IVD Analysers: Clarifications on Risk Classification and NEW SMDR Listing Option

11th September 2017

Health Sciences Authority

Medical Devices Branch

Outline

- Background on HSA's current approach
- Industry feedback
- Clarifications on risk classification
  - Online risk classification tool
- NEW SMDR listing option
- Updated/ NEW Guidance documents
- Case studies/ FAQs

HSA's current approach

Risk classification

- Risk classification rules for IVD medical devices can be found in GN-14

HSA's current approach

Product registration/ listing

- In closed IVD systems (reagents indicated for use with specific analysers), IVD analysers are grouped and listed on SMDR with reagents under the grouping of 'IVD SYSTEM'.

- Open-system Class A analysers (not indicated for use with specific reagents and with no specific intended medical diagnostic purpose) are not subject to product registration as they are supplied non-sterile.

- Analysers may be listed separately on SMDR ***only if*** they are standalone analysers of risk class B or higher based on their intended use (i.e. automated urine/ blood cell sediment analysers)

HSA's current approach

Change Notification

- For changes to closed-system IVD analysers, the CN evaluation route will depend on whether:
  - Performance specifications of the test kits are affected by the changes in specifications of the analysers; ***and if***
  - Changes fall within the closed list of Review Changes (for Class A and B device listings only)

HSA's current approach

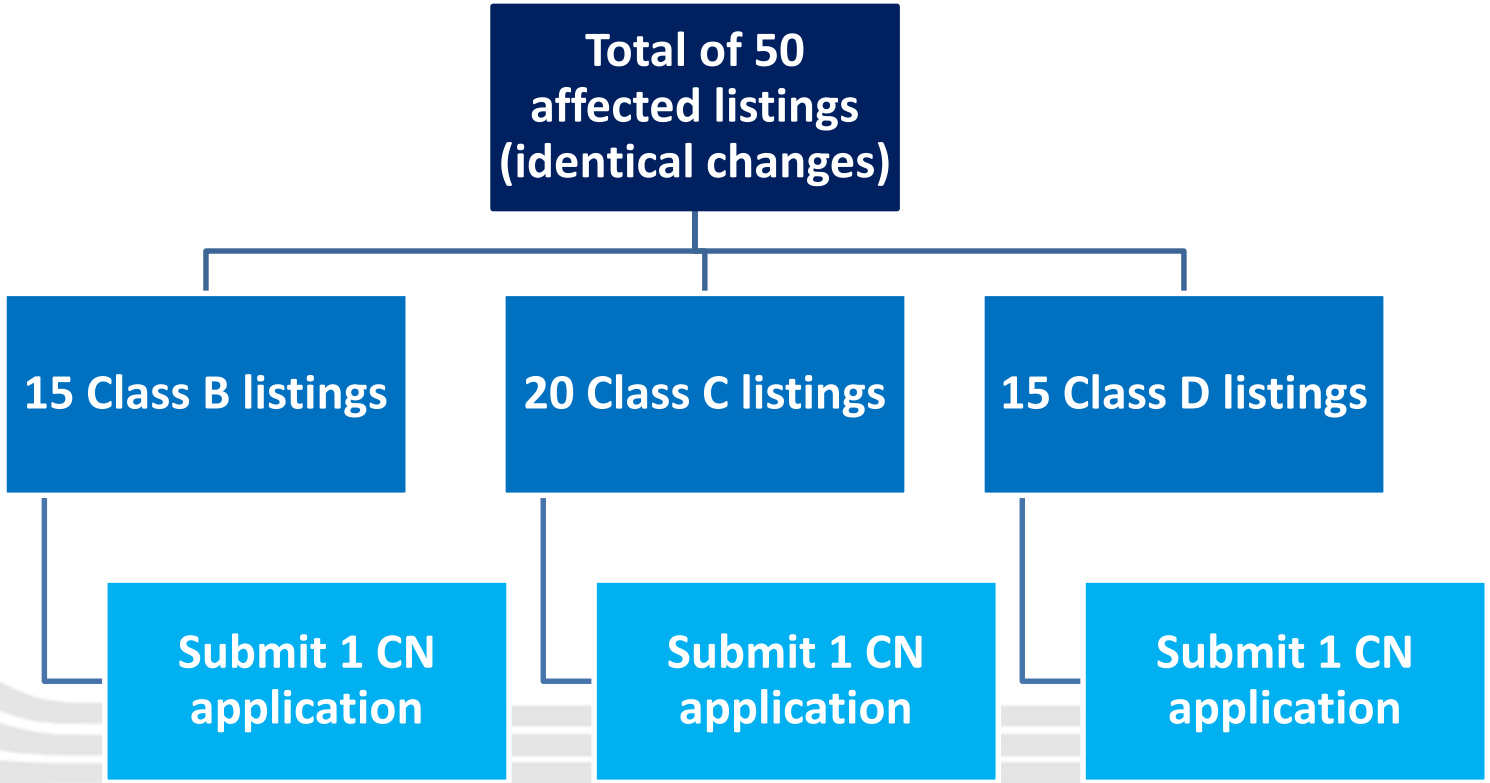
Change Notification

- Changes to closed-system analysers without impacting the performance specifications of the kits:
  - For **identical** changes affecting the same analyser in multiple device listings of the same risk class, 1 CN application can be submitted per risk class.
  - When multiple risk classes are involved, 1 application per risk class of the affected listings is to be submitted.

HSA's current approach

Change Notification

- Changes to analyser specifications/ analyser software with no impact on performance specifications of the kits



Industry feedback on current approach

- Software for analysers changes 2-3x/ year minimally. Changes can be more frequent if there are CAPA for FSCAs involving software upgrades.

- With the current listing mode, 1 analyser can be included in >100 device listings of multiple risk classes. Multiple analysers can also be contained within 1 device listing.

Industry feedback on current approach

- CN applications have to be submitted for a high number of listings multiple times annually.
  - Feedback that MEDICS loads slowly for applications with large number of device listings
  - Companies have to submit separate applications for listings of different risk classes when there are identical changes across listings
  - Amendments to model listing information have to be done manually

Companies have requested if analysers can be listed separately from the reagents to address their concerns

Industry feedback on current approach

Industry feedback → HSA reviews inputs

HSA's proposed enhancements

Focus group discussion with industry members

Feedback forms will be emailed to industry members → HSA reviewed inputs

Consensus

Industry briefing; finalised guidelines on registration of IVD analysers will be put up for wider stakeholder consultation

Implementation

Industry feedback on current approach

- Focus group session was held in 2016 with some IVD stakeholders to obtain feedback on HSA's proposed new approach for SMDR listing options concerning IVD analysers and related clarifications on risk classification.
- Overall feedback obtained was positive and industry felt that **SPLIT** listing options for IVD analysers (separate from the reagents) would assist in streamlining CN application processes.
- There were some common questions asked by industry members (will be addressed in the section on FAQs later).

