

Validation and verification process for IHC

What, why and how ?

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Note

- Purpose

The purpose of this presentation is to give background information about the verification and validation process for IHC. The point of view is that of the current regulations. Please check how this is reflected in your own national regulations, as they may vary from country to country.

- Disclaimer

This presentation has been prepared based on available information upon date. Some slides contain documents that are the intellectual property of the Pathology Lab AZ St. Lucas Brugge (B). They cannot be used for commercial purposes.

- Informative slides

Some slides in this handout were not handled during the actual presentation and were added to this handout for informative reasons. They are indicated by the “i” in the upper right corner.

Topics

1 Validation – Verification : WHAT ?

Terms/definitions, difference in terminology

2 Validation – Verification : WHY ?

Main reasons why we should perform validation/verification

3 Validation – Verification : HOW ?

How can we perform validations/verifications ?

4 Changes in verified - validated methods ?

Do changes affect verification/validation ?

Validation & verification : WHAT ?

Terms/definitions, different terminology

Validation & verification : definitions

Validation

- Demonstrate by means of objective evidence that performance characteristics fullfill predefined criteria or specific demands for a certain purpose or intended use

Verification

- Confirming by providing objective evidence that a test fullfils specifications (specific demands) or specified performance characteristics

In essence you need to proof “a test performs as it needs to do” or “what is intended for”.

Definitions : different elements

Validation

- **Demonstrate** by means of objective evidence that performance characteristics fullfill predefined criteria or specific demands for a certain purpose or intended use

Verification

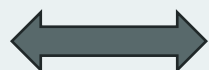
- **Confirming** by providing objective evidence that a test fullfils specifications (specific demands) or specified performance characteristics

In essence you need to proof “a test performs as it needs to do” or “what is is intended for”.

Definitions : different elements

- In order to “**demonstrate**” or “**confirm**”, a comparison of performance is needed between

NEW TEST/ASSAY



COMPARATOR TEST / REFERENCE / STANDARD

- Comparator test/reference or standard performed on :
 - *Types of samples with known morphology and expression of an antigen (e.g. iCAP (Immunohistochemistry Critical Assay Performance control))*
 - *Confirmed samples or controls stained with already verified/validated method (own lab or other lab)*
 - *Reference in e.g. IFU, literature about staining patterns, performance, etc*
 - *EQA samples (if available), other techniques, etc*
 - *Commercial available controls, cell lines, etc with known (standardized) properties*

Definitions : different elements

Validation

- Demonstrate **by means of objective evidence** that performance

Verification

- Confirming **by providing objective evidence** that a test fulfils

Objective evidence : demonstrated and documented (paper, software)

Cases & comparator test	Samples/cases ID used, control reference & validation, etc Comparator test ID, properties, known results, etc
Reagents	Type of reagents (Ab, detection) reference number, lotnumber, expiry date
Method	Selected method (IFY or other), who performed staining ? Etc
Staining platform(s)	Type, serial number, performed one or multiple staining platforms, etc Runlogs (staining platform software, LI(M)S)
Evaluation & signing off	Evaluation data of acceptance criteria for defined performance criteria Who did evaluation ? Signing of person & date, etc

Definitions : different elements

Validation

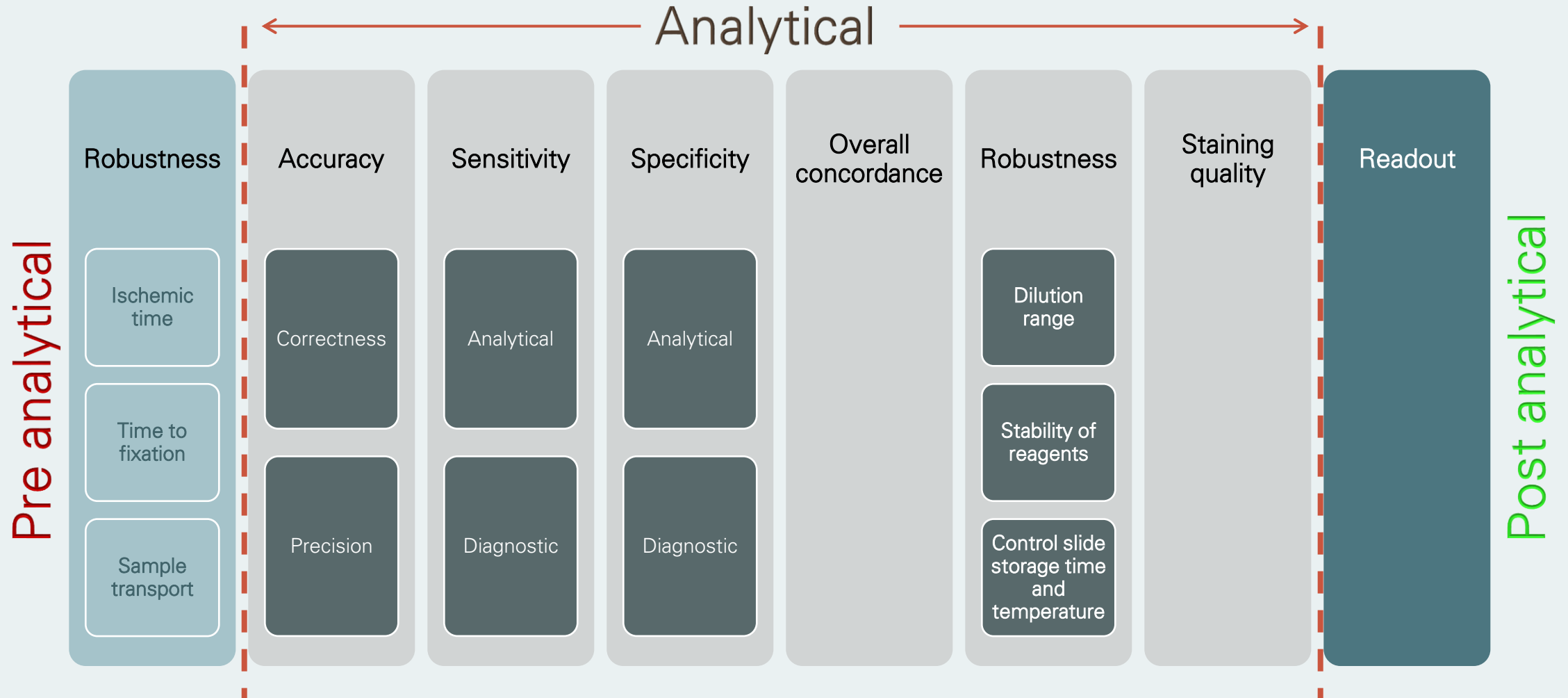
- Demonstrate by means of objective evidence that **performance characteristics** fullfill predefined criteria or specific demands for a certain purpose or intended use

Verification

- Confirming by providing objective evidence that a test fullfils **specifications (specific demands) or specified performance characteristics**

In essence you need to proof “a test performs as it needs to do” or “what is is intended for”.

Definitions : performance characteristics

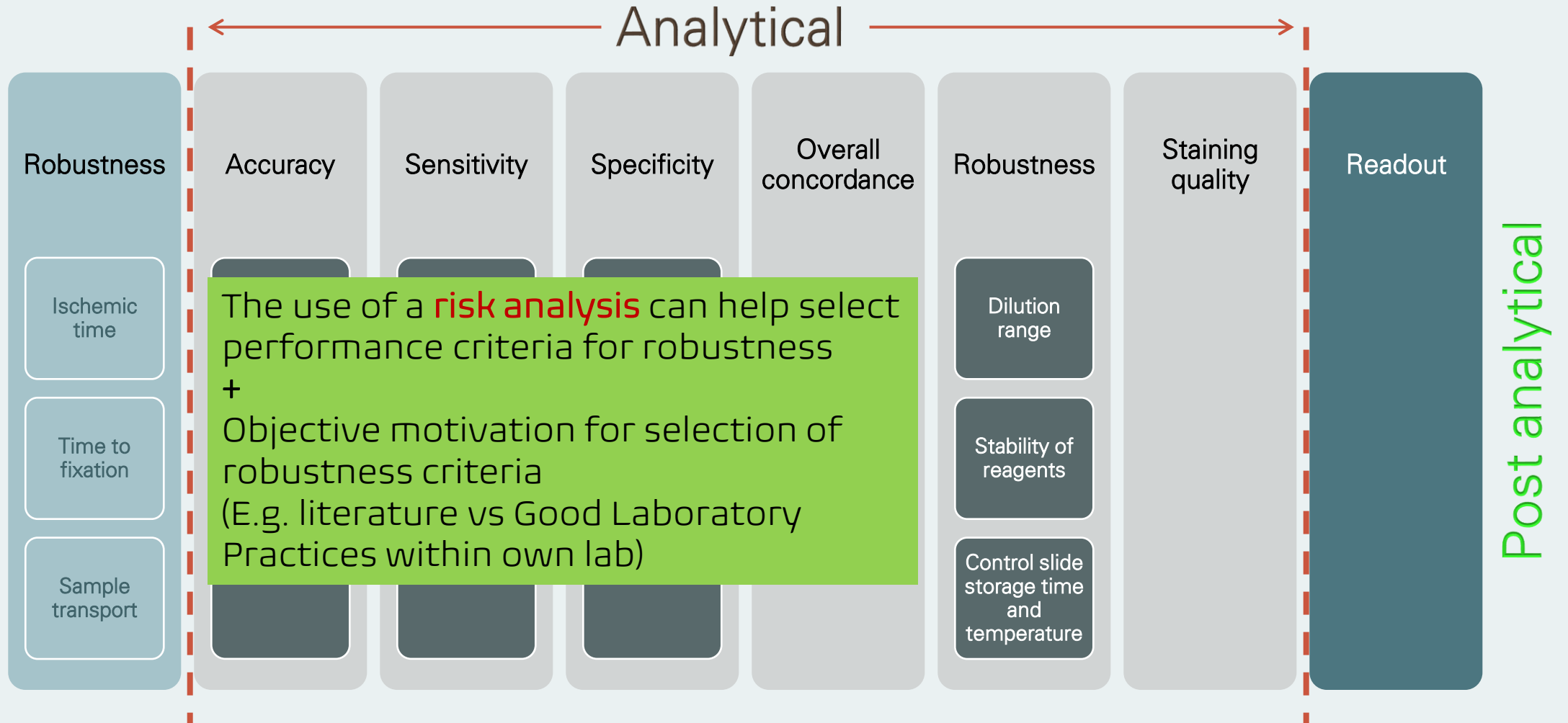




Definitions : performance characteristics

Tip!

Pre analytical





Definitions : performance characteristics

❖ **ACCURACY** : correctness & precision

- **Correctness : does it stain the correct items ?**

- Comparison with known results from validated tests (reference samples, validated testsamples (own or another lab))
- Comparison with other validated technique (e.g. ISH vs PCR), other validated instrument or other reagents (other manufacturer)
- Third line control (EQC or interlabcomparison)
- Populationstudy



Definitions : performance characteristics

❖ **ACCURACY** : correctness & precision

- **Precision** : How “repeatable” are stains in the same or different runs ?
 - Repeatability : intra run / within run tests
 - Intermediate precision : interrun / in between run tests
 - Reproducibility : inter-lab reproducibility
- 1 or more staining platforms : precision determined on all platforms !



Definitions : performance characteristics

❖ SENSITIVITY

- ❖ Analytical : ability of a test to detect small amounts of a substance (e.g. antigen)
= dilution range for detection limit or e.g. detecting weak expressors
- ❖ Diagnostic : evaluation of true positive staining vs false negative staining

	Reference (+)	Reference (-)	Total
New (+)	TP	FP	
New (-)	FN	TN	
Total			

Sensitivity : $TP / (TP + FN)$



Definitions : performance characteristics

❖ SPECIFICITY

- ❖ Analytical : ability of a test to detect a substance (e.g. antigen) without interference of cross reacting substances (interferention study)
- ❖ Diagnostical : evaluation of true negative staining vs false positive staining

	Reference (+)	Reference (-)	Total
New (+)	TP	FP	
New (-)	FN	TN	
Total			

Specificity : $TN / (TN + FP)$



Definitions : performance characteristics

❖ OVERALL CONCORDANCE

- ❖ Analytical : the degree of agreement between new test and reference
 $\pm$ = Correctness
- ❖ Diagnostical : evaluation of true positive and negative staining vs total of true and false positive and negative staining

	Reference (+)	Reference (-)	Total
New (+)	TP	FP	
New (-)	FN	TN	
Total			

Concordance : $\frac{TP + TN}{TP + TN + FP + FN}$



Definitions : performance characteristics

❖ ROBUSTNESS

What influences result ?

