

FDA Regulation of HIV IVDs

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CBER | US FDA

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Learning Objectives

- After this presentation you should understand:
 - The history of testing for HIV infection
 - How FDA evaluates in vitro diagnostics
 - Reclassification and the current status of HIV IVDs
 - How FDA is expanding access to testing

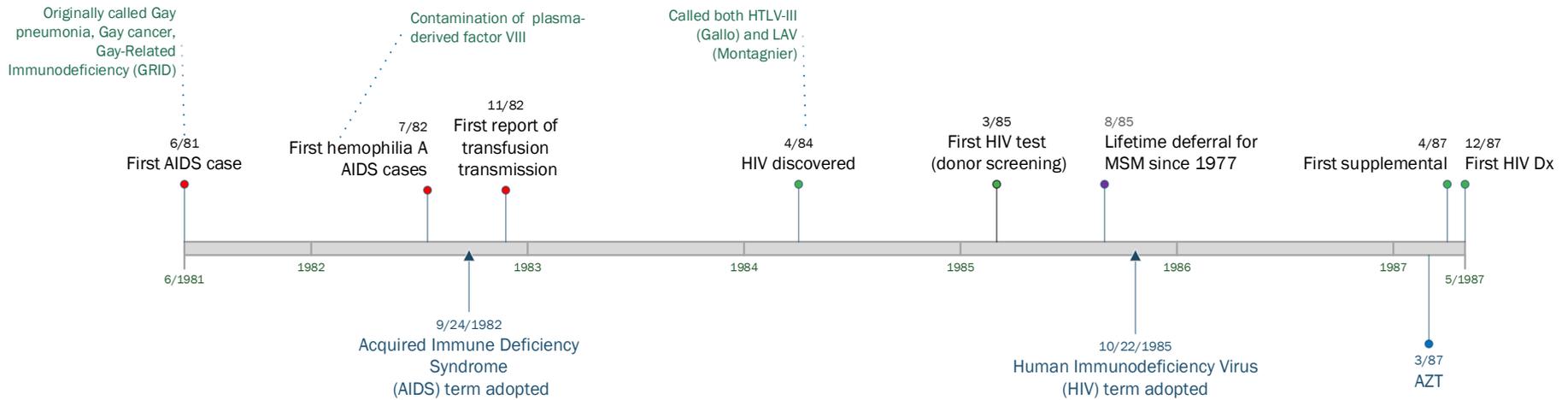
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The History of HIV testing

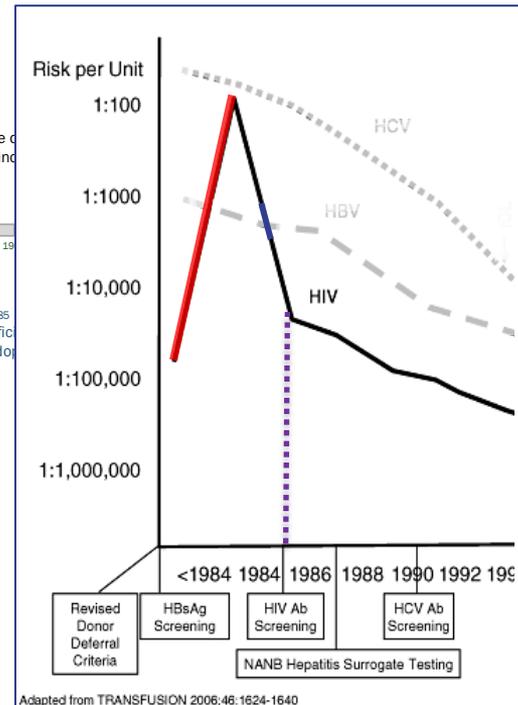
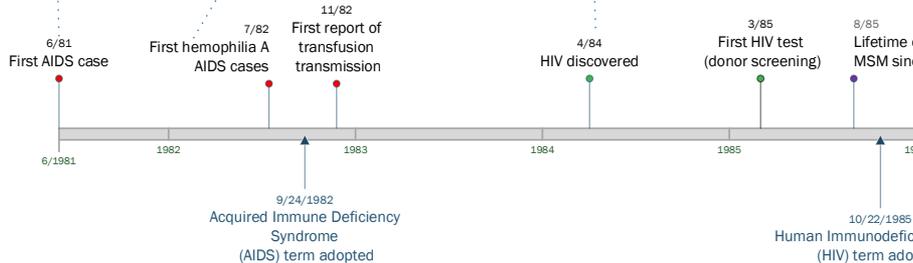
The first HIV tests were used for screening blood donors...



Originally called Gay pneumonia, Gay cancer, Gay-Related Immunodeficiency (GRID)

