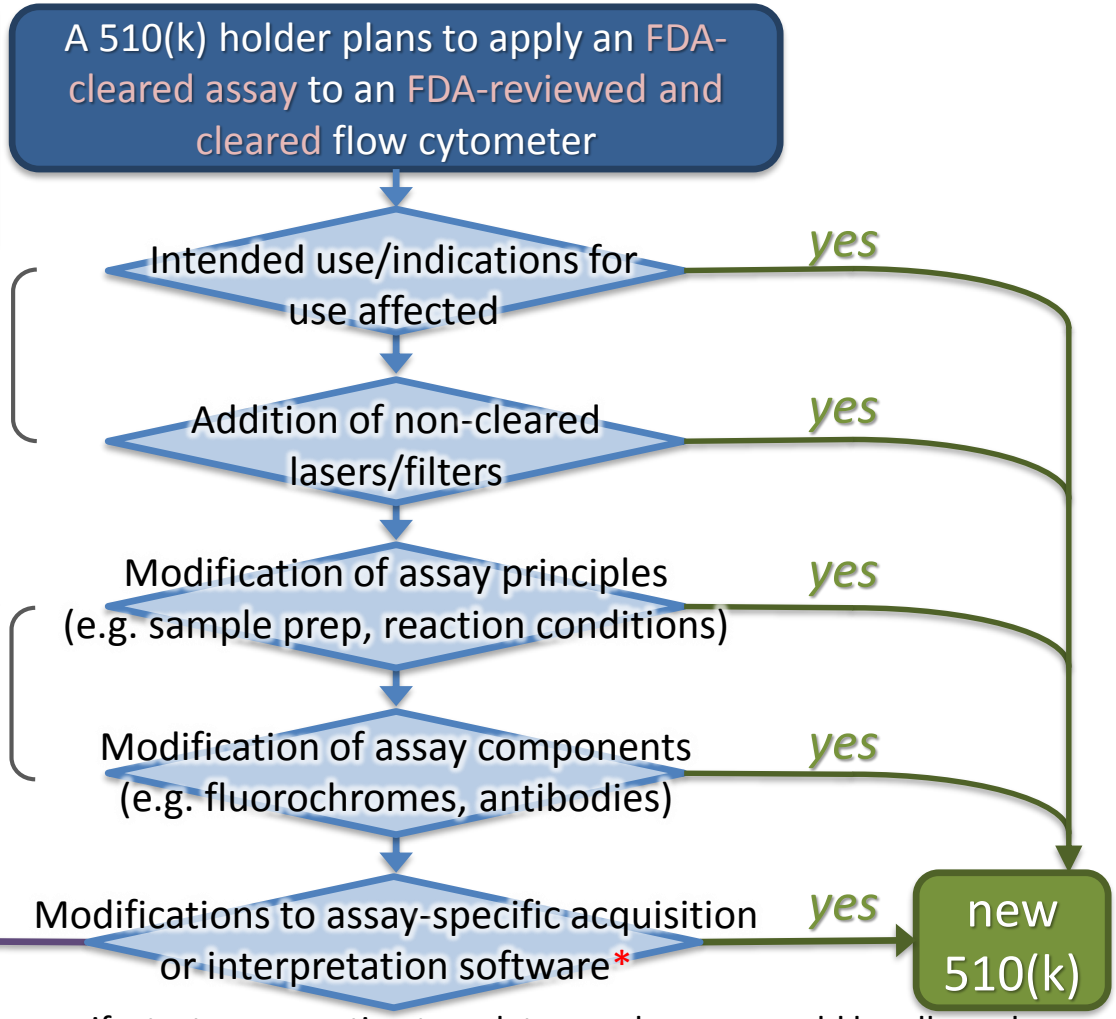
	Previously cleared	Not cleared
Assay	A	B
Analyzer	1	2

for an analyzer, "cleared" denotes that the analyzer was specified and used to demonstrate performance within a 510(k) for the cleared test system

Combination	Regulatory Pathway
A + 1	consider RRP as described in this guidance
A + 2	new 510(k), unless 2 is a family member of 1
B + 1	new 510(k)
B + 2	new 510(k)

Deciding to RRP: a flowchart

	Previously cleared	Not cleared
Assay	A	B
Analyzer	1	2



Basic requirements for use of RRP and Instrument Family Policy for all IVDs

We have not reviewed the complexity of these changes

- if a test uses a gating template, no changes would be allowed
- gating templates may be moved from instrument to instrument