- ❖ Ischemic time : time to fixation ?
- ❖ Fixation time :
 - Minimal and maximal fixation time ?*
 - Daily practice : different fixation times ?*
- ❖ Section thickness (IHC, ISH)
- ❖ Stability antigen : How long can pre-cut sections be stored ?? *How ? RT ?*
(Patientsamples, controls)
- ❖ Stability reagents : How long can a diluted concentrated Ab be stored ?
(e.g. dilutions from MSI Ab -> max 3 months)
- ❖ *Decal, etc*



Definitions : performance characteristics

❖ STAINING QUALITY

Stain quality : Scoring system to evaluate in an objective way, e.g. IHC* :

Staining criteria	Score			
Intensity	0 (none)	1 (weak)	2 (average)	3 (strong)
Uniformity	0 (none)	1 (uniform)	-	-
Specificity	0 (none)	1 (specific)	-	-
Absence of	0	1	2	
background staining	(strong)	(average)	(none)	-
Counterstaining	0	1	-	-
	(inadequate)	(adequate)		
Totaal				

Score : 0 - 4 : unacceptable
 5 - 6 : borderline
 7 - 8 : optimal

"Basic" evaluation of (analytical) sensitivity and specificity

(*) Reference : Audit and internal quality control in immunohistochemistry, P. Maxwell and W G McCluggage, J Clin Pathol 2000 53: 929-932



Definitions : performance characteristics

❖ READOUT

- ❖ *Type 1 (pathologist) vs type 2 (pathologist provides for treating physician)*
- ❖ *Validation/verification - initial :*
 - ❖ *Training of pathologists in e.g using scoring system by e.g. application specialist, professional organisations, etc*
 - ❖ *Readout new test from different pathologists vs expected results known cases/controls :*
 - *Verified by e.g. application specialist, expert panel, etc*
 - *Determine diagnostic sensitivity & specificity for different pathologists*
 - *Compare results pathologists and evaluate vs formulated acceptance criteria (e.g. >90% concordance)*
 - ❖ *Inter-observer tuning between different pathologists vs expected results*

Definitions : which performance characteristics ?

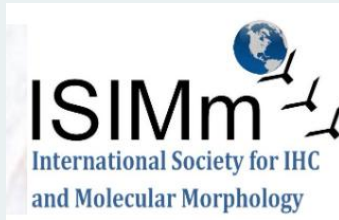
- Guidelines available ?



Type of test	Non Predictive	Predictive	Criteria
Unmodified FDA cleared/approved (each Ab)	✓	✓	Accuracy Precision Reportable range Overall concordance $\geq 90\%$
Non FDA cleared/approved (= <i>Laboratory Developed Tests</i>) Modified FDA cleared/approved (= <i>Laboratory Modified Tests</i>)	✓	✓	Accuracy Precision Analyt sensitivity Analyt specificity

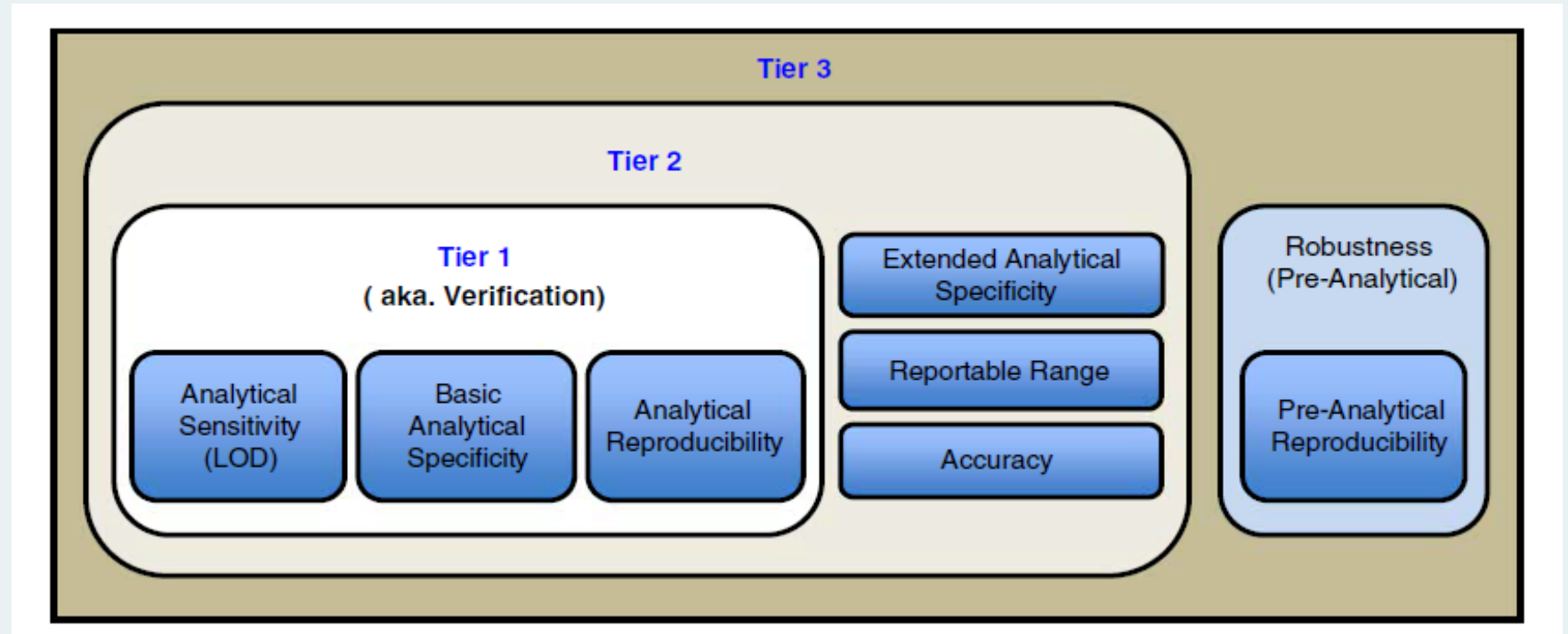
Definitions : which performance characteristics ?

- Guidelines available ?



	Tier 1	Tier 2	Tier 3
FDA / CE-IVD	✓	-	-
LDT	✓	✓	✓
Re- validation *	✓	✓	✓

Depending on reason for revalidation



E. Torlakovic et al *Appl Immunohistochem Mol Morphol* • Volume 25, Number 3, March 2017

Definitions : which performance characteristics ?

- Guidelines available ?

	Verification	Limited validation	Validation		
Performance characteristics	CE-IVD test	Modified CE-IVD with reference	Modified CE-IVD without reference	Non CE-IVD (RUO) with reference	Non CE-IVD without reference (In house developed)
Trueness	X	X	X	X	X
Precision	X	X	X	X	X
Sensitivity			X	X	X
Specificity			X	X	X
Robustness	x*	x*	x*	x*	x*
Inter operator variability	(x)	(x)	(x)	(x)	(x)



Belgian guidelines for Quality Management in Pathology labs.

Includes verification and validation of IHC methods

Federal Agency of Health – Sciensano

(Published 04/2022)

For Verification – LMT with reference :

“Basic” evaluation of sensitivity and specificity included in evaluation stain quality

x*: The performance of a risk analysis can be a useful tool to determine which parameters can be verified in the context of the robustness.

(x): Mainly applicable to semi-quantitative testing

Definitions : acceptance criteria ?

- Which **acceptance criteria** for the selected performance characteristics ? Guidelines ?
 - E.g. CAP : 90% overall concordance for every test used clinically
 - Defined by the number of samples in the validation :

Table 4. Validation Using 10- and 20-Tissue Validation Sets Against a 90% Concordance Benchmark			
No.	Concordance Estimate, % (95% CI)		
	0 Discordant	1 Discordant	2 Discordant
10	100 (68–100)	90 (57–100)	80 (48–95)
20	100 (81–100)	95 (75–100)	90 (69–98)

Abbreviations: CI, confidence interval; No., number of validation tissues.

Arch Pathol Lab Med—Vol 138, November 2014

Analytic Validation of Immunohistochemical Assays—Fitzgibbons et al

The higher the number of samples, the “easier” to get a high concordance

Acceptance criteria = minimum requirement/threshold value for verification/validation

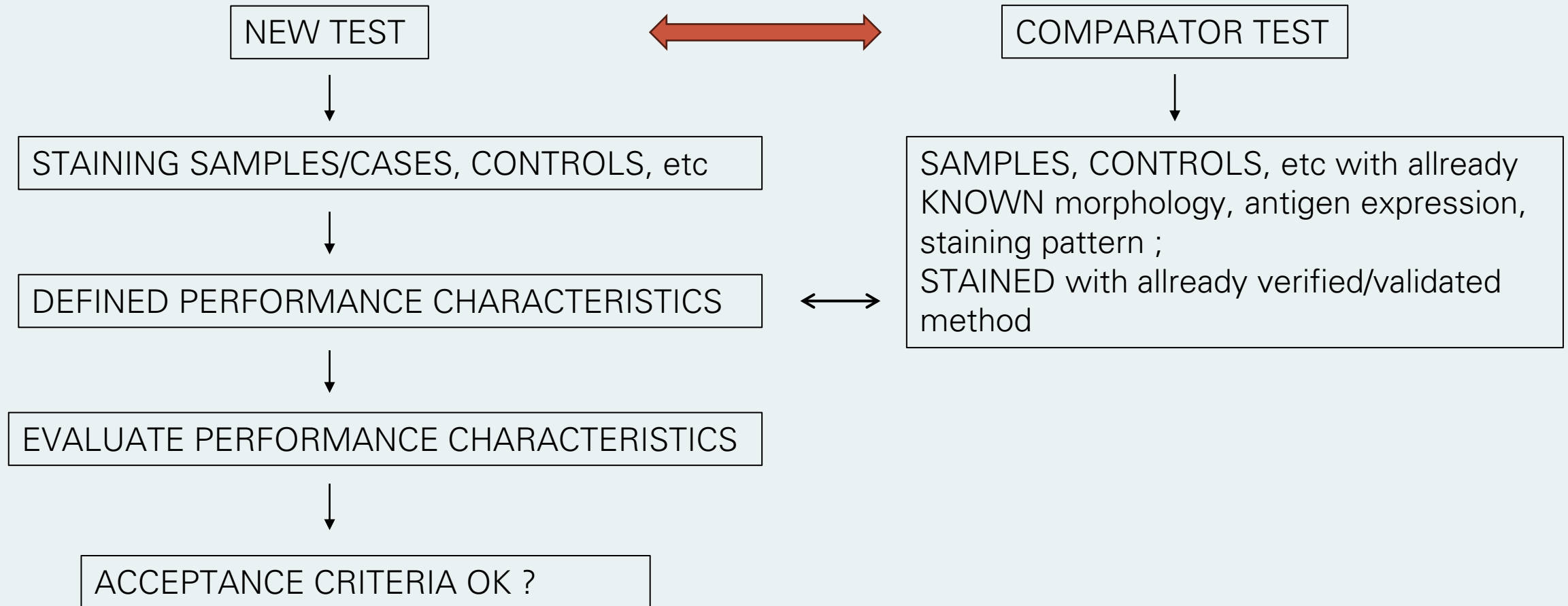
Definitions : essential elements

Summary

Validation	Verification	What does this mean ?
Demonstrate	Confirmation	Comparator test, reference, standard, etc
Objective evidence	Objective evidence	Demonstrate and document
Performance characteristics	Performance characteristics	Various performance characteristics & Acceptance criteria

Validation & verification : principle

Comparison of performance :



The Key Difference Between Validation and Verification ?