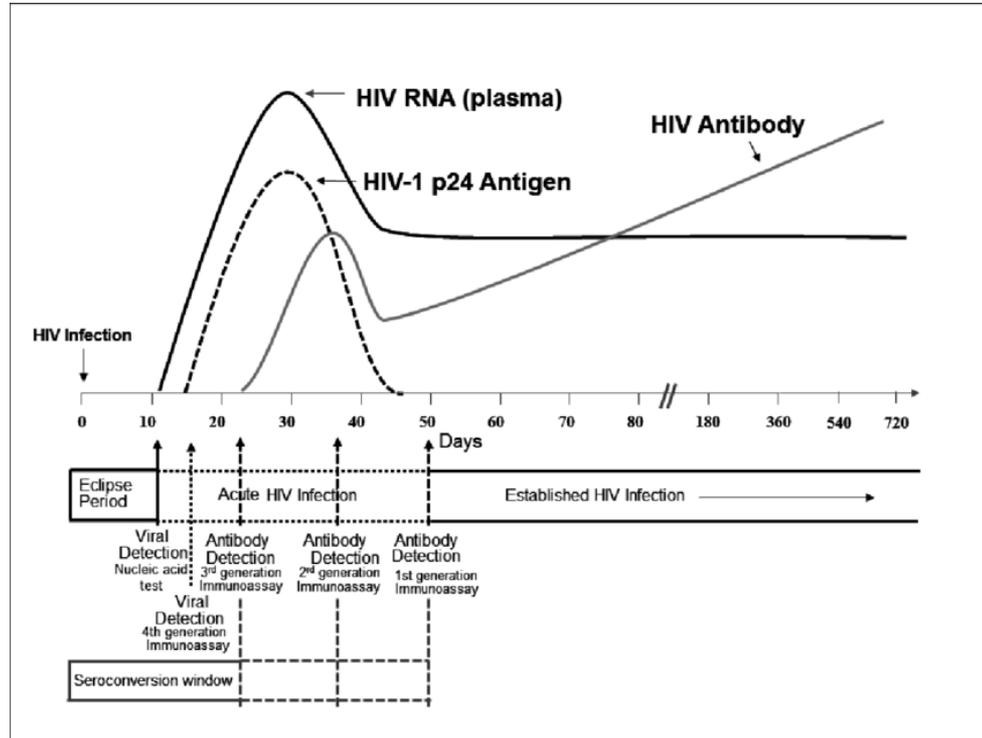


...because the risk of transmission of HIV from blood donations was so high



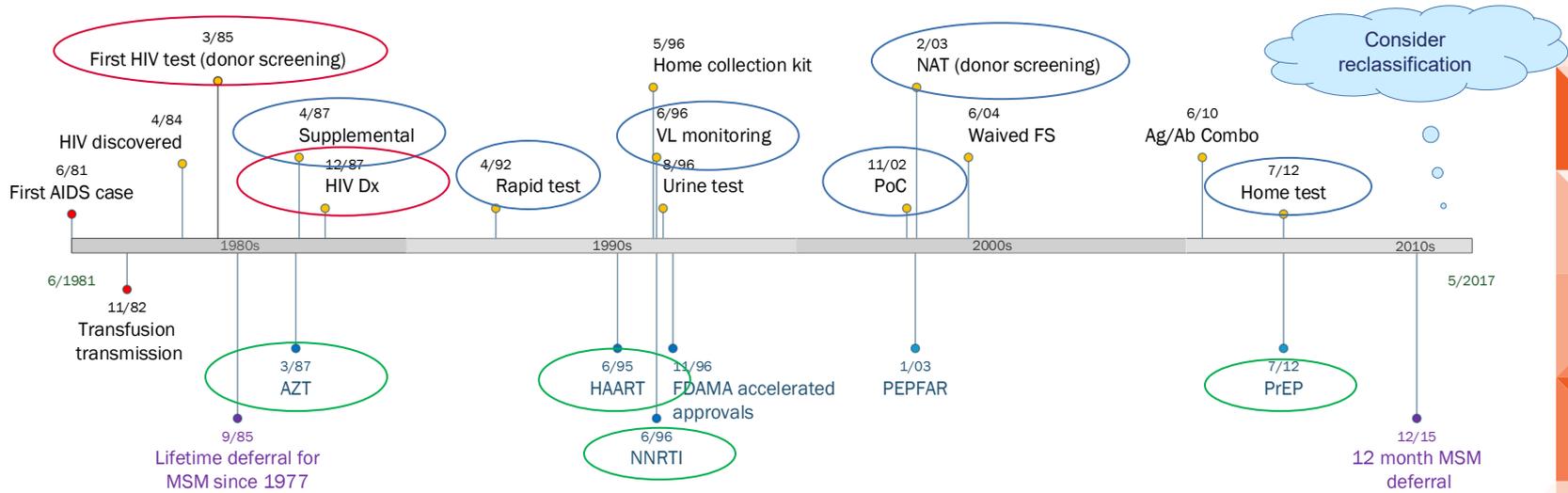
Adapted from TRANSFUSION 2006;46: 1624-1640

HIV IVDs detect different markers of infection



Branson, Bernard; et al;
2014/06/27; Laboratory
testing for the diagnosis of
HIV infection: updated
recommendations

By 2017 DETTD had authorized a variety of HIV IVDs



And HIV treatment advanced to make HIV a manageable disease

To understand reclassification, first we need to understand how FDA thinks about IVD review

IVDs are reagents, instruments, and systems intended for use :



In diagnosis of disease or other conditions...to cure, mitigate, treat, or prevent disease

In the collection, preparation, and examination of specimens taken from the human body

201(h)(1) of Food, Drug, & Cosmetic (FD&C) Act; 21 U.S.C 321 (21 CFR § 809.3)

Review of IVDs is based on:

The balance of
benefit
vs
risk of a wrong result
to the patient

The data providing a
reasonable assurance
of safety and
effectiveness of the
device

Who?

Pediatrics,
newborns,
pregnant women,
all ages

Mode?

Self-testing, Point
of care, lab-based

Intended Use
determines the
benefits and
risks

Indication?

HIV infection,
Syphilis infection,
cancer, flu

Analyte?

Antibodies to HIV,
HIV nucleic acid,
HIV antigen

Why?

Diagnosis (signs
and symptoms)
Monitoring (in care)
Screening
(no signs and
symptoms, not in
care)

An Intended Use statement includes all of the key elements

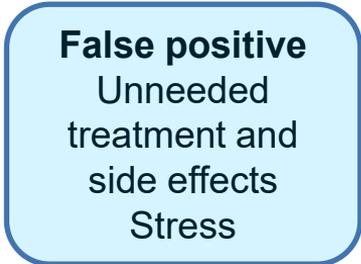


The **Acme HIV Combo** test is an **enzyme immunoassay** for the simultaneous **qualitative** detection of **HIV p24 antigen and antibodies** to HIV Type 1 (HIV-1 groups M and O) and HIV Type 2 (HIV-2) in **human serum or plasma**. This test is intended as **an aid in the diagnosis of HIV-1 and/or HIV-2 infection**, including acute or primary HIV-1 infection. The assay may also be used as an aid in the diagnosis of HIV-1 and/or HIV-2 infection in **pediatric subjects 2 years of age and older**.

The Acme HIV test is not intended for screening donors of blood, blood components or HCT/Ps.

A light blue rounded rectangular box with a dark blue border. It contains the text: **False negative**, No treatment, No further testing, and Transmission.

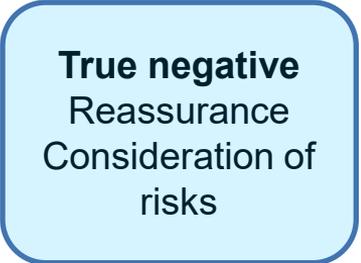
False negative
No treatment
No further testing
Transmission

A light blue rounded rectangular box with a dark blue border. It contains the text: **False positive**, Unneeded treatment and side effects, and Stress.

False positive
Unneeded
treatment and
side effects
Stress

FDA review is
based on the
balance of
risk and benefit
of *this* device

e.g., HIV testing

A light blue rounded rectangular box with a dark blue border. It contains the text: **True negative**, Reassurance, and Consideration of risks.