Industry feedback → HSA reviews inputs

HSA's proposed enhancements

Focus group discussion with industry members

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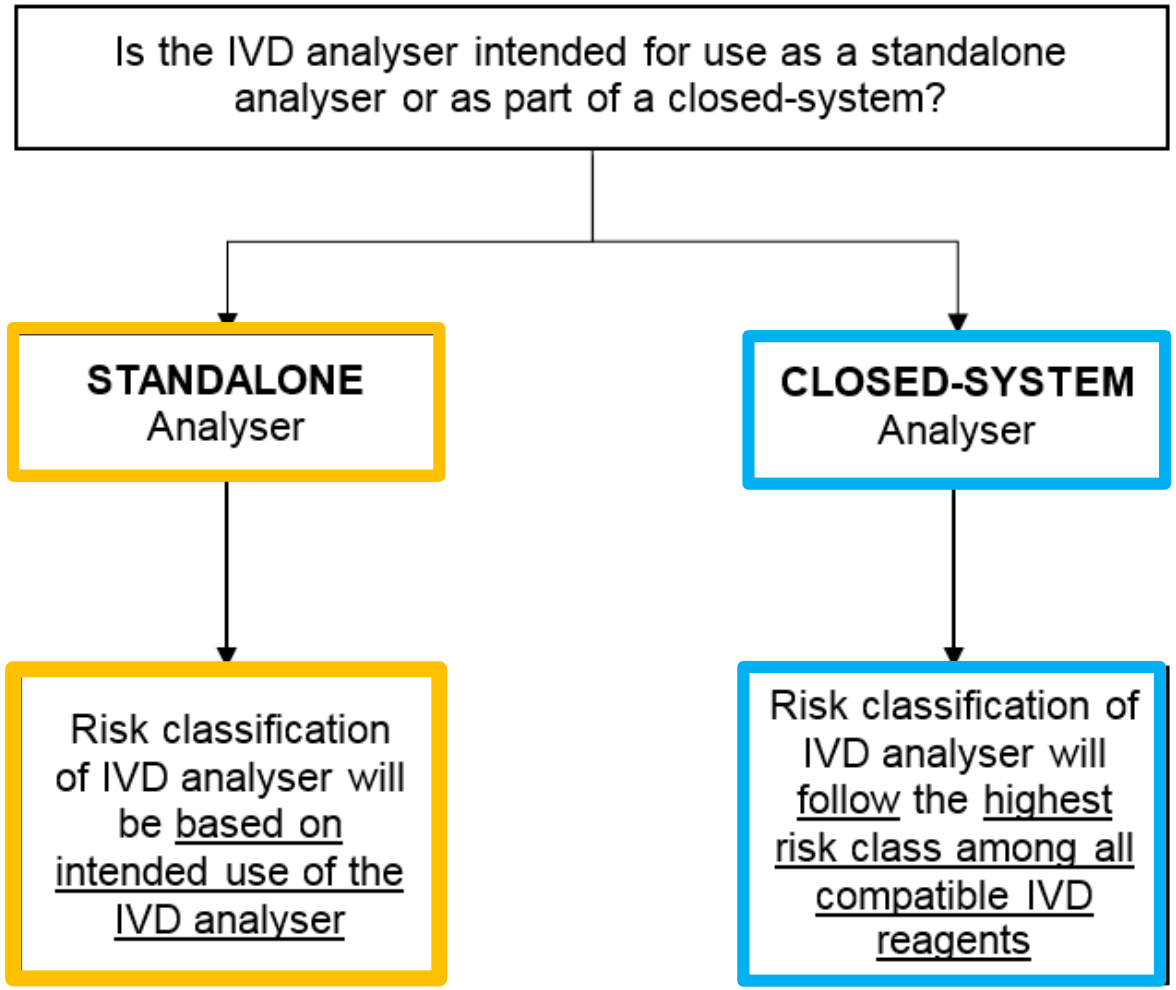
Consensus

Industry briefing; finalised guidelines on registration of IVD analysers will be put up for wider stakeholder consultation

Implementation

Clarifications on Risk Classification

- Flowchart on risk classification of IVD analysers



Clarifications on Risk Classification

- Risk class of the analyser to be based on the intended purpose of the analyser
  - Closed-system analyser's risk class to follow the highest risk class of the reagent among all reagents it is compatible for use with
  - Rule 5: Standalone analysers with no specific intended medical diagnostic purpose and not indicated for use with specific reagents are class A

- When applying the risk classification rules in the GN-14 Guidance on risk classification of IVD, do note that the term "IVD medical devices" includes reagents, controls, calibrators, analysers, analyser software and assay kits.

Clarifications on Risk Classification

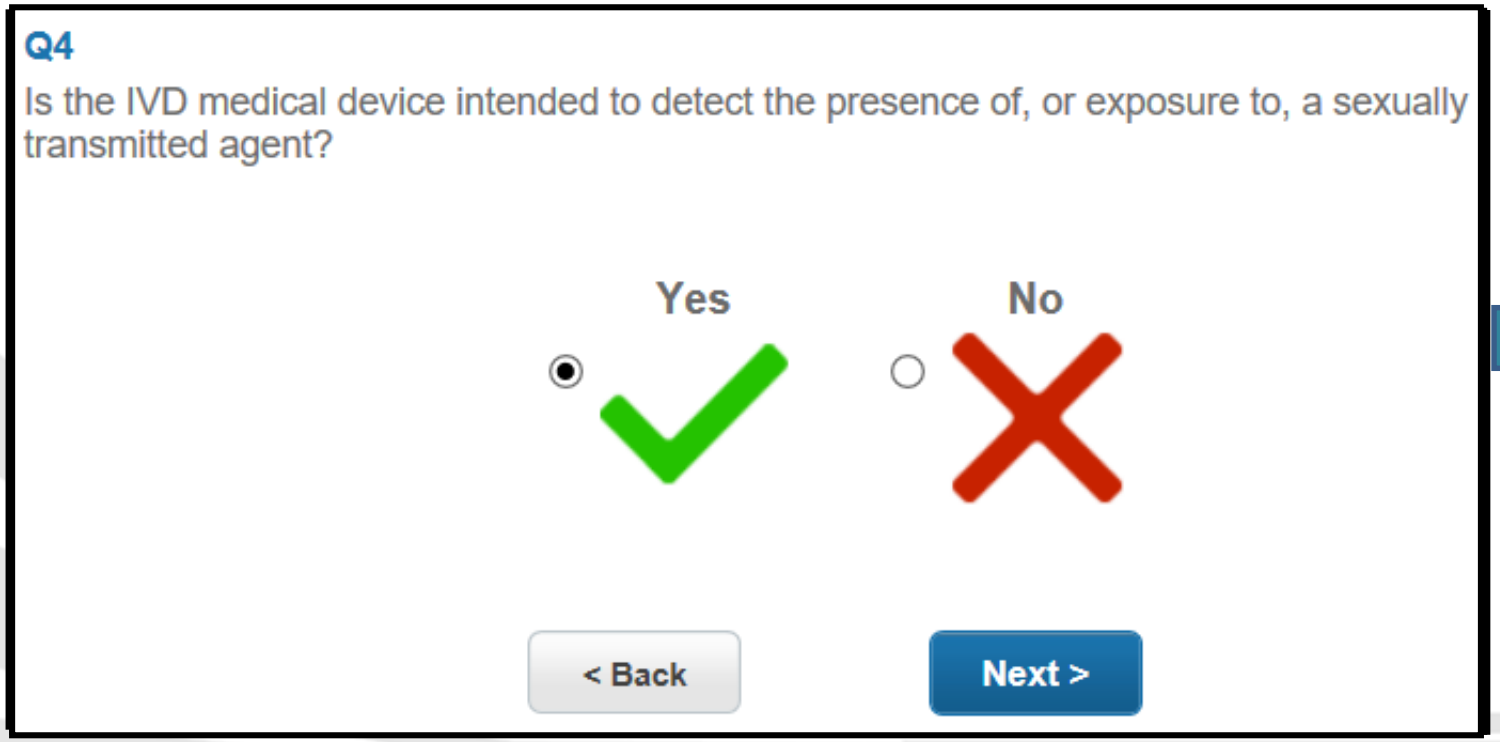
- Examples:
  - **Closed-system analyser YYY** is compatible for use with Class B, C and D reagent kits. Hence, the analyser's risk class will be Class D.
  - **Standalone analyser ZZZ** is used for the automation of an enzyme immunoassay. Its user manual does not indicate the analyser for use with specific reagents or for specific intended medical diagnostic purpose. Hence, the analyser's risk class will be Class A.