Difference between validation & verification in :

- ❖ The **extent** of type of tests performed and evaluated,
- ❖ **Performance criteria** used,
- ❖ Degree of evidence, documentation, etc required

Validation & verification : difference ?

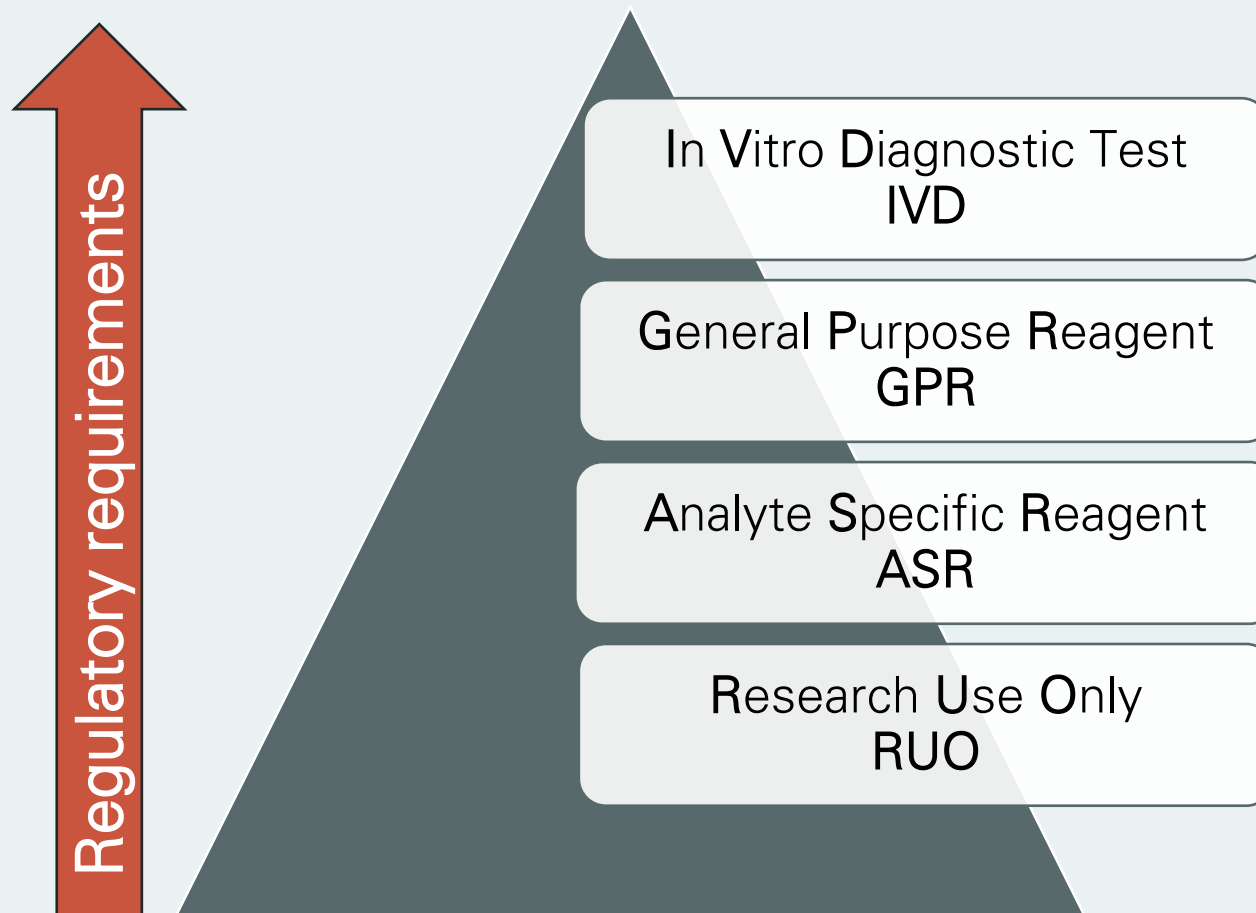
- What determines the use of “verification” or “validation” ?

Key questions ?	Verification	Validation
Type of test ?	CE – IVD Instructions For Use	All other (*)
Used according to IFU ?	YES	NO
Used for intended purpose ?	YES	NO

(*) Other include CE-IVD not according to IFU, non CE-IVD (e.g. RUO)

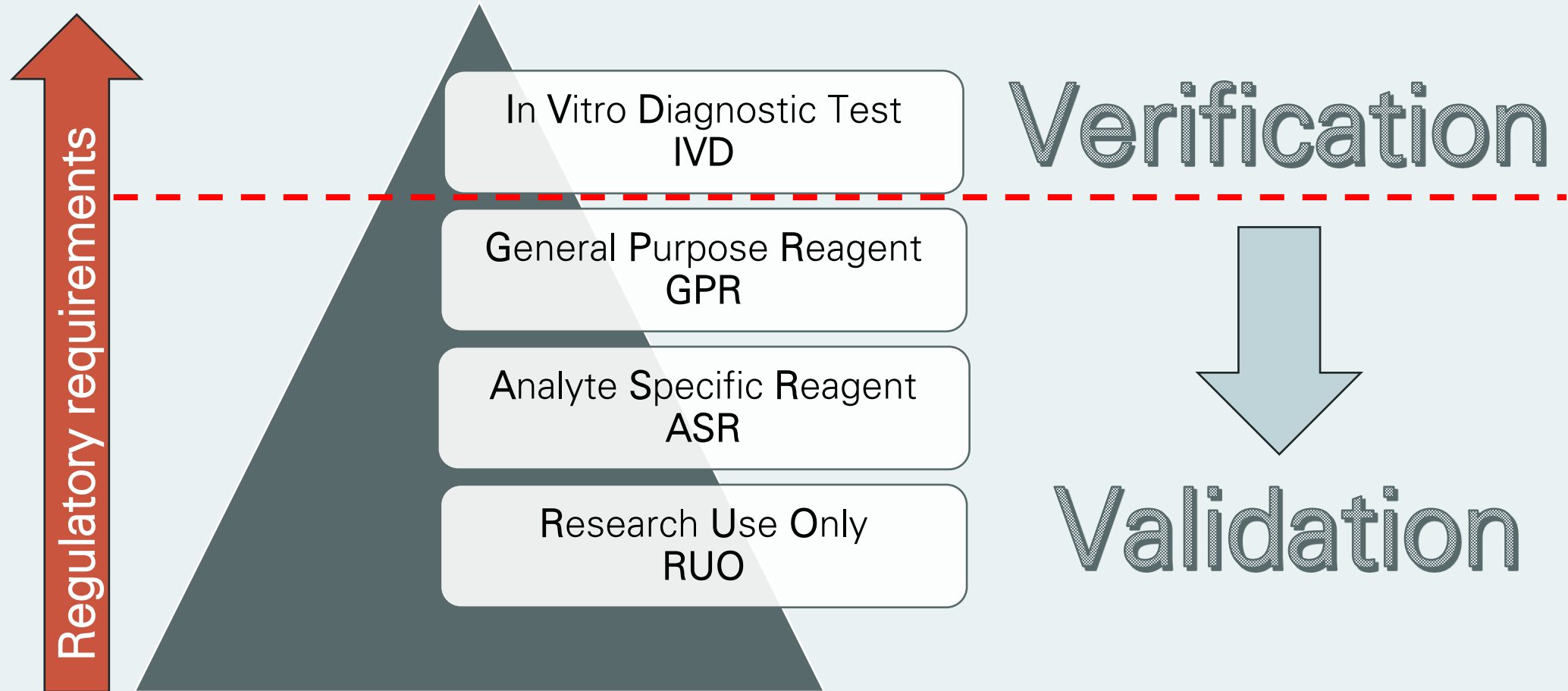
Validation & verification : difference ?

Question 1 : What type of test ?



Validation & verification : difference ?

Question 1 : What type of test ?





Validation & verification : difference ?

Question 1 : What type of test ?

❖ In Vitro Diagnostic Test (IVD) :

- **EU Regulation 217/746 :** In vitro diagnostic medical devices (IVDs) are tests used on biological samples to determine the status of a person's health. There is a broad range of IVDs. Some examples are self-tests for pregnancy, COVID-19 tests, cancer genetic tests or high-throughput testing of blood donations for infections such as HIV, performed in clinical laboratories.
- **FDA :** In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act (the act) and may also be biological products subject to section 351 of the Public Health Service Act, including when the manufacturer of these products is a laboratory. [21 CFR 809.3]
Like other medical devices, IVDs are subject to premarket and postmarket controls. IVDs are generally also subject to categorization under the Clinical Laboratory Improvement Amendments (CLIA '88) of 1988.



Validation & verification : difference ?

Question 1 : What type of test ?

❖ Research Use Only (RUO) :

- **EU Regulation 217/746** : No definition available. IVDR does not regulate the use of RUO reagents according to their Instructions For Use.
(= For research use, not for clinical use)
- **FDA** : RUO stands for For Research Use Only, designating a product intended for use in laboratory research, not for diagnostic or therapeutic purposes. While the FDA regulates products for human use, RUO products are generally unregulated, provided they are clearly labeled "For Research Use Only. Not for use in diagnostic procedures".



Validation & verification : difference ?

Question 1 : What type of test ?

❖ Investigational Use Only (IUO) :

- **EU Regulation 217/746** : No definition available.
- **FDA** : Investigational Use Only" (IUO) means a product, typically an in vitro diagnostic (IVD) or medical device, is still in clinical studies and has not yet been approved or cleared by the FDA for commercial marketing or sale. Such products are labeled with a specific disclaimer, such as "For Investigational Use Only. The performance characteristics of this product have not been established," and are used to gather data to support future FDA approval. The FDA regulates these products under an Investigational Device Exemption (IDE) to ensure that they are used in clinical studies to collect

Validation & verification : difference ?

Question 2 : What is “used according to Instructions For Use” - Method ?

- Instructions For Use (IFU) :
 - Clear instructions :
 - Pretreatment
 - Dilution of Ab (concentrated Ab)
 - Incubation times Ab, detection system, enhancing step, etc
 - Preprogrammed or full description of method ?



Always that clear – obvious – well described ?
Know if you work according to IFU or not ?

Validation & verification : difference ?

- What is “used according to Instructions For Use” ?

 **VENTANA®**

PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody

REF 790-2991
05278368001

IVD  50

INDICATIONS AND USE

Intended Use
This antibody is intended for use with the Ventana Medical System Monoclonal Primary Antibody intended for laboratory use of formalin-fixed, paraffin-embedded tissue for automated immunohistochemical assessment of breast cancer.

Table 2. Recommended Staining Protocols for PATHWAY anti-HER-2/neu (4B5) with *ultraView* Universal DAB Detection Kit.

Procedure Type	Platform or Method	
	BenchMark XT instrument	BenchMark ULTRA instrument
Baking	None	None
Deparaffinization	Selected	Selected
Cell Conditioning (Antigen Unmasking)	Cell Conditioning 1, Mild	ULTRA CC1, mild
Enzyme (Protease)	None required	None required
Antibody (Primary)	Approximately 16 minutes, 37°C	Approximately 12 minutes, 36°C
Counterstain (Hematoxylin)	Hematoxylin II, 4 minutes	Hematoxylin II, 4 minutes
Post Counterstain	Bluing, 4 minutes	Bluing, 4 minutes

 **Dako**

FLEX Monoclonal Mouse Anti-Human BCL6 Protein
Clone PG-B6p
Ready-to-Use
(Dako Omnis)

Code

Staining procedure overview*

Step		Comments
Fixation/embedding	Formalin-fixed, paraffin-embedded	Onboard deparaffinization
Pre-treatment	EnVision FLEX, High pH (Code V804)	30 in HIER
Antibody	Ready-to-use	12.5 min incubation
Negative Control	FLEX Negative Control, Mouse (Code GA750)	12.5 min incubation
Visualization	EnVision FLEX (Code V800) + EnVision FLEX+ Mouse LINKER (Code V821)	Block: 3 min; Link: 10 min; Polymer: 20 min; Chromogen: 5 min
Counterstain	Hematoxylin (Code C808)	3 min incubation
Control Tissue	Tonsil	Nuclear staining
Slides	FLEX IHC Microscope Slides (Code 8020)	Recommended for greater adherence of tissue sections to glass slides
Mounting	Non-aqueous, permanent mounting required	After staining, the sections must be dehydrated, cleared and mounted using permanent mounting medium
Instrumentation	Dako Omnis	Reagents are provided in instrument-specific vials

*The user must always read the package insert for detailed instructions of the staining procedure and handling of the product.