True negative
Reassurance
Consideration of
risks

A light blue rounded rectangular box with a dark blue border. It contains the text: **True positive**, Start life-saving treatment, and Entry into care.

True positive
Start life-saving
treatment
Entry into care

IVD device classification is based on mitigation of risks to patients

Intended Use

```
graph TD; A([Intended Use]) --> B[Are general controls sufficient to provide a reasonable assurance of safety and effectiveness?];
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Are general controls sufficient to provide a reasonable assurance of safety and effectiveness?

Controls provide this reasonable assurance of safety and effectiveness:

General Controls:
General provisions in the FD&C Act that apply to all devices

- Labeling
- Quality Systems
- Adulteration and Misbranding
- Adverse event reporting

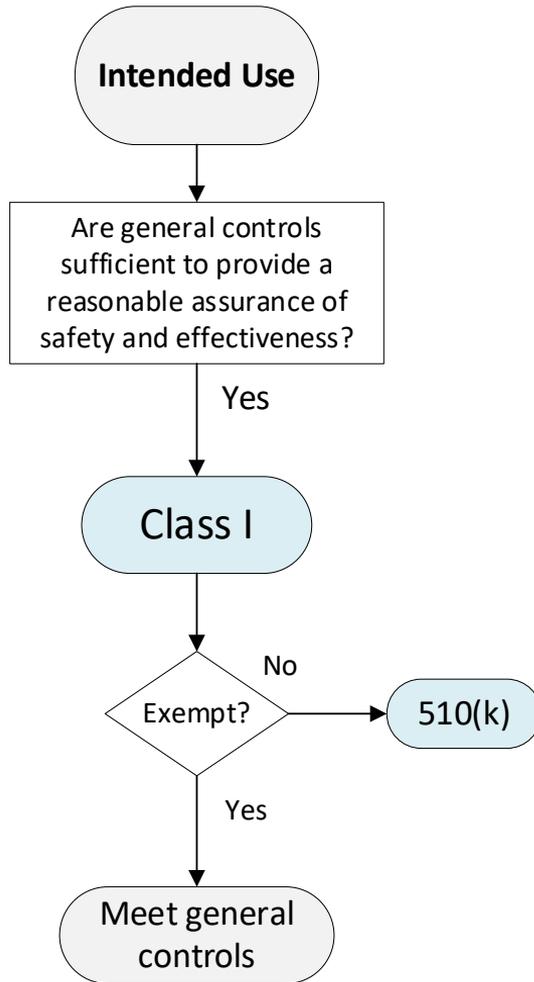
FD&C Act 513(a)(1)(a) Class 1, General Controls

Special Controls:
Device-type-specific controls that, along with general controls, provide a reasonable assurance of S&E

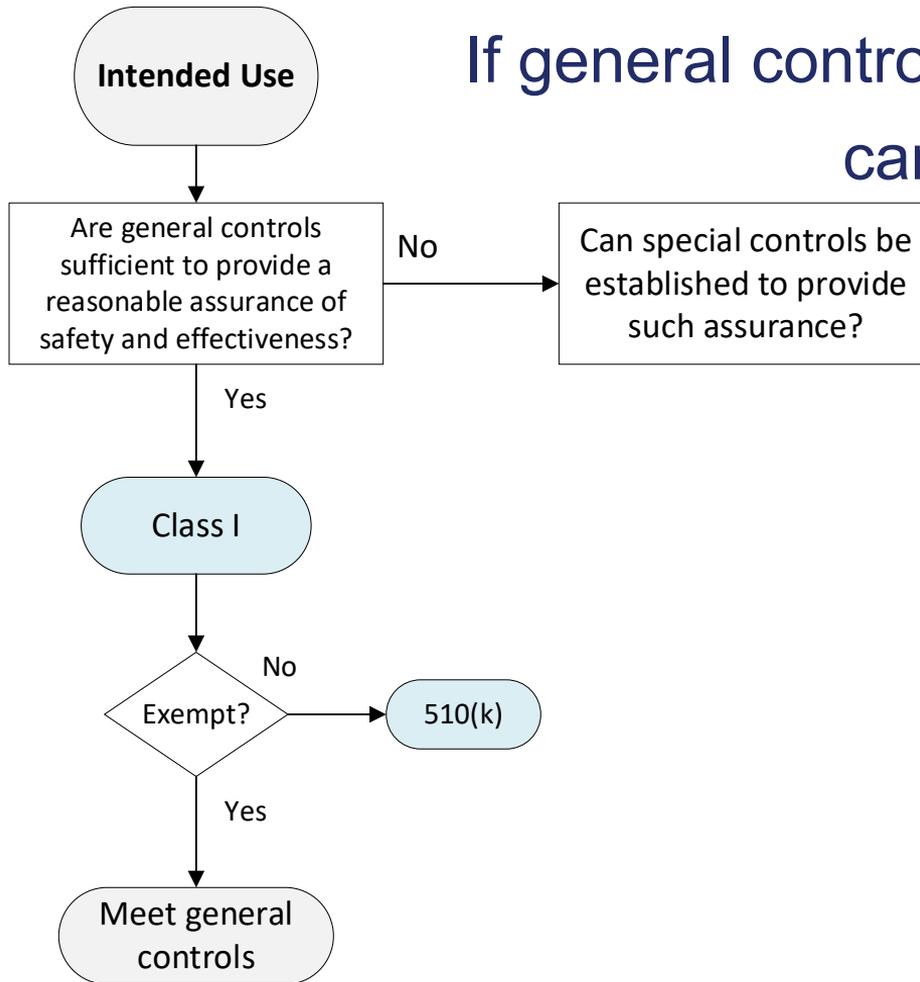
- Performance standards
- Patient registries
- Complaint reporting

FD&C Act 513(a)(1)(B), 21 U.S.C. 360c(a)(B): Class II, Special Controls

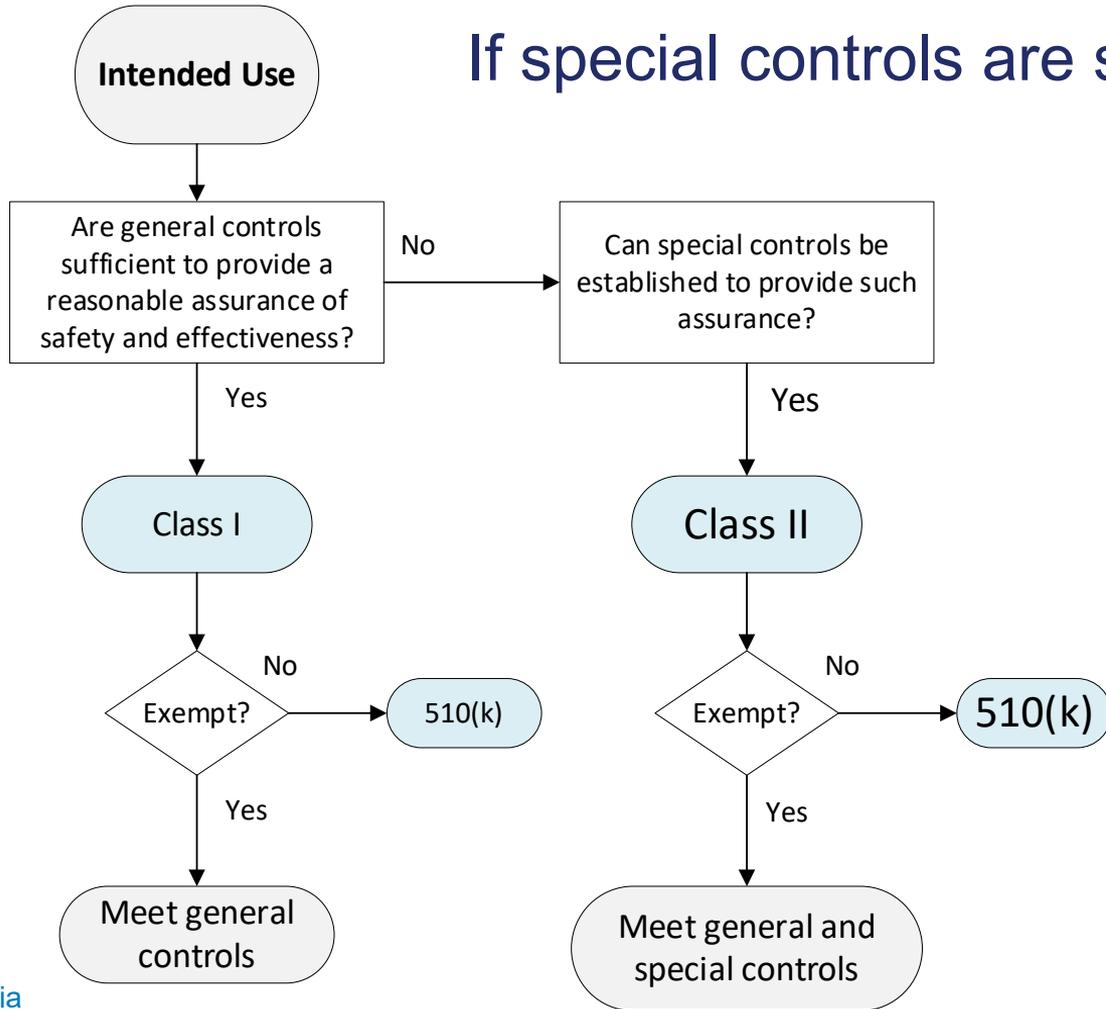
If general controls alone are sufficient to mitigate risks → class I



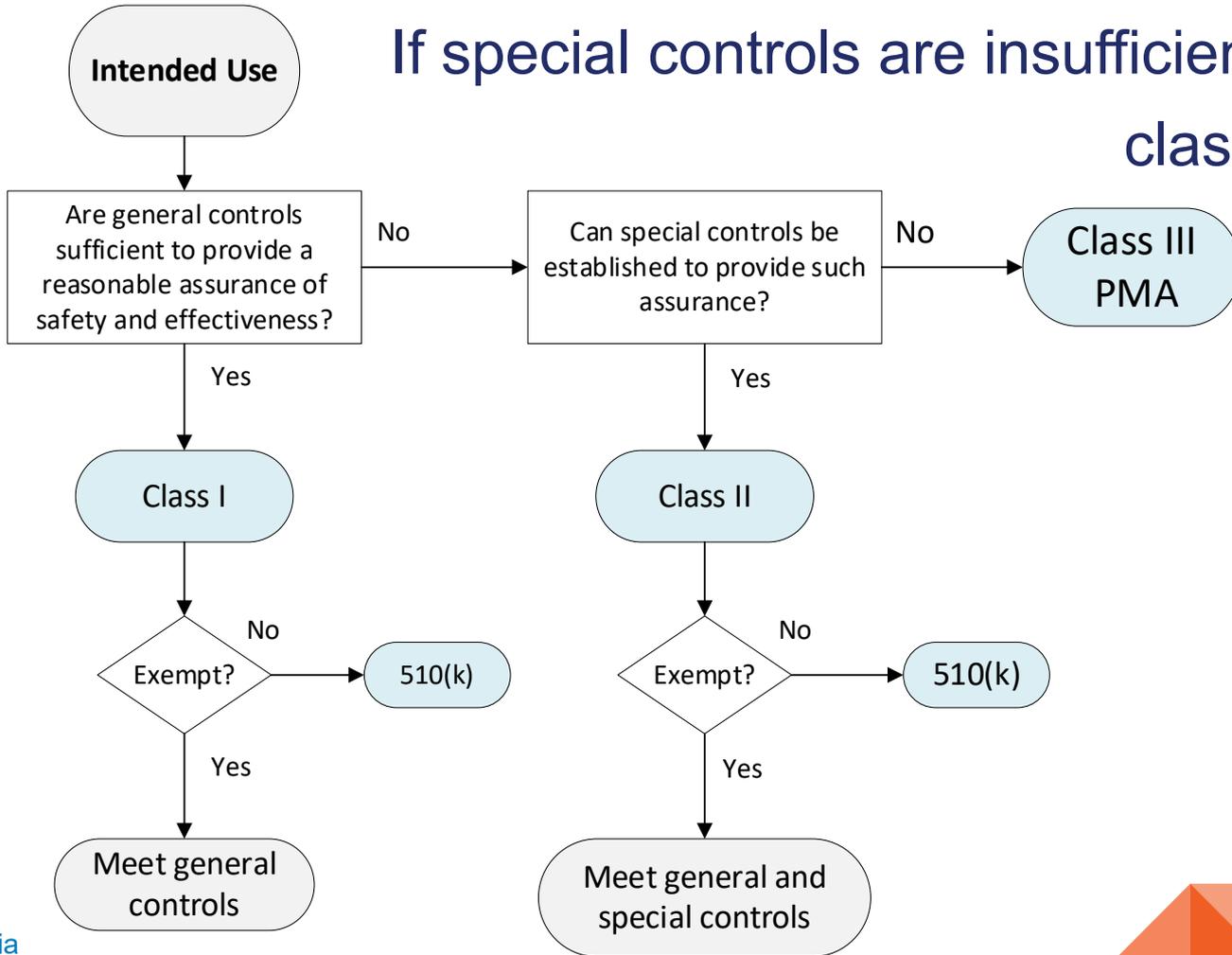
If general controls are insufficient can special controls mitigate risks?



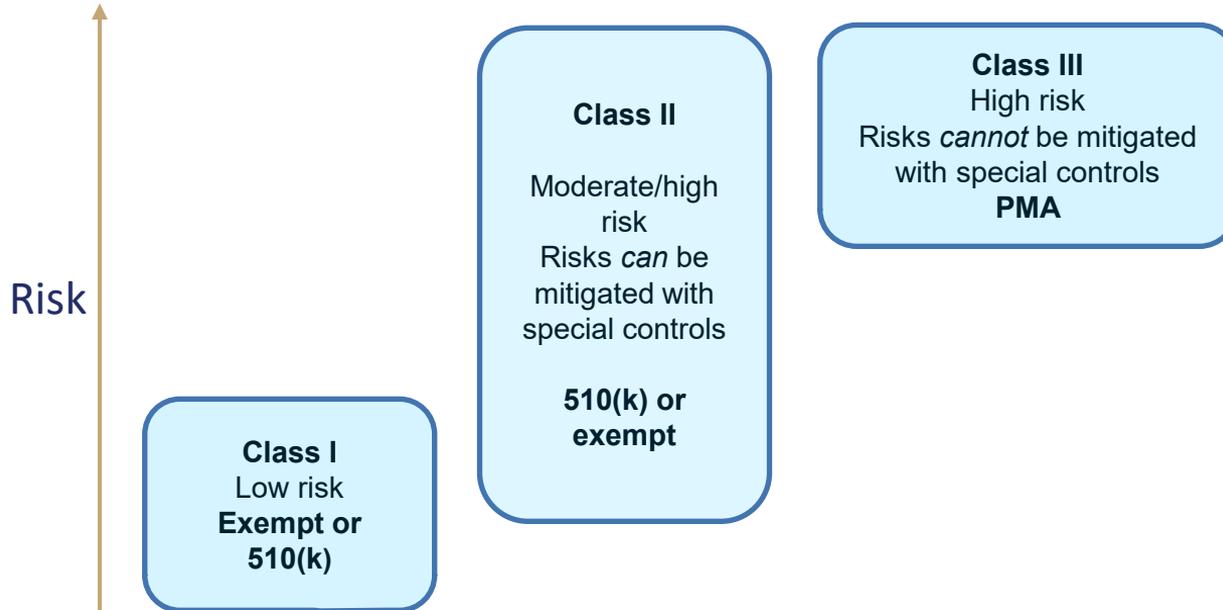
If special controls are sufficient → class II



If special controls are insufficient → class III



Device classification is based on risk and mitigation



Each class has its own review paradigm

	Class I	Class II		Class III
Risk	Low	Moderate or High		High
Clearance/ Approval	Not Required* Marketed	510(k)* Cleared	De Novo Granted	PMA Approved
Comparator	Not Required	Substantial equivalence to Predicate	Clinical Truth	Clinical Truth
Controls	General	General + Special Controls		General + clinical validity
Studies Submitted	Not Required*	Analytical and Clinical		

*Most class I and some class II IVDs are exempt from pre-market review, some Class I reserved devices require 510(k)