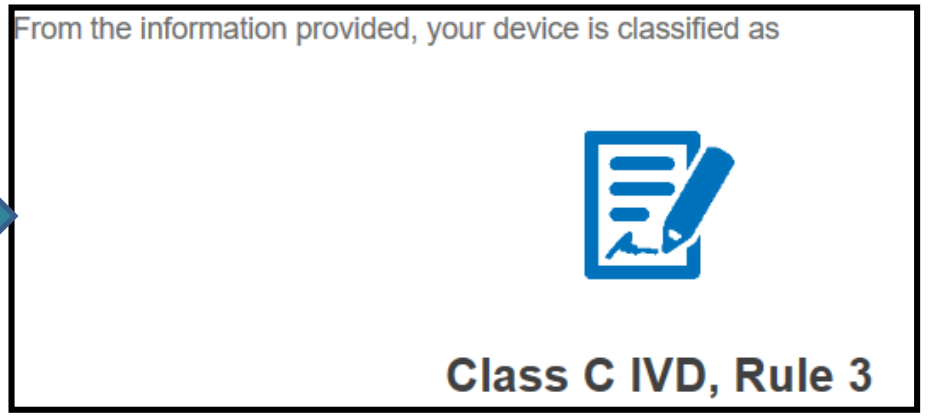
Online risk classification tool

- The term ‘IVD medical devices’ includes all IVD components like reagents, controls, calibrators, analysers, analyser software
- Common query from stakeholders when using the risk classification tool is with reference to question 17 (is the IVD medical device an instrument intended by the product owner specifically to be used in IVD procedures?).
- Addition of a footnote for greater clarity for the online risk classification tool (IVD)
  - NOTE: When using the risk classification tool for IVD medical devices, question 17 would refer to IVD analysers that are not intended for use in specific medical diagnostic purposes. Example: sample-preparation instruments

Online risk classification tool

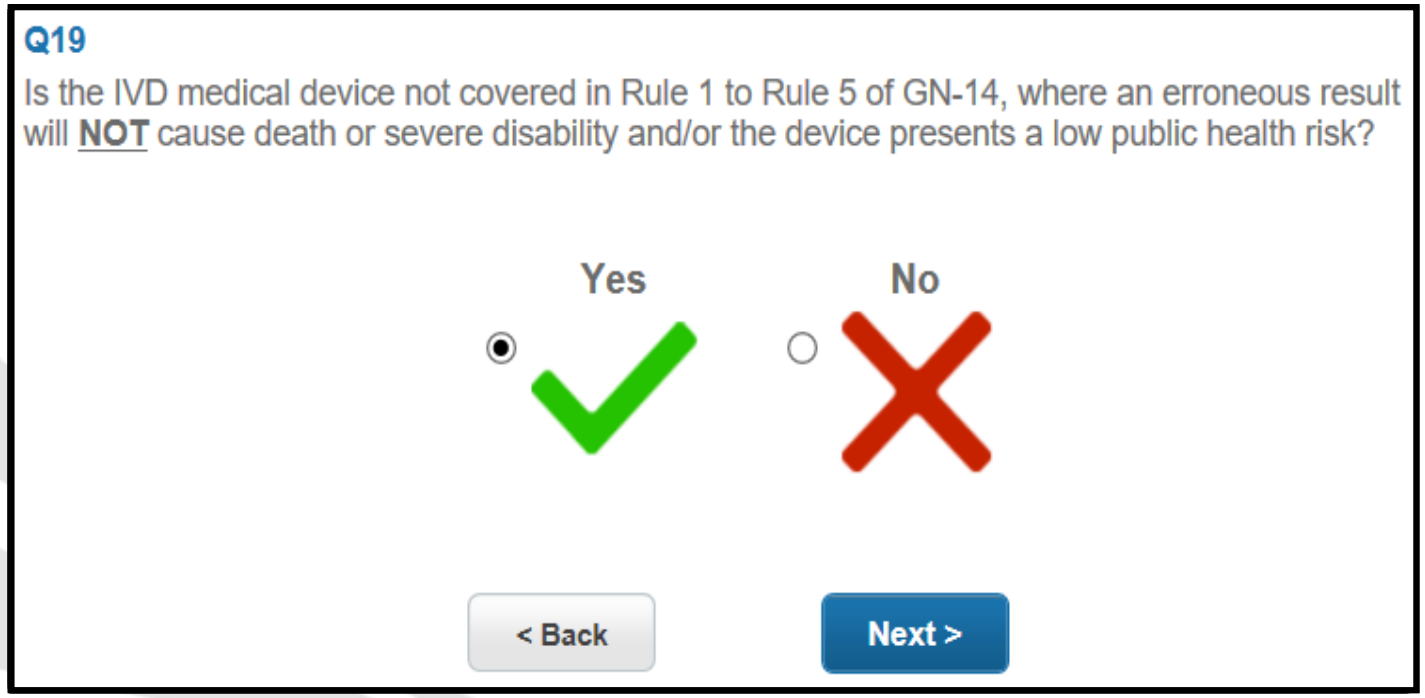
- Example 1 (analyser that is intended for use with a Neisseria gonorrhoea reagent)