Validation & verification : difference ?

- What is “used according to Instructions For Use” ?

**Novocastra™ Liquid
Mouse Monoclonal Antibody
Prostate Specific Antigen**
Product code: NCL-L-PSA-431

Intended Use

For in vitro diagnostic use.

NCL-L-PSA-431 is intended for the qualitative identification by light microscopy of human prostate specific antigen in paraffin sections. The clinical interpretation of any staining or its absence should be complemented by morphological studies using proper controls and should be evaluated within the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

Do I use 10 % NBF ?

Specimen Preparation

The recommended fixative is 10% neutral-buffered formalin for paraffin-embedded tissue sections.

Recommendations On Use

Immunohistochemistry on paraffin sections.

Suggested dilution: 1:100 for 30 minutes at 25 °C. This is provided as a guide and users should determine their own optimal working dilutions.

Visualization: Please follow the instructions for use in the Novolink™ Polymer Detection Systems. For further product information or support, contact your local distributor or regional office of Leica Biosystems, or alternatively, visit the Leica Biosystems Web site, www.LeicaBiosystems.com

The performance of this antibody should be validated when utilized with other manual staining systems or automated platforms.

Incubation temperature on my staining platform ?

Suggestion/recommendation
vs “No changes allowed” ?

Validation & verification : difference ?

- What is “used according to Instructions For Use” ?

Nordic BioSite AB
Propollorvägen 4A, 183 62 Täby, Sverige
T: +46 (0)8 544 433 40
info@nordicbiosite.com, www.nordicbiosite.com
Org. Nr: 556539-9374, Säte: Täby

BioSite
- in Life Science Research

BAP1 (C4) Mouse Monoclonal Antibody

Catalog No AZC-YN0M8R-0.1 (0.1 ml)
AZC-E0R3F3-7 (7 ml (prediluted))

CE IVD

Materials Provided

BAP1 (C4) Mouse Monoclonal in concentrated form or prediluted

Antibody Specifications Antibody as Purified antibody diluted in Tris-HCl buffer containing stabilizing protein and

Host Mouse

Isotype IgG1 / κ

Immunogen Synthetic peptide against 430-729 of human BAP1

Cellular Localization Nuclear

Concentrate Dilution Range 1:100

Positive control Malignant Mesothelioma

4. The user must validate incubation times and temperatures.

5. The prediluted, ready-to-use reagents are optimally diluted, and further dilution may result in loss of antigen staining.

6. The concentrated reagents may be diluted optimally based on validation by user. Normal Antibody Diluent (Nordic BioSite Normal Antibody Diluent [Tris Buffered]) is recommended. Any diluent used that is not specifically recommended herein must likewise be validated by the user for both its compatibility and effect on stability.

Optimization :
1: 50 or 1: 200 ?



According to IFU ?

Validation & verification : difference ?

Question 3 : Used for the intended purpose as described in Instructions For Use ?

- ❖ Purpose of a test = intended use at the time test was developed (manufacturer)
- ❖ May or may not be the same as (clinical) intended use (lab – user)
- ❖ “Fit for Purpose” = test has been validated for an intended use at the time the test was developed (both lab/technical assay and clinical use)

Relation between intended purpose and verification/validation :

Same purpose	According to IFU	Verification
Change purpose (= change test)	Not according to IFU	Validation

Purpose of a test can also determine if a verification or validation needs performed



Validation & verification : difference ?

Question 3 : Used for the intended purpose as described in Instructions For Use ?

❖ Purpose of a test :

❖ Related to “3D” : Disease – Diagnostic test – Drug

❖ Classification upon risk for patient :

TABLE 2. The Classification of Immunohistochemistry (IHC) Tests From the Perspective of the End User

Test Category	User-Based Classification	Example
Diagnosis in symptomatic patients (diagnostic)	Pathologist (type 1-IHC)	S100, VIM, CD45 and PAN-CK in diagnosis of unknown primary tumor
Disease screening (for an additional disorder) in symptomatic patients (diagnostic)	Treating physician (type 2-IHC)	MLH1, MSH2, MSH6 and PMS2 in colorectal cancer patients being screened for Lynch syndrome
Prognosis of a diagnosed disease (prognostic)	Treating physician (type 2-IHC)	CD10, Bcl-6, and MUM1 for cell of origin in diffuse large B-cell lymphoma
Predictive of treatment response or adverse reaction (predictive)	Treating physician (type 2-IHC)	ER, PR, HER2 for breast cancer, HER2 for gastric cancer

Diagnostic	Prognostic	Predictive
Type 1	Type 2a	Type 2b

Evolution of Quality Assurance for Clinical Immunohistochemistry in the Era of Precision Medicine: Part 1: Fit-for-Purpose Approach to Classification of Clinical Immunohistochemistry Biomarkers

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C. Blake Gilks, MD,‡‡§§ Jacqueline A. Hall, PhD,§§|| Jason L. Hornick, MD, PhD,¶¶
Merdol Ibrahim, PhD,## Antonio Marchetti, MD, PhD,*** Keith Miller, FIBMS,##
J. Han van Krieken, MD, PhD,††† Søren Nielsen, BMS,‡‡‡§§§ Paul E. Swanson, MD,|| ||
Clive R. Taylor, MD,¶¶¶ Mogens Vyberg, MD,‡‡‡§§§ Xiaoge Zhou, MD,####
and Emina E. Torlakovic, MD, PhD,*††††††††
From the International Society for Immunohistochemistry and Molecular Morphology (ISIMM)
and International Quality Network for Pathology (IQN Path)

Validation & verification : difference ?

Question 3 : Used for the intended purpose as described in Instructions For Use ?

❖ Purpose of a test ? Indicated in the Instructions For Use (IFU)

 **Dako**
FLEX
Polyclonal Rabbit
Anti-Helicobacter Pylori
Ready-to-Use
(Dako Omnis)

Code GA523

Intended use

For in vitro diagnostic use.

FLEX Polyclonal Rabbit Anti-Helicobacter Pylori, Ready-to-Use (Dako Omnis), is intended for use in immunohistochemistry together with the Dako Omnis instrument. This antibody is useful for the identification of infections with *H. pylori* in gastritis and gastric cancer (1-4). The clinical interpretation of any staining or its absence should be complemented by morphological studies using proper controls and should be evaluated within the context of the patient's clinical history and other diagnostic tests by a qualified pathologist.

= 1 well determined purpose

 **Dako**
FLEX
Monoclonal Mouse
Anti-Human
Cytokeratin 7
Clone OV-TL 12/30
Ready-to-Use
(Dako Omnis)

Code GA619

Intended use

For in vitro diagnostic use.

FLEX Monoclonal Mouse Anti-Human Cytokeratin 7, Clone OV-TL 12/30, Ready-to-Use (Dako Omnis), is intended for use in immunohistochemistry (IHC) together with the Dako Omnis instrument. This antibody labels glandular and transitional epithelial cells and is a useful aid for the classification of adenocarcinoma of the lung (1), breast and endometrium, thyroid gland (2) and ovary (3), as well as chromophobe renal cell carcinoma (4). Differential classification is aided by the results from a panel of antibodies. The clinical interpretation of any staining or its absence should be complemented by morphological studies using proper controls and should be evaluated within the context of the patient's clinical history and other diagnostic tests by a qualified pathologist. This antibody is intended to be used after the primary diagnosis of tumor has been made by conventional histopathology using nonimmunologic histochemical stains.

= 4 well determined purposes

Validation & verification : difference ?

Question 3 : Used for the intended purpose as described in Instructions For Use ?

❖ Purpose of a test ? Indicated in the Instructions For Use (IFU)

Some Ab used for different purposes !



Do I need to validate separately for each purpose ??

❖ Difference type 1 vs type 2 :

❖ **Type 1** : validation set/cases including cases for different intended purposes

❖ **Type 2** : validation according to purpose e.g. HER-2 on breast and gastric
validation according to specific scoring system used

= separate validation/verification per purpose/intended use or scoring system used

❖ Experience of lab/pathologist with test/biomarker/assay

❖ Implementation of IQC, EQA participation

❖ etc

Validation & verification : WHY ?

Main reasons why we should perform a validation/verification

Initial drivers for verification and validation

Requirements	Regulations	Technical
• Legal • Accreditation • Professional organisations	• EU IVDR • FDA	• Reagents • Instruments • Methods

N°1 = Patient best interest !

Initial drivers for verification and validation

1. Legal or accreditation requirements, guidelines, etc

- Requirements by Federal Agencies, National regulations, etc
- Guidelines by professional organisations : E.g. College of American Pathologists
- Accreditation requirements : E.g. ISO 15189 (2022) Medical laboratories – Requirements for quality and competence



Requirements under chapters :

7.3.2 Verification of examination methods

7.3.3 Validation of examination methods

+ other/additional requirements : e.g.

6.4.3 Equipment acceptance procedure

Initial drivers for verification and validation

2. EU Directive EU2017/746 In Vitro Diagnostics

- Revised IVD regulation, effective May 2022
- Guidelines for **manufacturing** and **use of IVD**

L 117/176	EN	Official Journal of the European Union	5.5.2017
REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL			
of 5 April 2017			
on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU			

Subject matter and scope

1. This Regulation lays down rules concerning the placing on the market, making available on the market or putting into service of in vitro diagnostic medical devices for human use and accessories for such devices in the Union. This Regulation also applies to performance studies concerning such in vitro diagnostic medical devices and accessories conducted in the Union.

= guidelines for “ **manufacturers**” to get **CE – IVD certification**
Different requirements throughout whole process from development and initial validation (for an intended purpose) to post market performance follow up,

➡ Intended to be **used** according to Instructions For Use.



Initial drivers for verification and validation

2. EU Directive EU2017/746 In Vitro Diagnostics

- Revised IVD regulation, effective May 2022
- Guidelines for **manufacturing** and **use of IVD**

L 117/176	EN	Official Journal of the European Union	5.5.2017
REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL			
of 5 April 2017			
on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU			

Subject matter and scope

1. This Regulation lays down rules concerning the placing on the market, making available on the market or putting into service of in vitro diagnostic medical devices for human use and accessories for such devices in the Union. This Regulation also applies to performance studies concerning such in vitro diagnostic medical devices and accessories conducted in the Union.

= guidelines for “ **manufacturers**” to get **CE – IVD certification**
Different requirements throughout whole process from development and initial validation (for an intended purpose) to post market performance follow up,

➡ Intended to be used according to Instructions For Use.



But what if one does not follow the IFU ?

Initial drivers for verification and validation

2. EU Directive EU2017/746 In Vitro Diagnostics

Only 2 categories of tests :

Type	Description	Manufacturer	User
CE-IVD	Used according to Instructions for Use (IFU)	Validation	Verification
All other	CE – IVD NOT used according to IFU Non CE – IVD NOT used according to IFU Lab Developed Test (LDT) In House Test, Home Brew Test	Validation	Validation

“Other” : NO specific terminology in EU IVDR Directive, but a definition :

“ **Devices manufactured and used within health institutions within EU** ”

- Commonly used term : Laboratory Developed Test (LDT)
- Other terminology ? Laboratory Modified test (LMT), CE-IVD with minor/major modifications, Home Brew Test, In House test

Initial drivers for verification and validation

2. EU Directive EU2017/746 In Vitro Diagnostics

- LDT definition : “ **Devices manufactured and used within health institutions** ”



Laboratory becomes a “**manufacturer**” of the LDT

- Manufactured ?