Flow cytometer Proposed Class II Exemption

Pros

- Clear instructions for performing validation testing
- Put flow on even par with other IVD instruments (e.g. immunoassay analyzers, mass spec, NGS)
- Simplify regulatory process for manufacturers and FDA
- Simplify labeling for RUO and clinical instruments
- Instruments come to market faster

Considerations

- Assays and reagents are not exempt

	Previously reviewed	Not reviewed
Assay	A	B
Analyzer	1	2

Proposed Exemption Determination

Determination is based, in part on:

- The Agency's knowledge of the device
- Experience reviewing these devices over the past 34 years
- Ability to review relevant functionality when they are used clinically with IVD reagents subject to review
- Relevant reports or studies on device performance
- The Agency's ability to limit an exemption
- Exemption is limited in scope
- Only applies to flow cytometer instruments under the listed conditions

Proposed Exemption Determination

Risks identified in the special controls guidance for automated differential cell counters

- Mitigated using an alternative approach, provides equivalent assurance of safety & effectiveness
- Manufacturer's design verification and validation should include documenting performance aspect mitigations (§7-15 of Guidance)
- Documentation should be included in design history file

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm092780.htm

Proposed Instrument Exemption

CFR Title 21, §864.5220: Automated differential cell counter

(a) Identification. An automated differential cell counter is a device used to identify one or more of the formed elements of the blood. The device may also have the capability to flag, count, or classify immature or abnormal hematopoietic cells of the blood, bone marrow, or other body fluids. These devices may combine an electronic particle counting method, optical method, or a flow cytometric method utilizing monoclonal CD (cluster designation) markers. The device includes accessory CD markers.

(b) Classification. Class II (special controls). The special control for this device is the FDA document entitled "Class II Special Controls Guidance Document: Premarket Notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells; Final Guidance for Industry and FDA."

The Agency has determined based on established factors that these devices, which are currently regulated by FDA under product code OYE, no longer require premarket notification to provide reasonable assurance of safety and effectiveness.

All other class II devices classified under FDA's automated differential cell counter regulation would continue to be subject to premarket notification requirements.

Proposed Exempted Regulation & Procodes

K number	Manufacturer	ProCode	Panel	Name
K832420	Becton Dickinson	GKL	HE	FACS Analyzer
K840195	Becton Dickinson	GKZ	HE	FACS Analyzer
K872166	Becton Dickinson	GKL	HE	FACScan
K914014	Becton Dickinson	GKZ	HE	FACStrak
K933486	Becton Dickinson	GKZ	HE	FACSCount
K953302	Becton Dickinson	GKZ	HE	FACS Loader
K963263	Beckman Coulter	GKZ	HE	EPICS XL
K030828	Beckman Coulter	GKZ	HE	FC500 MCL
K040725	Becton Dickinson	GKZ	HE	FACS Canto
K041074				
K053497				
K062087				
K071681				

ProCode	Device Description	Class	Reg
GKZ	Counter, Differential Cell	2	864.5220
GKL	Counter, Cell, Automated (Particle Counter)	2	864.5200
OYE	Flow Cytometric Reagents and Accessories	2	864.5220

Cytometer Exemption Conditions

1. The instrument must not include an indication for sorting and collecting cells for IVD use or other clinical purposes

   Reason: used to manufacture biologics

2. The instrument must not be or include an automated hematology analyzer or include an indication for performing an automated differential cell count

   Reason: used to determine CBC which is not application based, nor open platform

3. Design verification and validation for the instrument must include documenting the appropriate performance of each of the performance aspect mitigations identified in sections 7 through 15 of the FDA document entitled "Class II Special Controls Guidance Document: Premarket notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells"

Cytometer Exemption Performance

4. Design verification and validation for the instrument must include documentation of analysis and non-clinical testing that appropriately demonstrates:
    a. The linearity of all fluorescent detectors covers at least four orders of magnitude with less than 10 percent deviation from expected values across the linear range.
    b. The total imprecision of the measured fluorescence intensity for each detection channel is less than 10 percent Coefficient of Variation across the linear range of the detectors.

Reason: the above performance allows a reasonable assurance of safety and effectiveness

Helpful Links

Federal Register Notice (A Proposed Rule by the FDA):
https://www.federalregister.gov/documents/2019/03/06/2019-03967/medical-devices-exemption-from-premarket-notification-class-ii-devices-flow-cytometer-instruments

Request for Comments (closes May 6, 2019):
https://www.regulations.gov/docket?D=FDA-2018-N-4394

Summary

1. Learned how to apply RRP principles and practices to flow cytometry
2. Understand the rationale underlying the proposed Flow Cytometer Exemption

Thank you