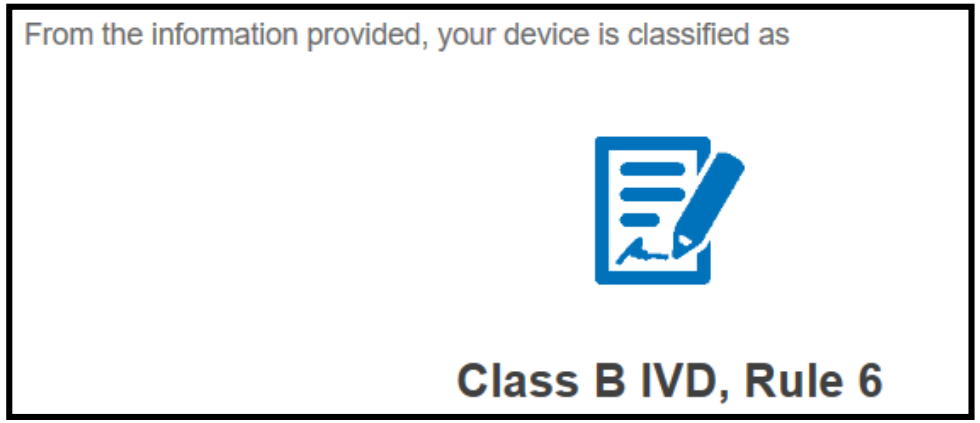




Online risk classification tool

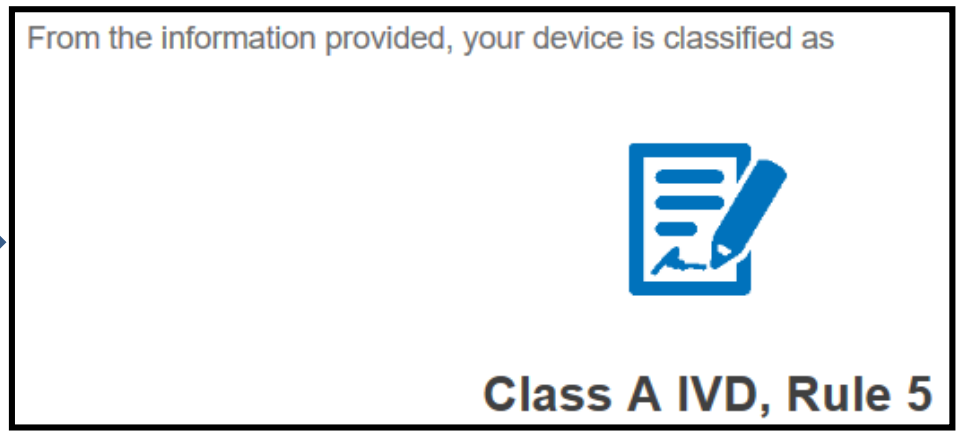
- Example 2 (analyser that is intended for use with a LDL cholesterol reagent)





Online risk classification tool

- Example 3 (analyser that is intended for sample preparation)



➢ **Footnote for addition** 'NOTE: When using the risk classification tool for IVD medical devices, question 17 would refer to IVD analysers that are not intended for use in specific medical diagnostic purposes. Example: sample-preparation instruments'

NEW SMDR Listing Option

- **For applicants' choice:** 2 SMDR listing options for IVD analysers

  - **IVD SYSTEM listing** (Option 1)**:** Analyser is listed together with its compatible reagent **(current listing approach)**

NEW!

  - **SPLIT listing** (Option 2)**:** IVD analyser is listed separately from its compatible IVD reagents.
    - Additional SMDR annual license retention fee will be incurred for the separate analyser listing

Note: Companies are not permitted to change their listing option upon approval of pre-market registration application

Upcoming

Industry feedback → HSA reviews inputs

HSA's proposed enhancements

Focus group discussion with industry members

Feedback forms will be emailed to industry members → HSA reviewed inputs

Consensus

Industry briefing; finalised guidelines on registration of IVD analysers will be put up for wider stakeholder consultation

Implementation

NEW Guidance: GN-34

- Draft version of GN-34: Guidance document for IVD analysers
- GN-34 is intended to act as a 'one-stop' document for IVD analysers and will cover the following areas:
  - Risk classification
  - SMDR listing options
  - FAMILY grouping criteria
  - Product registration
  - Change Notification

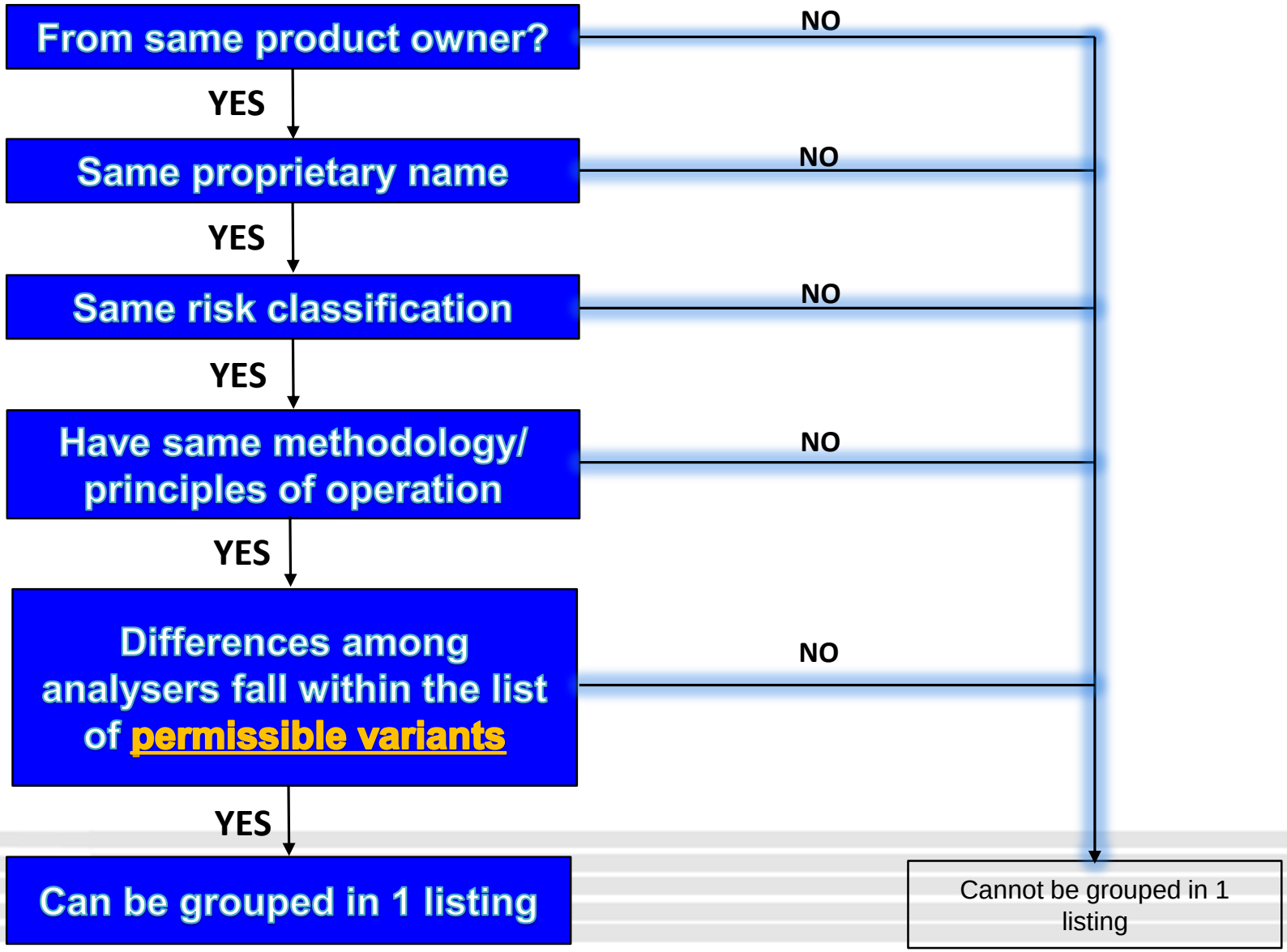
- Draft version of GN-34 will be uploaded on HSA website for comments
  - One month consultation period (till 15th October)