- **Manufacturing** from raw materials/parts/components
- **Combining** devices or products for a medical purpose
(no CE mark or combination not in line with original intended purpose
(e.g. Ab manufacturer 1 on staining platform manufacturer 2))
- **Significantly modifying** an existing device : not intended by the manufacturer and has impact on product conformity (= changing a method, intended use, etc)

What is “significantly modifying ” ?

What is the impact of the changes, especially to patient safety and test performance ?

Initial drivers for verification and validation

2. EU Directive EU2017/746 In Vitro Diagnostics

- Significant (major) vs non significant (minor) changes ? (MDCG 2022-6)

			Y	N
☐	Intended purpose	☐ Limitation ☐ Extended use ☐ Other (specimen type, etc)	☐ NS ☐ S ☐ S	☐ NS ☐ NS ☐ NS
☐	Design	☐ Testprinciple changed ☐ Negative effect on safety/performance or risk/benefit ratio	☐ S ☐ S	☐ NS ☐ NS
☐	Ingredients or materials	☐ Essential for testprinciple ☐ Negative effect on safety/performance or risk/benefit ratio	☐ S ☐ S	☐ NS ☐ NS
☐	Software	Software - driver, database (no bugfix, security update, etc)	☐ S	☐ NS
☐	Sterility or packaging	☐ Impact on sterility of the product ☐ Changed packaging with impact on product	☐ S	☐ NS
☐	CAPA	☐ CAPA evaluated and accepted by competent authority	☐ NS	☐ S

Source : MDCG 2022 – 6 Guidance on significant changes regarding the transitional provision under article 110(3) of the IVDR)

Initial drivers for verification and validation

2. EU Directive EU2017/746 In Vitro Diagnostics

- **Significant** (major) vs **non significant** (minor) changes ? (MDCG 2022-6)

			Y	N
☐	Intended purpose	☐ Limitation ☐ Extended use ☐ Other (specimen type, etc)	☐ NS ☐ S ☐ S	☐ NS ☐ NS ☐ NS
☐	Design	☐ Testprinciple changed ☐ Negative effect on safety/performance or risk/benefit ratio	☐ S ☐ S	☐ NS ☐ NS
☐	Ingredients or materials	☐ Essential for testprinciple ☐ Negative effect on safety/performance or risk/benefit ratio	☐ S ☐ S	☐ NS ☐ NS

Extended use :

- E.g. : Leica C-kit CD117 for Giardia staining (= significant) ; using PDL-1 other then specified in IFU (sample, staining platform, etc)

Other (specimen type) :

- Ab used on cytology (when not indicated in IFU) (= significant)

Ingredients/materials :

E.g. : Ab used on another platform then described in IFU

Changes to method outside IFU

❖ Effect of changes on performance/safety ? ➡ **Validation**

❖ Effect of changes vs risk/benefits ratio for patients ? ➡ **Risk analysis**

Initial drivers for verification and validation

2. EU Directive EU2017/746 In Vitro Diagnostics

- If a test is an “LDT” or “not an LDT” is about :

Changes on default method/materials/reagents or intended use

vs

Information in IFU

&

Effect of changes on performance/safety – or – risk/benefits ratio for patients

- LDT is **NOT** about the use of an RTU or a concentrated Ab as such :

- The use of a **concentrated Ab** does not make it by default an LDT, but it can, depends on the IFU
- The use of an **RTU reagent/Ab** does not by default clear it from being an LDT, depends on the IFU



Initial drivers for verification and validation

2. EU Directive EU2017/746 In Vitro Diagnostics

- Are lab's allowed to use LDT ? (Health Institutions within EU)
- EU IVDR Directive : CE-IVD test = first choice
LDT may be used if no "valid" CE- IVD is available and :
 - Clinical and analytical performance demonstrated
 - Risk analysis for the impact of changes vs IFU

OR

- Art 5.5c : Lab fullfils requirements of ISO15189 or – when applicable – appropriate national requirements (e.g. national guidelines regarding accreditation, requirements for certification of lab, etc)
- + Comply with Annex 1 of IVDR



Initial drivers for verification and validation

2. EU Directive EU2017/746 In Vitro Diagnostics

Additional requirements (= documentation per test)

IVDR

- Used under Quality Management System
- Fullfills ISO15189 requirement or appropriate national guidelines regarding accreditation
- Justification of the use of LDT
 - Specific needs patient population
 - No CE-IVD available that fullfills requirements or performance criteria (EUDAMED database)
 - + periodic review of availability CE-IVD
 - + Declaration to competent authority
 - + Incident reporting

IVDR Annex 1

General Safety & Performance Requirements (GSPR)

- Risk management for “production” & usage
- Risk mitigating actions
- Performance of LDT (analytical and clinical performance is demonstrated + continuously evaluated upon use + CAPA)
- Documentary requirements :
 - Information on “production”
 - Instructions for Use (IFU)
 - Labelling (specific requirements !)

+ Post – market evaluation of performance of tests (both CE-IVD and LDT)



Initial drivers for verification and validation

2. EU Directive EU2017/746 In Vitro Diagnostics

– Classification of IVD tests based upon risk for patients :

Class	Risk profile	Application
A	Low individual risk and low public risk	Basic stains (e.g. H&E), histochemical stains
B	Moderate individual risk and low public risk	Some IHC stains like e.g. HP
C	High individual risk and/or moderate public risk	IHC stains, ISH, molecular testing
D	High individual risk and high public risk	/

Inspection by competent authority : class D or C&D (depending on country)

Initial drivers for verification and validation

3. Technical considerations

- IHC test by manufacturer:

- Developed under certain conditions
- For a certain purpose / intended use

- Instructions For Use :

- Contains (well) described method
- Sample usage : e.g. Formalin Fixed, Paraffin Embedded (FFPE), frozen section, etc
- Staining platform to be used on (recommended or not)
- etc

Initial drivers for verification and validation

3. Technical considerations

- IHC test by manufacturer:

- Developed under certain conditions
- For a certain purpose / intended use

- Instructions For Use :

- Contains (well) described method
- Sample usage : e.g. Formalin Fixed, Paraffin Embedded (FFPE), frozen section, etc
- Staining platform to be used on (recommended or not)
- etc

However...

Initial drivers for verification and validation

3. Technical considerations

Manufacturer – development of a test

- ❖ Developed under certain conditions and for a certain purpose / intended use
- ❖ Instructions for use :
 - ❖ Sample usage : e.g. FFPE
 - ❖ Described method
 - ❖ Staining platform

Customer/lab using test

- ❖ Used for intended purpose or use ?
- ❖ Performed as prescribed by manufacturer ?
- ❖ Instructions for use :
 - ❖ Sample usage : e.g. **FFPE**
 - ❖ Tissue processing protocol ?
 - ❖ Fixative used ? Fixation times ?
 - ❖ Section thickness ?
 - ❖ Section preparation method ?
 - ❖ Etc

Influencing results and therefore calibration/optimalization and validation/verification is needed before use on patient samples in daily routine.

Initial drivers for verification and validation

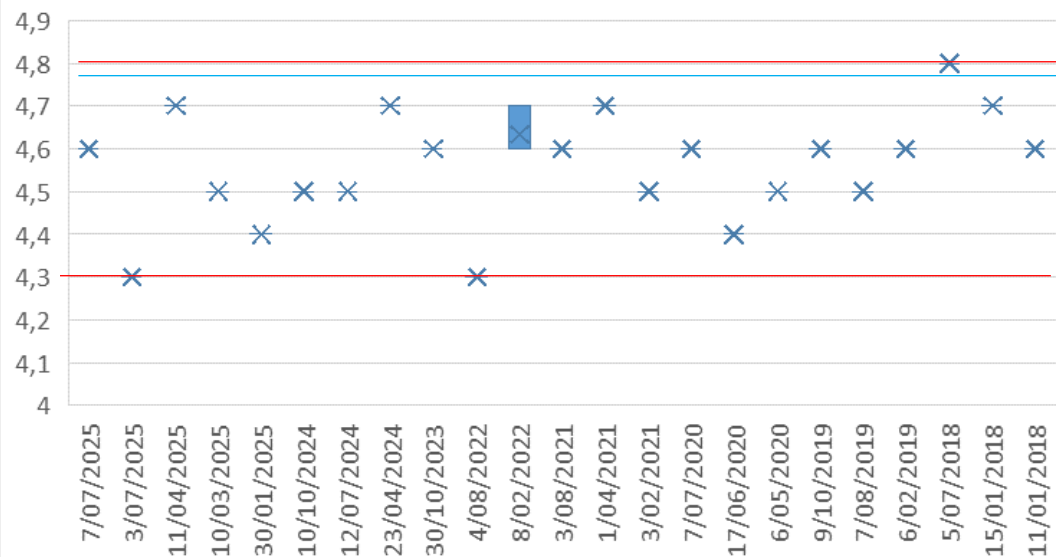
3. Technical considerations

Novocastra™ Liquid
Mouse Monoclonal Antibody
Prostate Specific Antigen
Product code: NCL-L-PSA-431

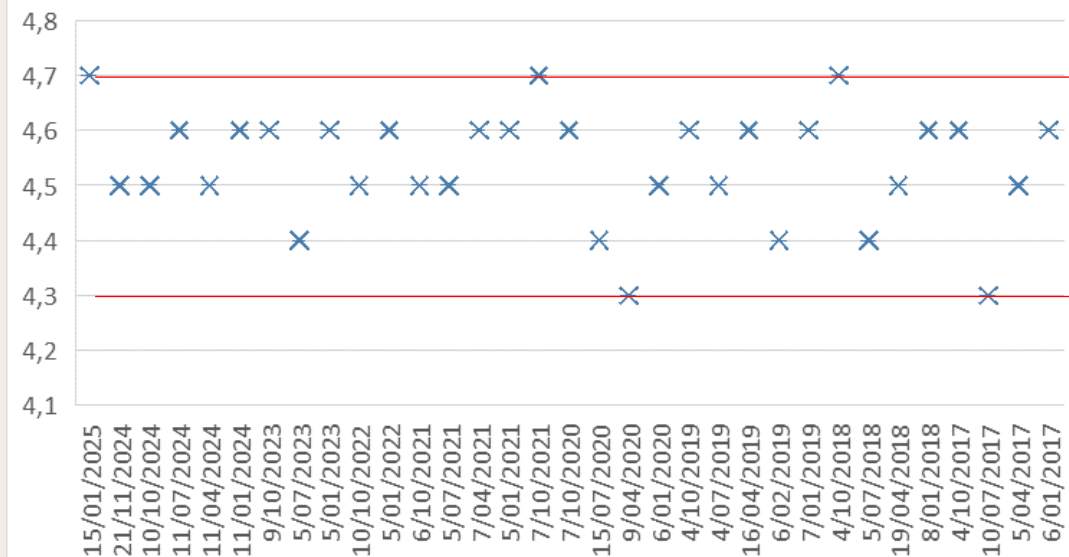
Specimen Preparation

The recommended fixative is 10% neutral-buffered formalin for paraffin-embedded tissue sections.