Comparison of class I/II and class III

	Class II and Class I reserved 510(k)	Class III Pre-market Approval PMA
Performance Standard	Substantial equivalence	Safety and effectiveness
Clinical Studies	May require clinical studies	Almost always require clinical studies
Analytical data, line data review	Same	
Software/instrumentation	Same	
Labeling	Clear draft labeling	Approve final labeling
Chemistry, manufacturing, controls	Internal documentation of adherence	Reviewed in submission

Comparison of class I/II and class III

	Class II and Class I reserved 510(k)	Class III Pre-market Approval PMA
Pre-market inspection/ BIMO inspection	No pre-clearance inspection/ No BIMO inspection	Pre-approval/BIMO inspections customary
Post-market inspection	Same	
Adverse event reporting	Same	
Least burdensome provisions	Same	
Changes in critical reagents, IU	New 510(k)	PMA supplements
Timeline- FDA days	90 days	180 days

Challenge question #1

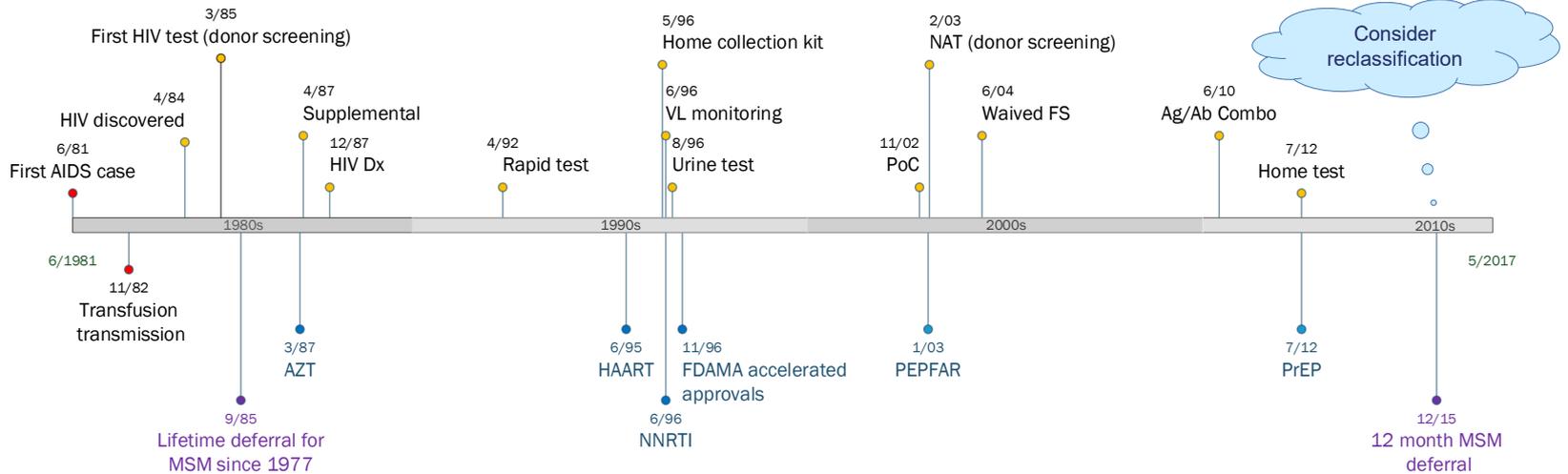
Does classification of a diagnostic test into class II mean that FDA considers the condition for which it tests to be less serious than a class III device?

- A. Yes, because class II = moderate risk
- B. No, because class II devices can be high risk or moderate risk
- C. No, because device classification is based on the risk to a patient of a wrong result and if/how that risk can be mitigated, not the seriousness of the condition

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HIV Device reclassification

After 30+ years, FDA had sufficient experience with HIV IVDs to consider reclassification



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Status of HIV IVDs in 2017

- **Class II: 510(k)**
 - Drug resistant mutation (DRM) tests
 - Genotyping tests
- **Class III: PMA**
 - Diagnostic and supplemental serology and NAT tests
 - Viral load monitoring tests
 - PoC serology tests
 - Self-tests
 - Self-collection devices
- **BLA:**
 - Blood donor screening devices

FDA considers both benefits and risks to reclassification:



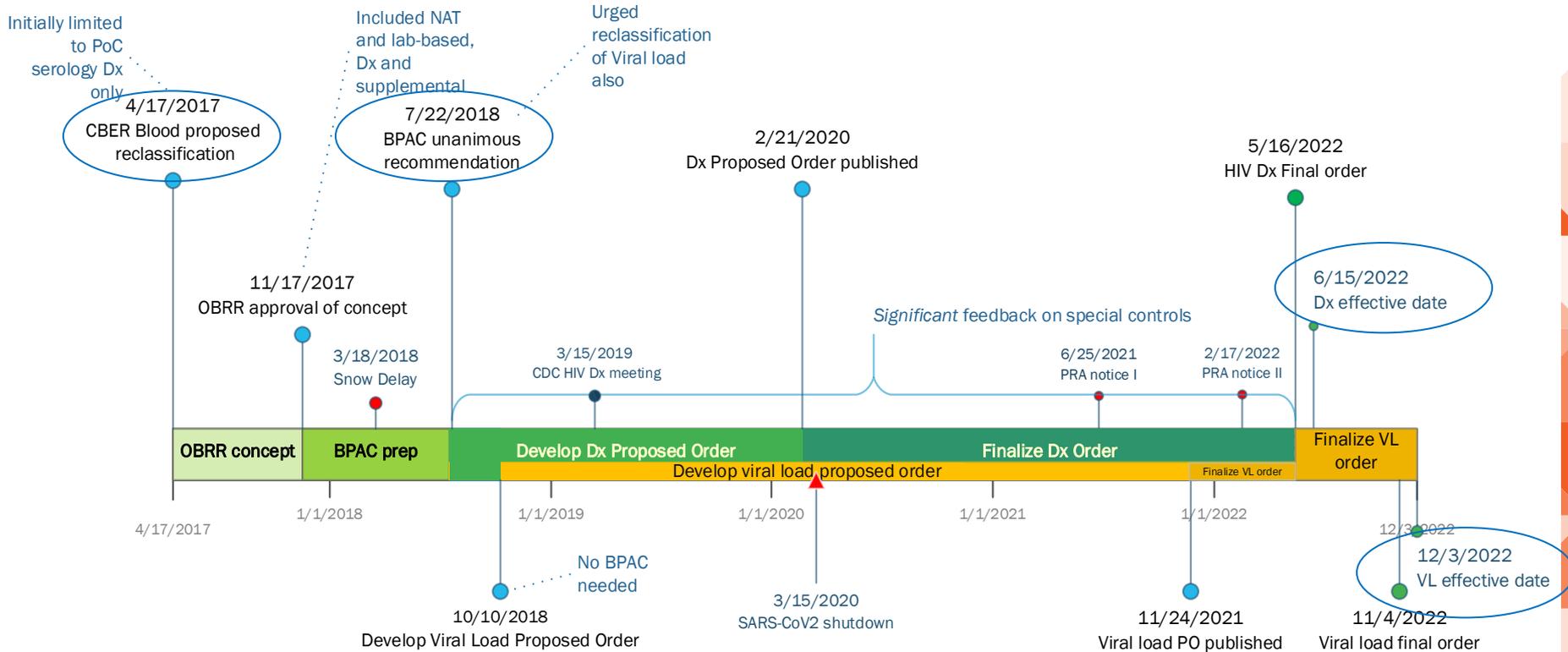
Benefits:

- Shorter review time
- Lower user fees
- No annual reports or supplements
- Earlier entry to market

Risks:

- New devices may not meet performance of PMA devices