Updates to current guidances

- Other guidance documents impacted by this revised approach for IVD analysers will be updated
  - **GN-12-1**: Guidance on Grouping of Medical Devices for Product Registration - General Grouping Criteria
  - **GN-12-2**: Guidance on Grouping of Medical Devices for Product Registration - Device Specific Grouping Criteria
  - **GN-14**: Guidance on the Risk Classification of In Vitro Diagnostic Medical Devices
  - **GN-15**: Guidance on Medical Device Product Registration
  - **GN-21**: Guidance on Change Notification for Registered Medical Devices
  - **GN-22**: Guidance for Dealers on Class A Medical Devices Exempted from Product Registration

IVD Analyser FAMILY Grouping

Updates to GN-12-2 (device-specific grouping):
NEW section on grouping of IVD analysers



IVD Analyser FAMILY Grouping

Permissible Variants	Non-Permissible Variants
1. Features that do not impact the diagnostic function • Throughput • Differences in user interface • Printing function • Wireless capability • Software • Sample volume • On-board stability claim • Calibration frequency	**1. Features that impact the diagnostic function or lead to different performance characteristics for their compatible reagent kits, for example, but not limited to:** • Sensitivity • Specificity • Linearity • Measuring range **2. Methodology/ Principles of Operation**

Product Registration Requirements

For NEW Analyser

- Technical requirements remain unchanged
  - Include analyser in Annex 2 List of Configurations
  - Inform HSA of preferred listing option: Option 1 (IVD system listing), Option 2 (SPLIT listing).

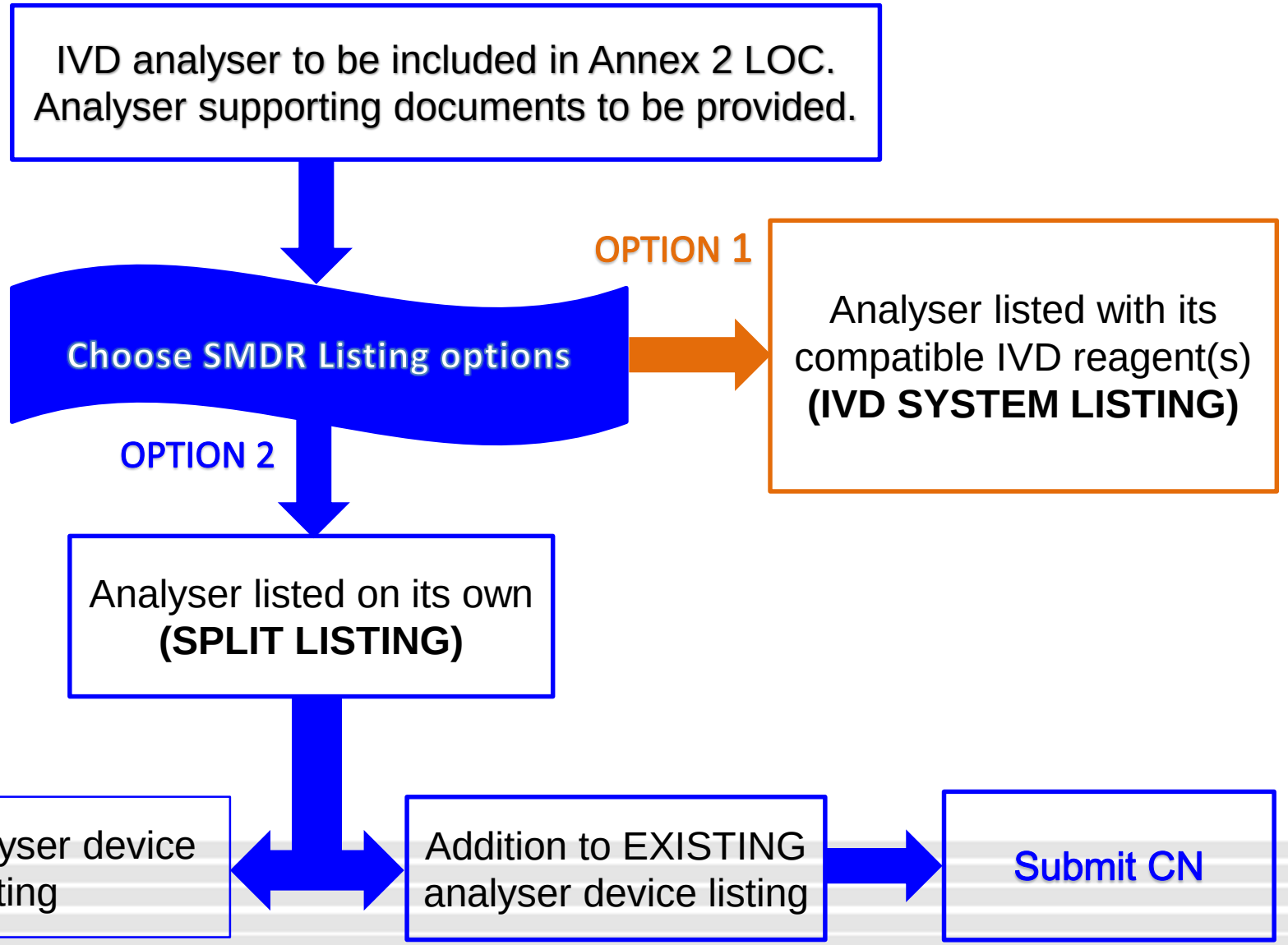
Note: Not permitted to change listing option upon approval

- **SPLIT** listing (Option 2): IVD analyser is listed separately from its compatible IVD reagents.
  - Listed on its own OR
  - Listed with other registered IVD analysers that fulfil the FAMILY grouping

Product Registration Requirements

For NEW Analyser

- **SPLIT** listing (Option 2): IVD analyser is listed separately from its compatible IVD reagents.
  - Listed on its own
  - Listed with other IVD analysers that fulfil the FAMILY grouping criteria



Product Registration Requirements

Analyser is already listed in its own listing

- If premarket application includes an IVD analyser that is already listed in a **SPLIT** listing on SMDR:
  - Analyser is excluded from Annex 2 List of Configurations
  - Analyser supporting documents **DO NOT** need to be submitted.

Product Registration of compatible reagent

Are there changes to registered analyser?