Formalin 10 L cubitainers acceptance testing



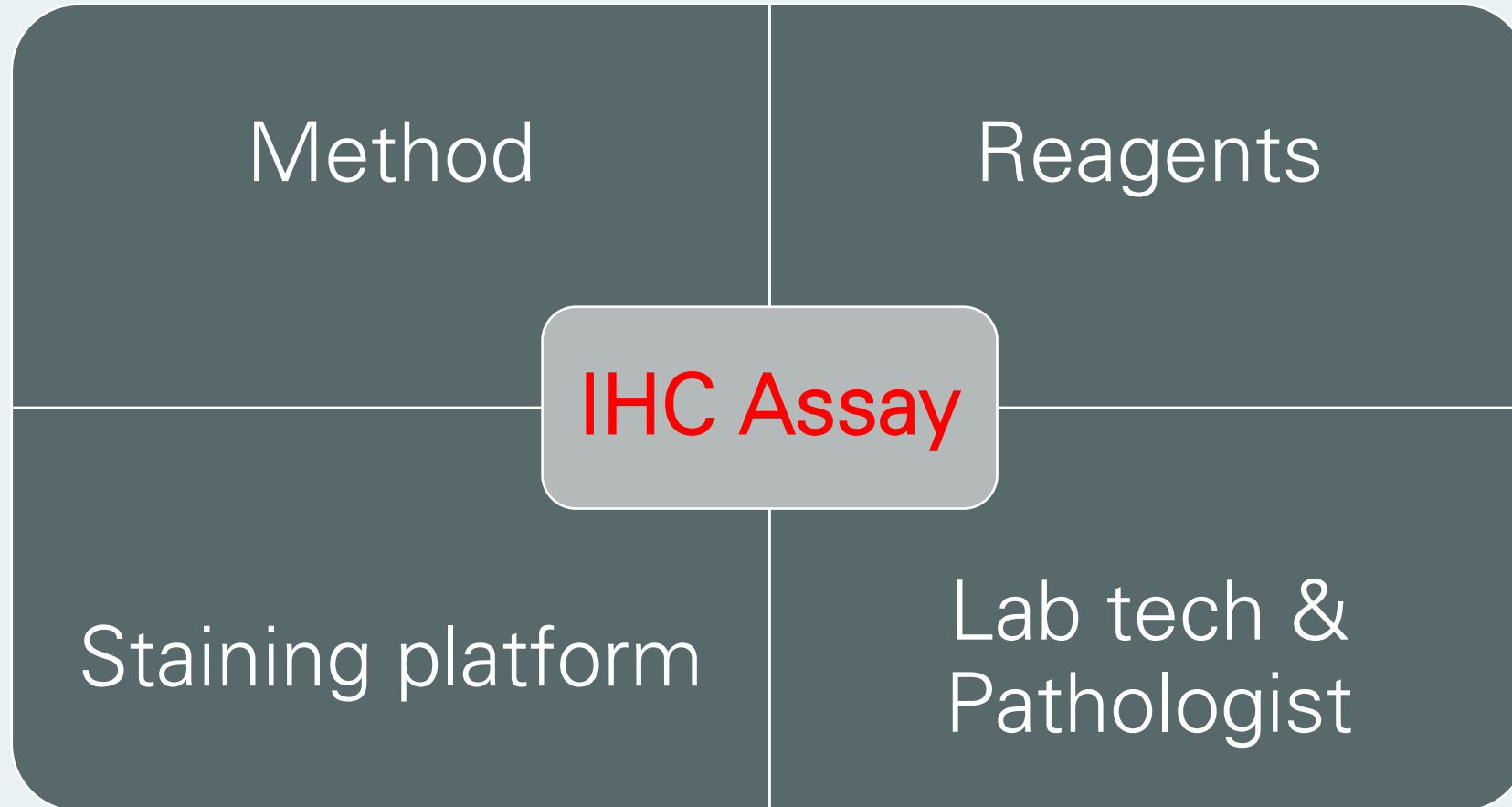
Formalin 60 ml vials acceptance testing



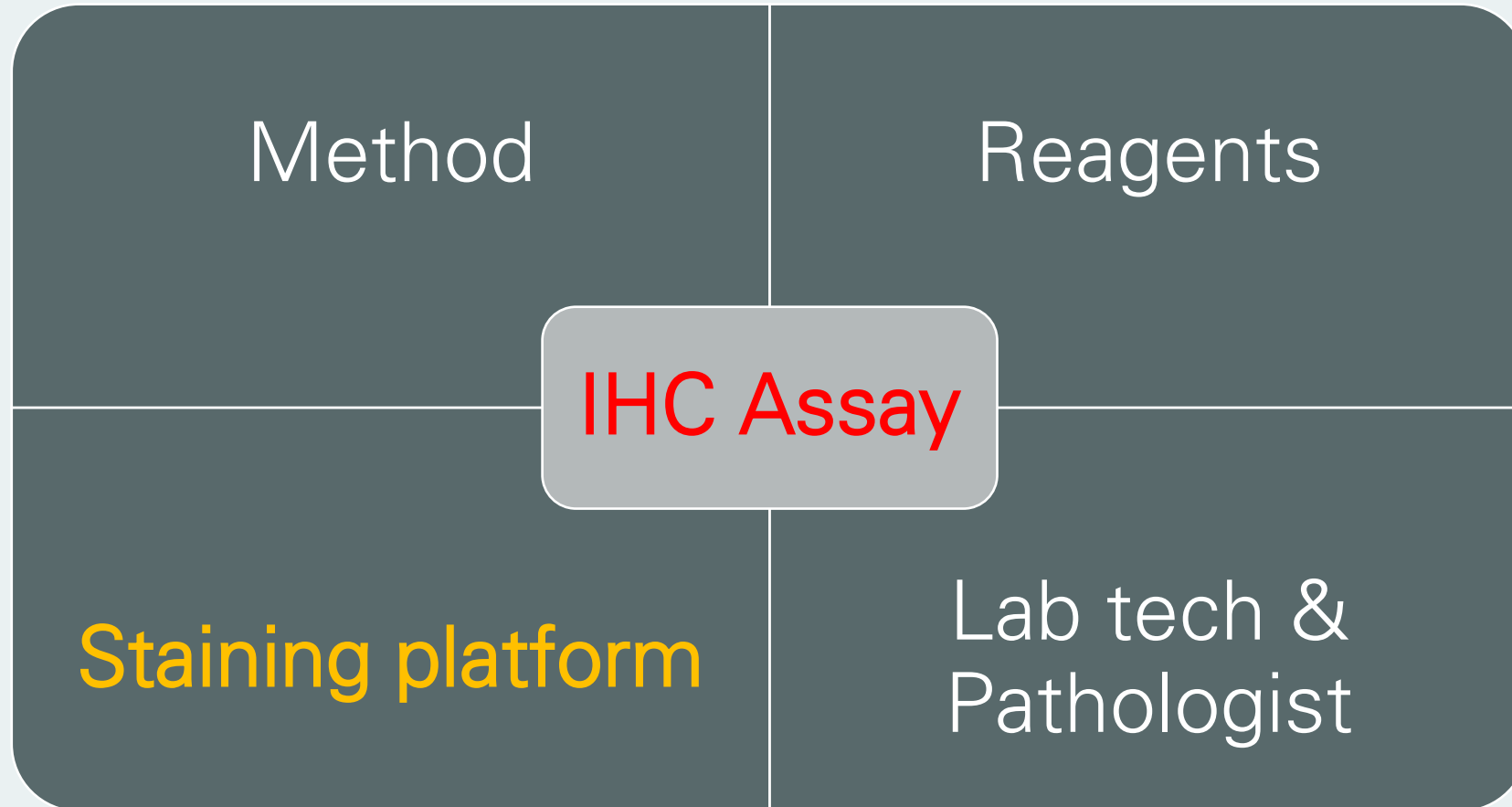
Validation & verification : How ?

Practical approach on how we should perform a validation/verification

Verification & validation : How ?



Verification & validation : How ?



Verification of automated staining platforms

IHC staining performed on automated staining platform(s) ? → Verification of staining platform(s)

Verification steps for automated staining platform



Applies **for every staining platform** in use (different or same manufacturer).

Verification of automated staining platforms

Installation Qualification (IQ)

- Performed by manufacturer/distributor/installing company
- Check if manufacturers requirements for installation are met
 - Lab space :
 - Enough free floor and desk space ?
 - Accessibility ? (doors, acces route for delivery, etc)
 - Accessibility staining platform for maintenance
 - Utilities ? (enough power outlets, back up power supply, LI(M)S connection, etc)
 - Other : e.g. bulk reagent containers, waste disposal, etc

Additionally :

- Pre – install visit allows necessary adaptations to be performed (e.g. labdesk, power supply, moving other instruments, furniture, etc)
- LEAN workflow – workplace organisation
- Objective evidence : documents provided by service engineer manufacturer, etc

Installation Qualification (IQ)

Agilent Dako Omnis Installation checklist

Roche Benchmark Ultra pre-install report

Roche Benchmark Ultra installation report

Verification of automated staining platforms

Operational Qualification (OQ)

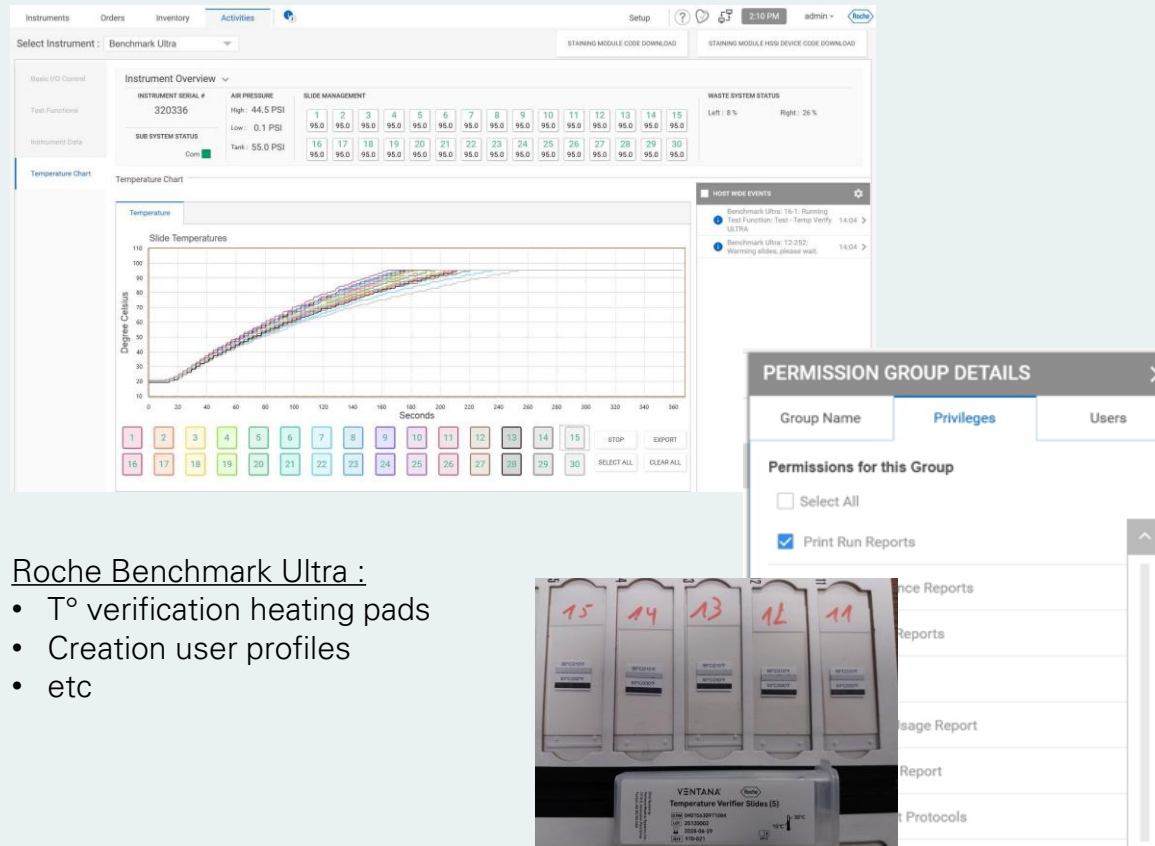
- Performed by manufacturer/distributor/installing company
- Check if all technical functional components work according to manufacturers requirements
 - Test of :
 - Check of alignment of moving parts (e.g. robotic arm, carrousel, etc)
 - Temperature verification (heating pads, waterbaths, etc)
 - Liquid volume dispensing, pressure, valves, etc
 - Emergency power supply, emergency stops, etc
 - Etc
- Objective evidence : documents service engineer manufacturer calibration certificated for used measuring instruments



Tip!