- No review of manufacturing

Reclassification is lengthy and complex



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After the unanimous BPAC recommendation on July 7, 2018, FDA proceeded with reclassification of HIV lab-based and point-of-care diagnostic and supplemental serology and NAT tests, developing the proposed order

Based on BPAC and stakeholder feedback, FDA decided also to proceed in parallel with separate reclassification of HIV viral load monitoring devices under 21 CFR 513(f)(3)

Special controls
provide a
reasonable
assurance of
safety and
effectiveness of
the device

- Device-type-specific regulatory requirements that **must** be followed to provide a reasonable assurance of safety and effectiveness
- All devices with the same Intended Use—even if class II exempt—must meet special controls
- May include, but not limited to,
 - Performance standards
 - Postmarket surveillance
 - Patient registries
 - Premarket data
 - Special labeling requirements

FD&C Act 513(a)(1)(B), 21 U.S.C. 360c(a)(B): Class II, Special Controls.

Special controls include performance requirements



	PoC		Lab-based	
	Range of Point estimates (%)	Range of 95% CI lower bounds (%)	Range of Point estimates (%)	Range of 95% CI lower bounds (%)
Approved devices				
Sensitivity (Se)	98.9–100	98–99.5	100	99.4–99.8
Specificity (Sp)	98.6–100	98.4–99.8	99.6–100	99.1–99.9
Special Control	LB of the 95% CI for Se and Sp \geq 98%		LB of the 95% CI for Se and Sp \geq 99%	

Requirements consistent with that of already approved devices

Viral load reclassification proceeded without a BPAC

Special controls included

- Describe primers
- Analytical Se, Sp, precision, etc.
- Perform multisite method comparison *or* clinical study
- Agreement between the two tests across the measuring range of the assays must have an r^2 of ≥ 0.95 .
- The bias between the test and comparator assay, as determined by difference plots, must be ≤ 0.5 log copies/mL

Reclassifications were finalized in 2022

Federal Register / Vol. 87, No. 94 / Monday, May 16, 2022 / Rules and Regulations 29661

ARIAC date	State	City	Post Office
10-Jun-22	OR	Reedmond	Reedmond
10-Jun-22	OR	Reedmond	Reedmond
10-Jun-22	TX	Austin	Austin
10-Jun-22	ID	Grangeville	Grangeville