- Specifications
- Software
- Labels
- User Manual

NO → Submit declaration (Annex 1 to GN-34)

For IVD analysers in SPLIT device listings

- Declaration that there is no change to the currently-approved IVD analyser device specifications AND labelling (Annex 1 to GN-34)

Declaration template for registered IVD analyser(s) in split IVD analyser device listing(s)

[To be printed on Company Letterhead of Applicant]

Medical Device Branch
Pre-Marketing Division
Health Products Regulation Group
Health Sciences Authority

[Date]

Dear Sir/Madam,

[Name of Company], the Applicant for registration of the medical device(s) stated below, hereby declare that:

The compatible analyser(s) for the medical device(s) in this application is as per indicated in Table 1: list of compatible analyser(s).

Table 1: List of compatible analyser(s)

Name of analyser (as per device labelling)	Software version	Device Registration Number

The compatible analyser(s) for the medical device(s) in this application is as per indicated in Table 1: list of compatible analyser(s).

er(s)
relevant user

Table 1: List of compatible analyser(s)

Name of analyser (as per device labelling)	Software version	Device Registration Number

analyser device
list of registered

There are no changes to the currently approved compatible analyser(s) specifications, including the analyser software versions, labels and relevant user manuals.

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er Section 37(1)

A change notification application shall be submitted for the affected analyser device listing(s) upon approval of this pre-market application to update the list of registered compatible reagents with the analyser.

List containing SMDR-listed reagents compatible with the analyser

- The template for the list can be found in Annex 2 to GN-34 (will be uploaded to HSA website in Microsoft Excel format)
- Company is advised to keep this spreadsheet updated for traceability and housekeeping purposes.
- Example below:

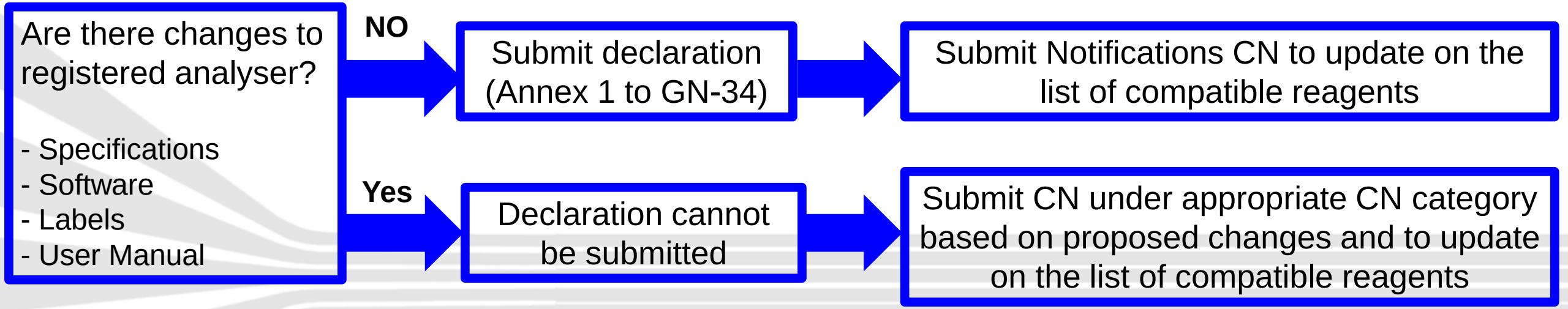
	Compilation of compatible reagents with <name of analyser e.g. Analyser A>		
Analyser identifier	<indicate identifier of analyser>		
Software version (s)	<indicate currently-approved software version i.e. X.XX.XX>		
Date of addtion (DD/MM/YYYY)	**Date of removal (DD/MM/YY)**	**Name of reagent (as per device labelling)**	**SMDR number**
Example:			
7/5/2017		XYZ reagent	DE1234567

Product Registration Requirements

Analyser is already listed in its own listing

- If premarket application includes an IVD analyser that is already listed in a **SPLIT** listing on SMDR:
  - Analyser is excluded from Annex 2 List of Configurations
  - Analyser supporting documents **DO NOT** need to be submitted.

Product Registration of compatible reagent



Case-study A

Pre-market Registration

Company XYZ would like to submit a pre-market registration application for a ***Class B Albumin assay***. The compatible analyser, ***Analyser YYY*** is already listed on SMDR in its own analyser listing.

Analyser YYY is updated with new software and changes to the user manual

- Should ***Analyser YYY*** be included in the Annex 2 List of configurations?

  No
- Should analyser-related documents be submitted in the pre-market registration?

  No
- Do they need to submit CN application for the analyser device listing?

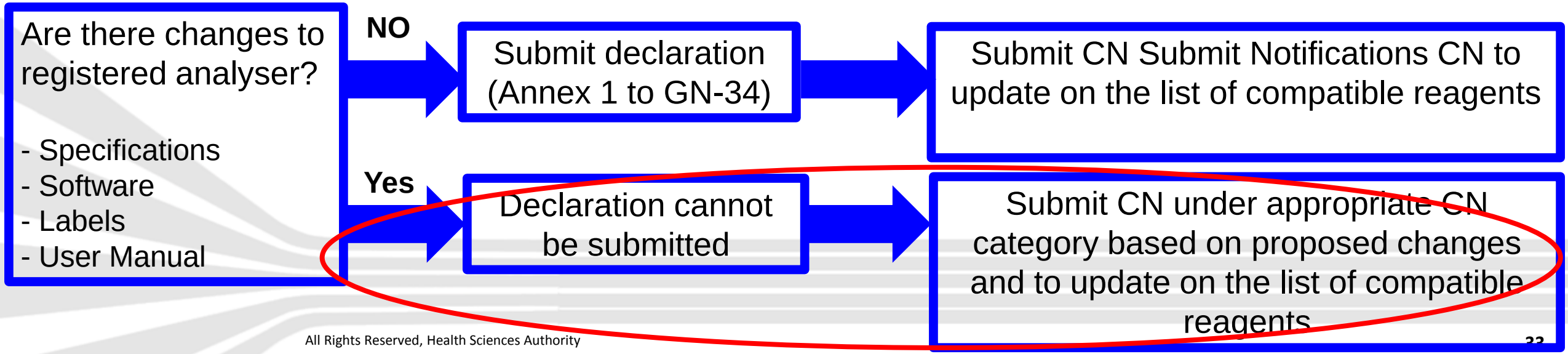
  Yes

Product Registration Requirements

Analyser is already listed in its own listing

- If premarket application includes an IVD analyser that is already listed in a **SPLIT** listing on SMDR:
  - Analyser is excluded from Annex 2 List of Configurations
  - Analyser supporting documents **DO NOT** need to be submitted.

Product Registration of compatible reagent



Case-study A

Pre-market Registration

- ❑ Since Analyser YYY is already listed on SMDR in a SPLIT listing, it need not be included in the Annex 2 List of Configurations
- ❑ Analyser YYY-related documents need not be provided in the application dossier
- ❑ Upon approval of the application, CN is to be submitted to:
  - ➢ update list of compatible SMDR-listed reagents with Analyser YYY, AND
  - ➢ the proposed changes to Analyser YYY's software and user manual

Change Notification

- No changes to mandatory CN documents (Annexes 2 and 3 of GN-21)

- CN submission to update list of compatible SMDR-listed reagents with the analyser (template for list: Annex 2 to GN-34)
  - Route: Other Notification Changes (Verified by HSA prior to submission)

Case-study B

CN to update list of compatible IVD reagents

Company XYZ has opted for the SPLIT analyser listing option for ***Analyser YYY***. The total number of SMDR-listed compatible reagent kits for this analyser is 8 kits.