Verification of automated staining platforms

Operational Qualification (OQ)



Roche BenchMark Ultra :

- T° verification heating pads
- Creation user profiles
- etc

Operational Qualification Certificate BenchMark ULTRA



Date: 28-Apr-26

General Information

Site Name	Instrument SN #	Case ID
AZ Sint-Lucas Brugge	320336	WO-36392591
Site Number	Computer SN #	Host ID
0042700457	MXL2481NVB	20790
Host Software Version	VSS 14.1	

Service Tools

Tool	Equipment Number	Next Calibration Date	N/A
Digital Scale	cs2110A0461	29-September-26	☐
Pressure Gauge	64503/3	18-Jun-26	☐
Flow Meter	41401440017	06-Jan-27	☐
Multimeter	49120105	23-September-26	☐

Inspection

- ☒ Inspect the compressor muffler
- ☒ Inspect fluid path fitting
- ☒ Verify instrument grounding (only required after electrical repair)

Air Pressure and Air Flow

- ☒ Verify the air tank pressure calibration

45.0 psi	High system pressure	2975 ml/min	Barcode blowoff flow
13.10 psi	Low system pressure	4013 ml/min	Label blowoff flow

Vortex Mixers:	4	1	2	3
Inner	504 ml/min	510 ml/min	509 ml/min	509 ml/min
Outer	480 ml/min	478 ml/min	480 ml/min	492 ml/min

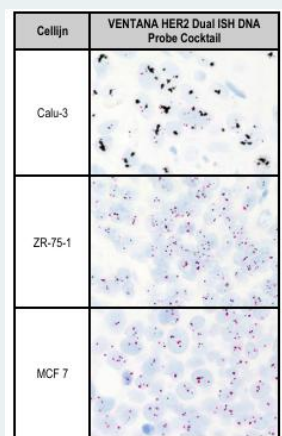
Alignments and Verifications

- ☒ Verify operation of bulk bottle sensors
- ☒ Verify slide detect sensor calibration
- ☒ Verify overflow sensor operation
- ☒ Verify reagent detect sensor calibration
- ☒ Verify reagent tray position to position alignment
- ☒ Verify operation of slide drawers in/out

Verification of automated staining platforms

Performance Qualification (PQ)

- Performed by manufacturer/distributor/installing company & Lab
- Check if staining platform delivers consistent stainings that fulfill specified performance criteria **under routine conditions**
- **Manufacturer (Application Specialist) :**
 - Test of certain stainings on defined tissue samples (e.g. Ab panel, specific clone, etc)
 - Check if stainings meet predefined (performance) criteria



Roche HER-2 Dual ISH
Xenograft slides

Rack #1 (TRS, high pH):				
CD45 – PQ Tissue	CD45 – Blank Glass	CD45 – Blank Glass	CKAE1AE3 – PQ Tissue	CKAE1AE3 – Blank Glass
Rack #2 (TRS, low pH):				
Empty	Ki67 – PQ Tissue	Empty	Empty	Ki67 – PQ Tissue
Rack #3 (TRS, high pH):				
Empty	Empty	CK7- PQ Tissue	CD45 – PQ Tissue	Empty
Rack #4 (TRS, low pH):				
Ki-67 – PQ Tissue	Ki67 – Blank Glass	Ki67 – Blank Glass	Ki67 – Blank Glass	Ki67 – Blank Glass
Rack #5 (TRS, high pH):				
Empty	CKAE1/AE3 – PQ Tissue	CK7-PQ Tissue	Empty	Empty
Rack #6 (TRS, low pH):				
Empty	Empty	Empty	Empty	Ki67 – PQ Tissue

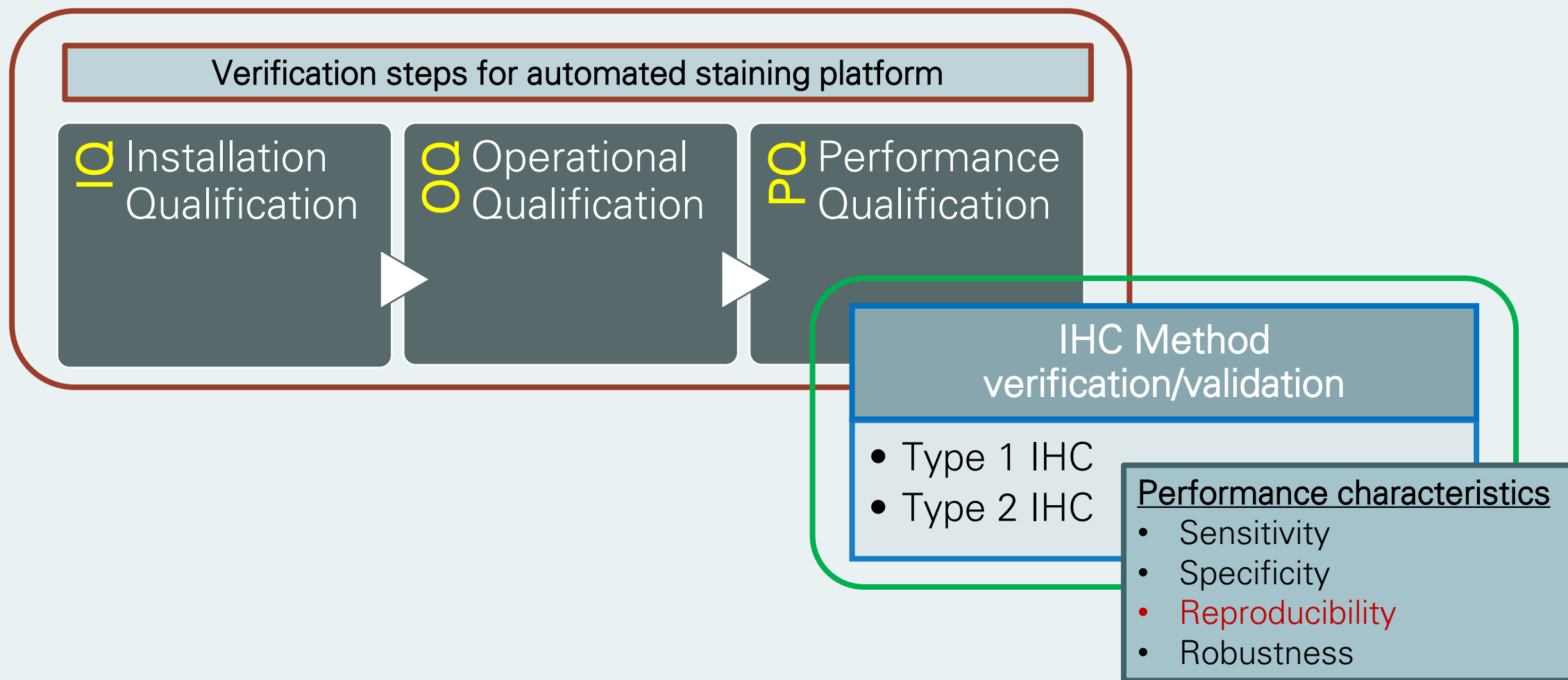
Agilent Dako Omnis validation slide set

Verification of automated staining platforms

Performance Qualification (PQ)

- Performed by manufacturer/distributor/installing company & Lab
- Check if staining platform delivers consistent stainings that fulfill specified performance criteria under routine conditions
 - **Lab :**
 - Staining platform for general or specific use (e.g. dedicated stainer for breast, haematology, back-up, etc)
 - Multiple stainers : verification of each platform
 - LI(M)S connection
 - Type 1 & 2 IHC
 - Overlap with **method verification/validation**

Verification of automated staining platforms

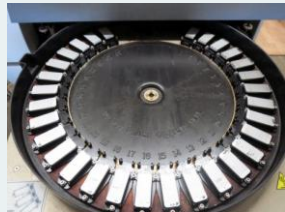


Verification of automated staining platforms

Reproducibility : Within and in between run

BATCH LOADING

Carousel



Benchmark GX

Slide trays



Autostainer

CONTINUOUS LOADING

Fixed slide position

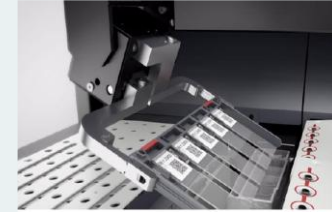


Bond MaX & III



Intellipath

NON Fixed slide position



Omnis

Single piece loading



Benchmark Ultra



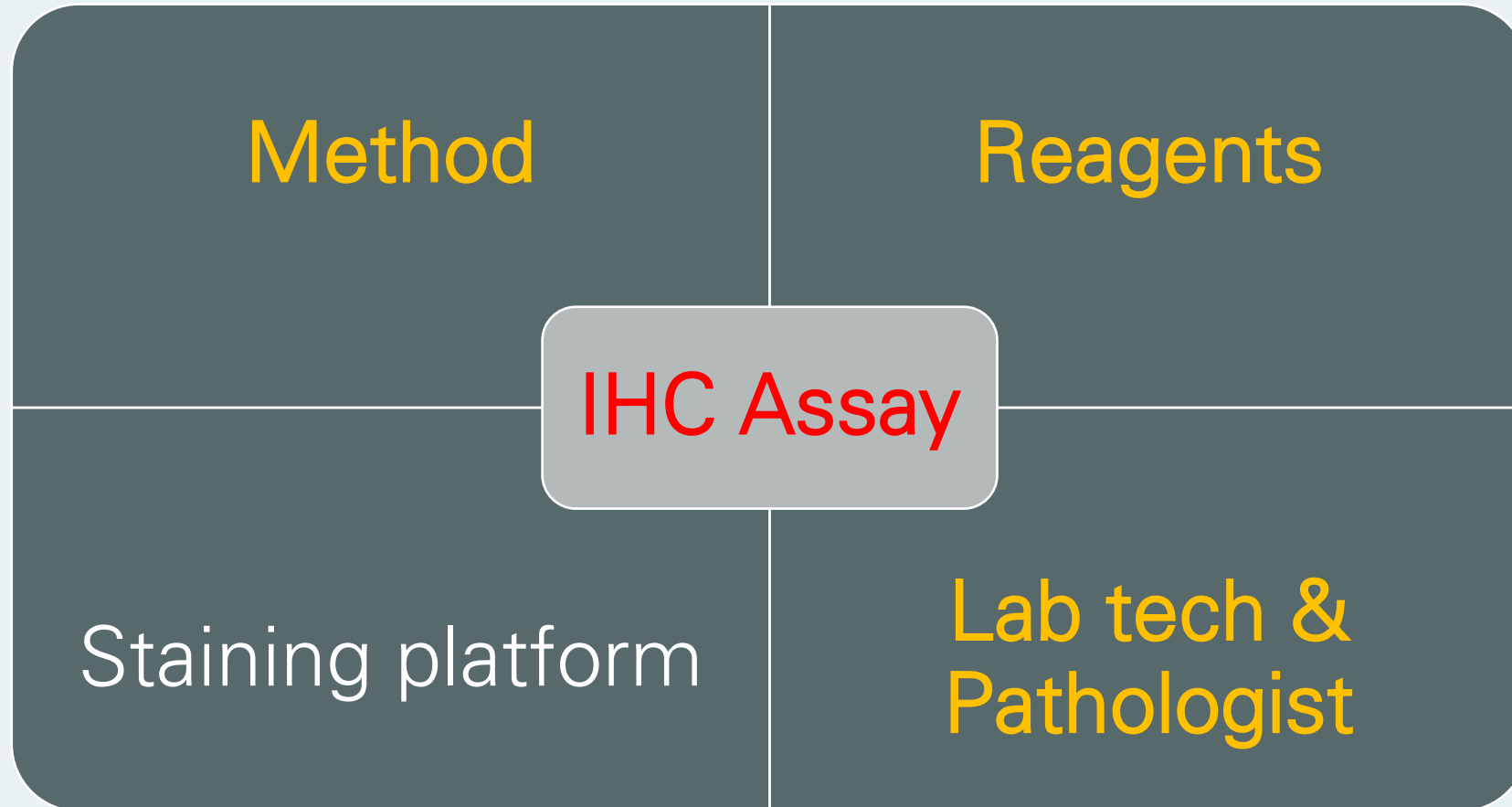
Genie



Prime

Different working principles
require different approach.

Verification & validation : How ?



Validation & verification : How ?