10-Jun-22	TX	Beaumont	Beaumont
10-Jun-22	TX	Beaumont	Beaumont
10-Jun-22	TX	Ennis	Ennis
10-Jun-22	PA	Duster	Duster

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

21 CFR Part 866
[Docket No. FDA-2019-N-5192]

Microbiology Devices; Reclassification of Human Immunodeficiency Virus Serological Diagnostic and Supplemental Tests and Human Immunodeficiency Virus Nucleic Acid Diagnostic and Supplemental Tests

AGENCY: Food and Drug Administration, HHS.
ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA, we, or the Agency) is issuing a final order to reclassify certain human immunodeficiency virus (HIV) serological diagnostic and supplemental tests and HIV nucleic acid (NAT) diagnostic and supplemental tests, postamendments class III devices with the product code MZF, into class II (special controls), subject to premarket notification. Through this final order, FDA is also adding two new device classification regulations and identifying special controls that the Agency believes are necessary to provide a reasonable assurance of safety and effectiveness for these device types. This final order will reduce the regulatory burden on manufacturers of these devices.

Comments: In commenting on this device type, manufacturers stated that the device is substantially equivalent, in accordance with section 513(b) of the FD&C Act, to a predicate device that does not require premarket approval. FDA determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act and part 807 (21 CFR part 807), subpart E, of the regulations. A postamendments device that has been initially classified in class III under section 513(f)(1) of the FD&C Act may be reclassified into class I or II under section 513(f)(3) of the FD&C Act.

Comments: Several comments

21 CFR 866.3956 (serology) and 866.3957 (NAT)

Federal Register / Vol. 87, No. 213 / Friday, November 4, 2022 / Rules and Regulations 66545

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

21 CFR Part 866
[Docket No. FDA-2020-N-2297]

Microbiology Devices; Reclassification of Human Immunodeficiency Virus Viral Load Monitoring Tests

AGENCY: Food and Drug Administration, HHS.
ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is issuing a final order to reclassify human immunodeficiency virus (HIV) viral load monitoring tests, postamendments class III devices with the product code MZF, into class II (special controls), subject to premarket notification. Through this final order, FDA is also adding a new device classification regulation along with special controls that are necessary to provide a reasonable assurance of safety and effectiveness for this device type. The final order reclassifies this device type from class III (premarket approval) to class II (special controls) and will reduce the regulatory burdens associated with these devices because manufacturers will no longer be required to submit a premarket approval application (PMA) for this device type.

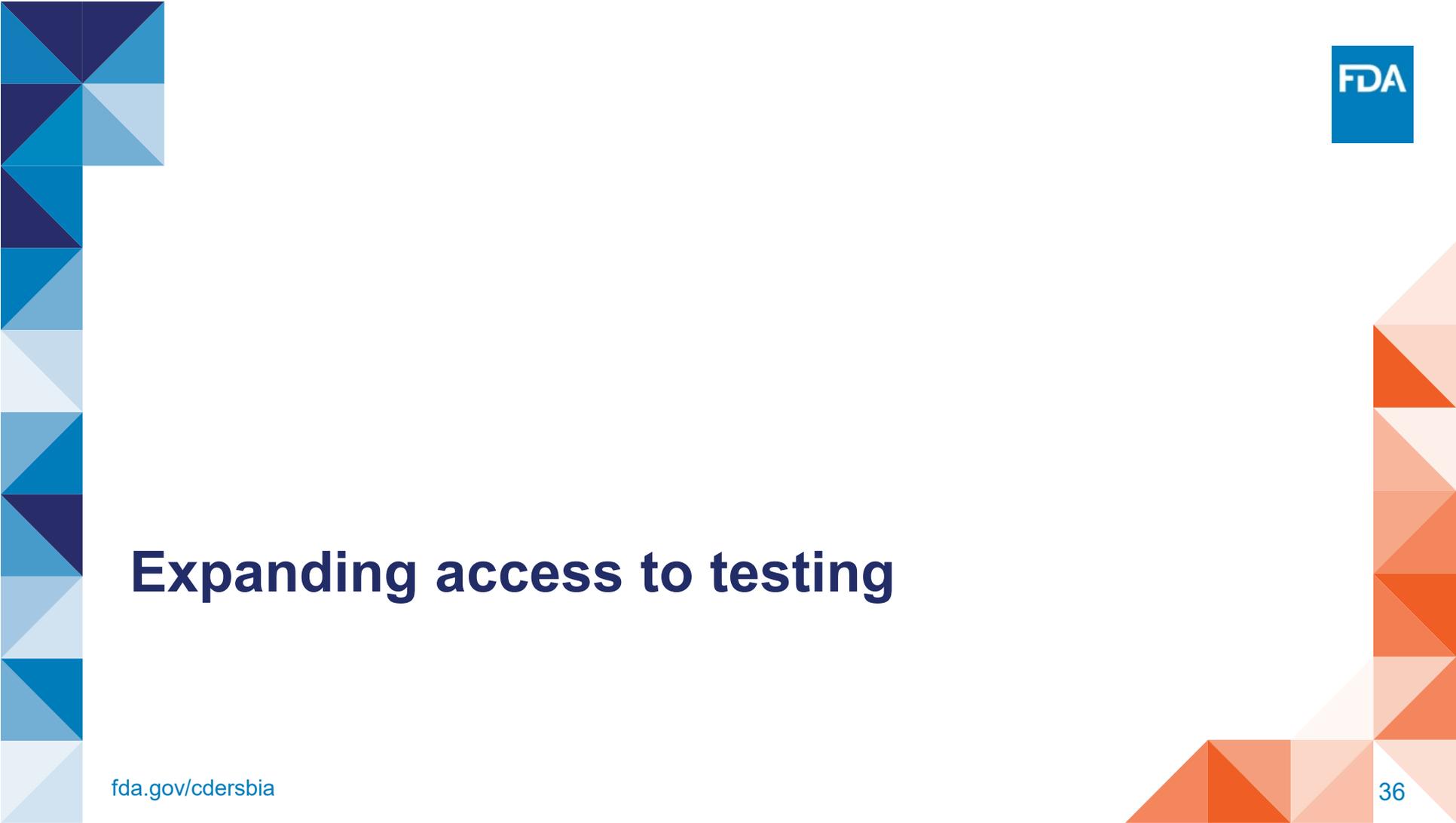
Comments: In commenting on this device type, manufacturers stated that the device is substantially equivalent, in accordance with section 510(k) of the FD&C Act, to a predicate device that does not require premarket approval unless, and until, (1) FDA reclassifies the device into class I or class II, or (2) FDA issues an order finding the device to be substantially equivalent. In accordance with section 513(f) of the FD&C Act, to predicate a device that does not require premarket approval, FDA determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act and part 807 (21 CFR part 807), subpart E, of the regulations. A postamendments device that has been initially classified in class III

21 CFR 866.3958

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Status of HIV IVDs in 2024

- **Class II: 510(k)**
 - Drug resistant mutation (DRM) tests
 - Genotyping tests
 - Diagnostic and supplemental serology and NAT tests
 - PoC Viral load monitoring tests
- **Class III: PMA**
 - Self-tests
 - Self-collection devices
- **BLA:**
 - Blood donor screening devices

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Expanding access to testing

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FDA
considerations for
PoC viral load
assays

- Viral load PoC were reclassified under in December 2022, so submission will be a 510(k)
- PoC viral load devices follow Special Controls in 21 CFR 866.3958