In 2018, ***Company XYZ*** decides to cancel device listings for 3 of the compatible IVD reagent kits.

- What should ***Company XYZ*** do?

  Submit CN to Analyser YYY's device listing

Case-study B

CN to update list of compatible IVD reagents

- Submit CN for ***Analyser YYY*** device listing
  - Update Annex 2 to GN-34: List of compatible IVD reagents

Compilation of compatible reagents with Analyser YYY			
Analyser identifier	81302B		
Software version (s)	V1.021		
Date of addtion (DD/MM/YYYY)	**Date of removal (DD/MM/YYYY)**	**Name of reagent (as per device labelling)**	**Singapore Medical Device Registration (SMDR) number**
12/12/2017	1/2/2018	Reagent AAA	DE1234567
13/12/2017	1/2/2018	Reagent BBB	DE2134567
14/12/2017	1/2/2018	Reagent CCC	DE3134567
15/12/2017	NA	Reagent DDD	DE4134567
16/12/2017	NA	Reagent EEE	DE5134567
17/12/2017	NA	Reagent FFF	DE6134567
18/12/2017	NA	Reagent GGG	DE7134567
19/12/2017	NA	Reagent HHH	DE8134567

- This will be a Notification CN
- All mandatory documents for CN must be submitted (Annexes 2 and 3 to GN-21)

Change Notification

- Other changes to IVD analyser listing may be submitted together
  - Other CN categories as per GN-21: Guidance on Change Notification for Registered Medical Devices
  - All documents pertaining to the proposed analyser changes.
  - CN route will follow highest category

Change Notification

Addition of IVD analyser to a device listing

Change type 6Aiv:

‘Unless changes only involve the **addition of Class A medical device** accessories that complement the registered medical device as a closed system’

- **Applicable** only to standalone IVD analysers with no specific intended medical diagnostic purpose and not indicated for use with specific reagents

Addition of analyser(s) via CN

Addition of analyser to a SPLIT analyser listing

Fulfil FAMILY grouping criteria?

- Same product owner
- Same proprietary name
- Fulfils permissible variants

NO

Cannot be added to the **SPLIT** IVD analyser listing

New analyser is to be listed in its own standalone IVD analyser listing

YES

Addition of analyser impacts the performance specifications of IVD test kit?

YES

Change Notification category 6Ai

Class C&D: Technical
Class A&B: Review

NO

Change Notification category 6Aiii

All risk classes: Notification

NO

Change Notification category 6Aiii

All risk classes: Notification

Addition of analyser to a SYSTEM listing (Analyser listed with compatible reagent)

Addition of analyser impacts the performance specifications of IVD test kit?

YES

Change Notification category 6Ai

Class C&D: Technical
Class A&B: Review

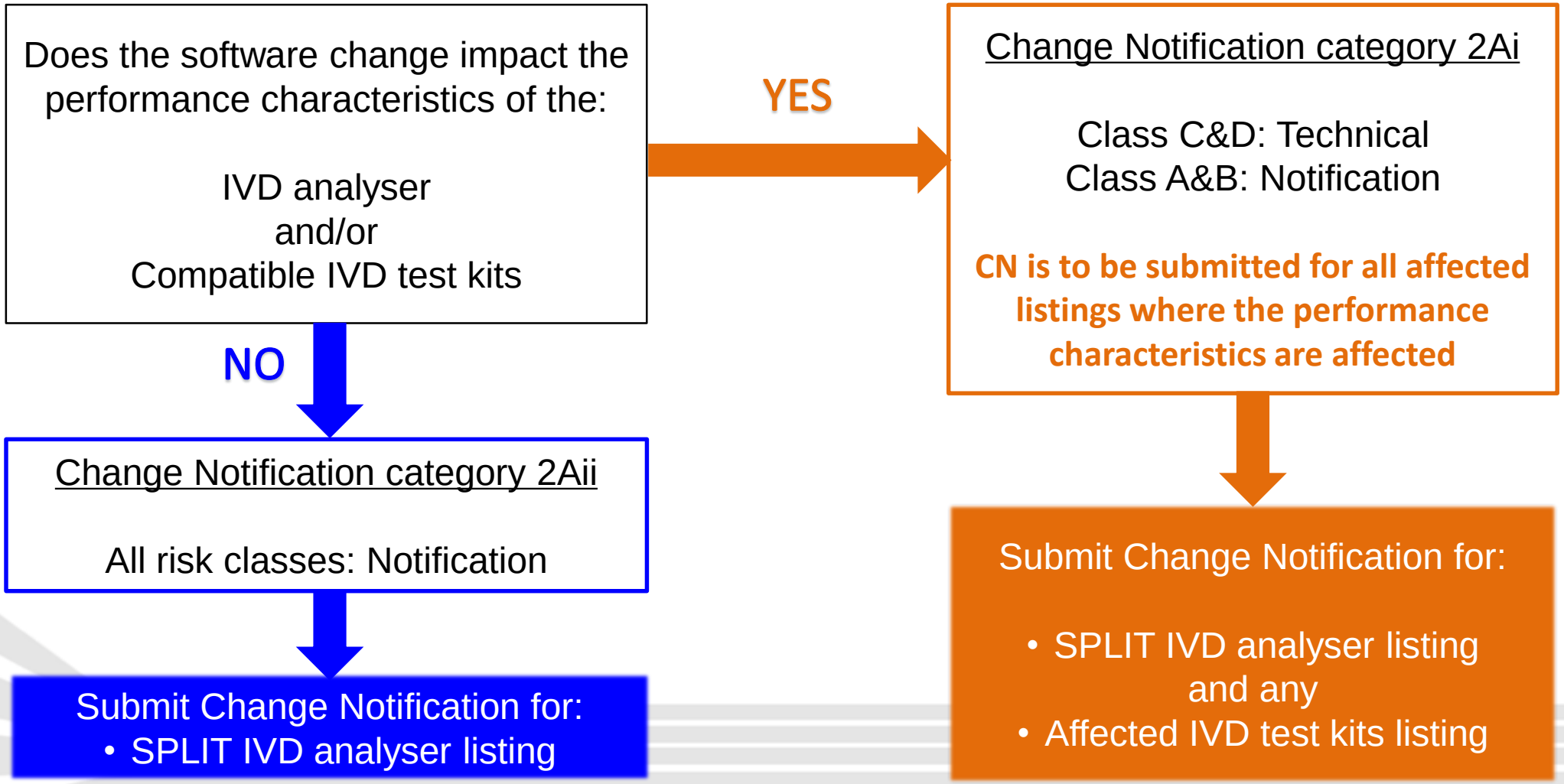
NO

Change Notification category 6Aiii

All risk classes: Notification

Change Notification

Change to software (SPLIT Listing)



Case-study C

CN for software update

Company XYZ has opted for split listing for ***Analyser YYY*** (class B) intended for use with an ***LDL cholesterol assay*** and an ***albumin assay***.

Analyser YYY is undergoing software upgrade from V1.011 to V1.012.

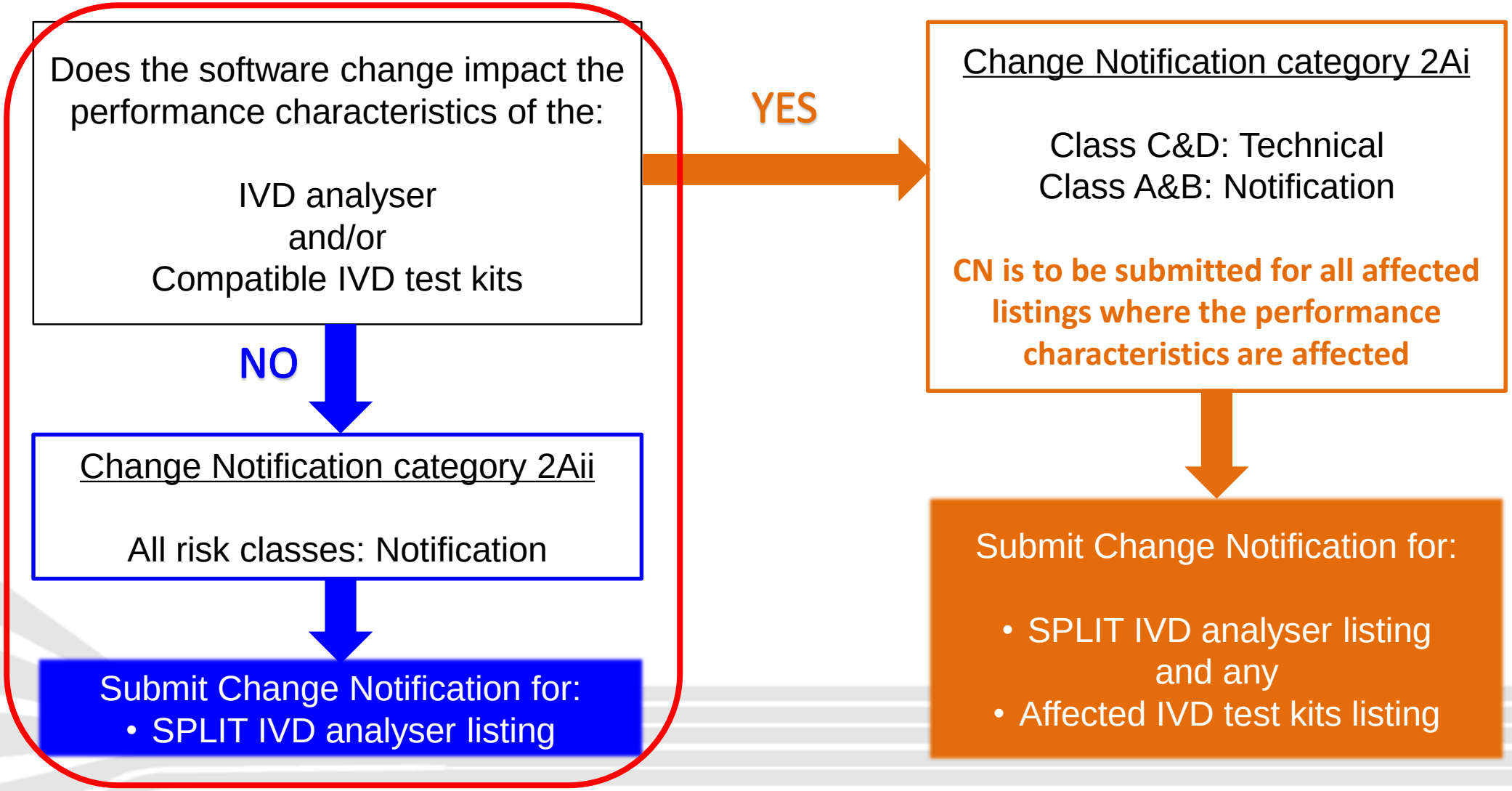
The software upgrade involves the following:

- Fix minor software bugs
- No added functionalities
- No change in performance specifications of LDL cholesterol assay and albumin assay

- Which device listing should CN be submitted for?
  IVD analyser listing
- Which CN category would be applicable?
  Notification CN

Case-study C

CN for software update



FAQs

Q: What if companies wish to list analysers separately from their compatible reagents for registered IVD systems already listed on SMDR?

A: Please send in your request to HSA_MD_INFO@hsa.gov.sg, after the date of implementation, with the subject header: 'Request to opt for SPLIT analyser listing for registered IVD systems'. Officers will be assigned to follow-up with your request.

FAQs

Q: How will Class A accessories intended for use with the analysers (e.g. consumables) be listed if companies opt to list the analysers separately from the reagents?

A: Accessories intended for use with the analysers may be listed with the analyser in the IVD analyser listing.

FAQs

Q: As the proposed changes affect multiple guidance documents (i.e. GN-14, GN-15, GN-21, GN-22 etc.), will these documents be updated?

A: Yes, HSA will publish a guidance document (GN-34) specifically for the changes to IVD analysers to provide clarity on the changes to be made to product registration and CN process. All existing affected guidance documents will also be updated and released at the same time.

Q: When is the proposed date of implementation?

A: 1st December 2017 (tentatively)

Overview

HSA's revised approach

- Overall, with the proposed approach towards risk classification and listing of IVD analysers:
  - Greater clarity on risk classification of analysers
  - Companies have an additional SMDR Listing Option for analysers
  - Lessen CN burden for industry:
    - for changes to analyser/analyser software (no change to performance specifications of reagents)
    - companies need only file 1 CN application for the affected analyser device listing ***(if companies opt for this listing option)***

Overview

HSA's revised approach

Current Approach	Updated approach
Risk Class: As per risk classification rules in GN-14 **Product registration:** - Closed-System analysers submitted in the same application as their compatible reagent kit. Standalone analysers of Class B and higher to be submitted in one application. **Device listing:** - Analysers to be listed in the device listing of every compatible reagent kit **CN (For changes affecting analysers ONLY):** - CN must be submitted for all affected device listings containing the analysers	**Risk Class:** Clarifications made to rule 5 of GN-14. **Product registration:** - No change for closed-system analysers (no additional product registration fees incurred). Standalone analysers would require product registration based on their intended use. **Device listing:** - Companies can opt for the current listing approach **OR** - Opt for the analysers to be listed separately from the reagent kits (additional license retention fee will be incurred) **CN (For changes affecting analysers ONLY):** - No change if company opts for the current listing approach - If company opts for the proposed listing approach, then CN needs to be submitted for only the affected analyser device listing

Collation of industry feedback

- Presentation slides, drafted guidelines for the IVD analysers, and the feedback form will be uploaded on the MDB regulatory updates webpage at: http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/Medical_Devices/Regulatory_Updates.html

- For any comments and feedbacks on the above documents, please email us at HSA_MD_INFO@hsa.gov.sg using the feedback template form with the email subject header of ***'Feedback on IVD analyser enhancements'.***

- Please provide your feedback by 15th October 2017.

Health Sciences Authority

Medical Devices Branch