- FDA considers the benefits of increased access versus risk of (possibly) reduced performance for PoC devices
- FDA is keen to obtain feedback on requirements for PoC viral load: limit of detection, output, etc.

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HIV Self-Testing
(HIVST) devices
are class III
medical devices,
require approval
of a PMA

- There is one approved self-testing device (OraQuick HIV in-home test, BP120001, approved in 2012)
- FDA agrees that there is an urgent need to improve access to HIVST
- FDA is working with manufacturers to streamline the regulatory pathway
 - Add HIVST to approved PoC devices
 - Consider using data generated OUS to demonstrate sensitivity

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Self-collection kits are IVDs and require FDA authorization to be distributed legally *

- Self-collection: individual collects their own sample without training or supervision
- Adequate and appropriate sample collection is essential to ensure the proper device performance
- A lab receiving the sample can't be sure that the sample was collected correctly
- FDA reviews instructions for collection and device performance with the self-collected sample

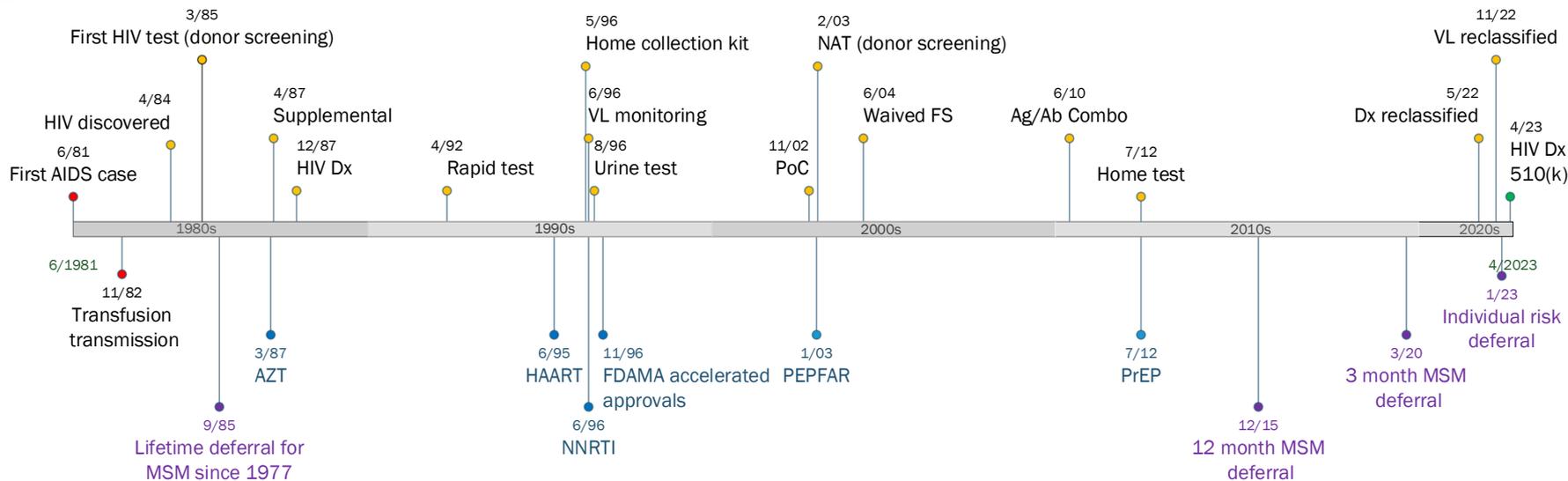
(*Otherwise, they are adulterated and misbranded under section 501(f)(1)(B) of the Food, Drug, and Cosmetics (FD&C) Act, 21 U.S.C. § 351(f)(1)(B) (adulterated) and section 502(o) of the Act, 21 U.S.C. § 352(o) (misbranded)

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How has FDA improved access to HIV devices?

- Reclassified HIV diagnostic and supplemental, lab-based and PoC, serology and NAT devices from class III to class II
- Reclassified HIV lab-based and PoC viral load monitoring devices from class III to class II
- Streamlined validation process for HIV self-tests
- Held workshops, advisory committee, and public meetings to obtain community feedback
- Breakthrough devices program prioritizes novel devices

New devices continue to protect and promote public health



Come talk to us!

Guidance on the Qsub process: *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program Guidance for Industry and Food and Drug Administration Staff (June 2023)*

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program>