1. Plan and prepare practical execution

- Selection of the antibody and clone
 - Available information ?
 - Instructions For Use or other information from manufacturer (e.g. application specialist), literature references, EQA results ?
 - Information about staining patterns, tissue elements stained, etc (non specific staining)
 - Information about appropriate controls, weak expressors (iCAP's), etc
- Guidelines about validation/verification ? National guidelines, professional organisations

Determines verification or validation strategy

Validation & verification : How ?

1. Plan and prepare practical execution

- Formulate verification/validation strategy/plan :
 - Verification or validation ?
 - Select **comparator test/reference**
 - Select appropriate **performance characteristics**
 - Determine **acceptance criteria** for the selected performance characteristics
- Tasks, competences and responsibilities (who does what ?)
- Type of samples/cases/controls
- Number of cases/slides

Validation & verification : How ?

1. Plan and prepare practical execution

- Determine **number of samples/cases/controls**
 - Determined by **type of test** :
 - CE-IVD or not
 - Type 1 vs type 2 IHC
 - Determined by **the way test is used**
 - Performed according to IFU or not (method, type of sample, staining platform)
 - Used for the same purpose/intended use or not

Validation & verification : How ?

- Determine number of samples/cases/controls : **guidelines or references** ?

Available references referring to actual number of cases needed is limited.

Principles of Analytic Validation of Immunohistochemical Assays

Guideline From the College of American Pathologists Pathology
and Laboratory Quality Center

*Patrick L. Fitzgibbons, MD; Linda A. Bradley, PhD; Lisa A. Fatheree, BS, SCT(ASCP); Randa
Regan S. Fulton, MD, PhD; Jeffrey D. Goldsmith, MD; Thomas S. Haas, DO; Rouzan G. Karaba
Patti A. Loykasek, HT(ASCP); Monna J. Marolt, MD; Steven S. Shen, MD, PhD; Anthony T. Smith, M*

Accepted for publication February 3, 2014.



COLLEGE of AMERICAN
PATHOLOGISTS

Principles of Analytic Validation of Immunohistochemical Assays

Guideline Update

*Jeffrey D. Goldsmith, MD; Megan L. Troxell, MD, PhD; Sinchita Roy-Chowdhuri, MD, PhD; Carol F. Colasacco, MLIS, SCT(ASCP);
Mary Elizabeth Edgerton, MD, PhD; Patrick L. Fitzgibbons, MD; Regan Fulton, MD, PhD; Thomas Haas, DO;
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Nicole E. Thomas, MPH, CT(ASCP)^{CM}; Paul E. Swanson, MD; Andrew M. Bellizzi, MD*

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Validation & verification : How ?

- Determine number of samples/cases/controls



Type of test	Non Predictive	Predictive	Criteria
Unmodified FDA cleared/approved (each Ab)	10 (+) & 10 (-) - OR - Labdirector	≥ 20 (+) & 20 (-) Different expression levels ER/PR/HER-2 guidelines	Accuracy Precision Reportable range Overall concordance ≥ 90%
Non FDA cleared/approved (= Laboratory Developed Tests) Modified FDA cleared/approved (= Laboratory Modified Tests)	10 (+) & 10 (-) - OR - An appropriate tissue set	ER/PR/HER-2 : ≥ 40 (+) & 40 (-) Other : 20 (+) & 20 (-)	Accuracy Precision Analyt sensitivity Analyt specificity

“The more samples run in a validation set, the higher the likelihood that the concordance estimate reflects the “true” performance of a test.”

Availability of controls/cases, use in panel or stand alone, experience of lab, cost ?

Validation & verification : How ?

- Determine number of samples/cases/controls : Belgian guidelines CE-IVD

CE-IVD volgens bijsluiter of gewijzigde CE-IVD MET referentie												
INITIEEL MET ERVARING ¹ OF HISTORISCH							INITIEEL ZONDER ERVARING ¹					
		Juistheid ²	Precisie ^{2,3}		Robuustheid ²	Andere ^{2,4}		Juistheid ²	Precisie ^{2,3}		Robuustheid ²	Andere ^{2,4}
			Intra	Inter					Intra	Inter		
3 IHC/ISH Type 1 panel 15 AL (methodevalidatie)	perAL AC ^o	5s (+) 5s (-) ≥ 90%	3s x 3gl ⁵ (1 AL) ≥ 90%	3s x 3gl ⁵ (1 AL) ≥ 90%		I/U/S/A/T : > X	perAL AC ^o	10s (+) 10s (-) ≥ 90%	3s x 3gl ⁵ (1 AL) ≥ 90%	3s x 3gl ⁵ (1 AL) ≥ 90%		I/U/S/A/T : > X
IHC/ISH Type 1 vanaf 16de AL	perAL AC ^w	2s (+) 2s (-) ≥ 75%				I/U/S/A/T : > X	perAL AC ^w	2s (+) 2s (-) ≥ 75%				I/U/S/A/T : > X
4 IHC/ISH Type 2a (specifieke verificatie/validatie)	Initiële matrix AC ^d	7s (+) 7s (-) ≥ 90% ¹⁰	3s x 3gl ≥ 90%	3s x 3gl ≥ 90%	5s(+) 5s(-) ≥ 90%	I/U/S/A/T : > X 5s(+) en 5s(-) interobserver ≥ 90%	Initiële matrix AC ^d	15s(+) 15s (-) ≥ 93% ¹⁰	3s x 3gl ≥ 90%	3s x 3gl ≥ 90%	5s(+) 5s(-) ≥ 90%	I/U/S/A/T : > X 5s(+) en 5s(-) interobserver ≥ 90%
IHC/ISH Type 2b	Initiële matrix AC ^w	10s (+) 10s (-) ≥ 90% ¹⁰	3s x 3gl ≥ 90%	3s x 3gl ≥ 90%	5s(+) 5s(-) ≥ 90%	I/U/S/A/T : > X 5s(+) en 5s(-) interobserver ≥ 90%	Initiële matrix AC ^w	20s(+) 20s (-) ≥ 95% ¹⁰	3s x 3gl ≥ 90%	3s x 3gl ≥ 90%	5s(+) 5s(-) ≥ 90%	I/U/S/A/T : > X 5s(+) en 5s(-) interobserver ≥ 90%

Experience

No experience

- ISO15189 based quality management system
- Emphasis shift to ongoing validation (e.g. IQC)

Taking into account : experience of a lab, availability controls, achievability, costs, etc

(*) Belgian Recommendations for Analytical Verification and Validation of Immunohistochemical Tests in Laboratories of Anatomic Pathology - PMC (nih.gov)
App Immunohistochem Mol Morphol - 2023

Validation & verification : How ?

1. Plan and prepare practical execution

- Determine **type of samples/cases/controls**
 - Related to purpose – intended use of test (IFU) (e.g. specific tissue type)
 - Controls (preferably “in house” = same processing)
 - Known patient cases
 - Different expression levels (weak/moderate/strong), different tissue types, etc
 - Single piece samples
 - Sausage blocks or multi-tissue blocks, Tissue Micro Array (TMA), etc
 - Same processing as clinical samples in daily routine (preferably)

Slides/cases preparation according to manufacturer/guidelines + storage before and during validation !

Validation & verification : How ?

2. Selection of protocol/method to be used for verification/validation

- Starting point : default protocol according to IFU + selection of appropriate controls/cases
- Evaluation of staining :

Tip!

Use of a scoring system can help guide further optimization/calibration

Stainingcriteria	Score			
Intensity	0 (none)	1 (weak)	2 (average)	3 (strong)
Uniformity	0 (none)	1 (uniform)	-	-
Specificity	0 (none)	1 (specific)	-	-
Absence of	0	1	2	
backgroundstaining	(strong)	(average)	(none)	-
Counterstaining	0	1	-	-
	(inadequate)	(adequate)		
Totaal				

Optimal	
Good	Comment
Weak	Comment

- Stain/method OK : proceed to verification/validation
- Stain not OK : optimize/calibrate untill ok

! Method optimization within IFU = verification
Method optimization outside IFU = validation



Validation & verification : How ?

3. Performing stainings

- ❖ Default protocol according to IFU or optimized protocol used to stain verification or validation set/cases
 - Select cases, controls, etc
 - Prepare necessary cases according to IFU or guidelines (time, temperature, storage)
- ❖ Perform stains required to evaluate performance characteristics
 - ❖ Staining runs (accuracy, sensitivity, specificity, etc)
 - ❖ Staining runs within run precision
 - ❖ Staining run in between run precision
 - ❖ Robustness, etc

Validation & verification : How ?

4. Evaluation of stainings

- ❖ Compare staining results from default protocol according to IFU or optimized protocol with staining of reference / comparator for selected performance characteristics

Document staining results :

- List up, use 2 x 2 matrix, etc
- Paper, Excel, etc
- ❖ Evaluate / determine / calculate performance characteristics

	Reference (+)	Reference (-)	Total
New (+)	TP	FP	
New (-)	FN	TN	
Total			

5. Conclusion & signing off

- ❖ Acceptance criteria for performance characteristics met ?
YES = OK for use in daily / clinical practice
- ❖ Sign of by e.g. lab director, pathologist, quality manager

Validation & verification : How ?

6. Implementation

❖ Staff competence and autorisation

Competence	<u>3 steps to ensure competence :</u> • Introduction - demonstration • Initiation – guided practice • Perfecting – independent execution	Objective evidence provided Traceability (e.g. paper forms, staining platform software, LI(M)S) etc
Autorisation	Specific tasks (e.g. verification/validation)	Authorized by e.g. lab director

ISO15189 : 2022

6.2.2 Competence requirements

6.2.3 Authorization

Validation & verification : How ?

6. Implementation

- ❖ Procedures
- ❖ Communication to prescribing clinicians e.g. in case of changed method with impact on interpretation of results, impact on treatment, etc
- ❖ Logistics :
 - Ordering information, stock, etc
 - Switch in software staining platform to validated status/ diagnostic use, etc
 - Laboratory Information System (LIS) : e.g. bidirectional connection to (software) staining platform for automatic entering of task

Validation & verification : How ?

Summary

Step 1	Plan & prepare	Information about Ab, guidelines, etc Plan verification/validation : selection of appropriated cases/controls, prepare necessary slides, etc
Step 2	Selection method/protocol	Default method (IFU) vs acceptance criteria Additonal optimization (within IFU or not)
Step 3	Perform stainings	Use selected method/protocol Perform according to performance criteria / set up/plan
Step 4	Evaluation of staining results	Evaluation of selected performance criteria
Step 5	Conclusion & signing off	Acceptance criteria for selected performance criteria
Step 6	Implementation	Staff competence & autorisation Procedures, logistics, etc

Validation & verification : How ?

Practical example : HER-2 conc Ab

- Select reagent and determine intended use (e.g. breast, stomach)
- Check literature – Instructions For Use – recommended controls, etc
- Determine comparator test : Roche HER-2 (4B5)
- Validation plan : determine performance criteria & acceptance criteria

Code	Performance criteria – breast tissue	Expected result
FLEX – 15	Accuracy	Stain quality – accuracy >95% (equal to comparator)
FLEX – 16	Precision	Precision : Correlation within en between run >95%
FLEX – 17	Sensitivity	Sensitivity : >90 % (diagnostic positive vs false negative)
FLEX – 18	Specificity	Specificity : >95% (diagnostic negative vs false positive)
FLEX – 19	Staining quality	Stain quality score ≥ 7
FLEX – 20	Interpretation - readout	Readout – interpretation >90%
FLEX – 21	Interobserver	Interobserver tuning > 95%
FLEX – 22	Ongoing – Internal Quality Control	Available internal quality control (IQC) system
FLEX – 23	Documentation - IFU	Instructions For Use available (IFU)
FLEX – 24	Robustness – Cold Ischemia Time	Cold ischemic time <1h
FLEX – 25	Robustness – Fixation time	Fixationtime between 6 – 72h
FLEX – 26	Robustness - Overfixation	Robustness technique for fixationtime >72u
FLEX – 27	Robustness – storage of sections	Storage of paraffin sections determined, minimal 1w
FLEX – 28	Robustness – Mounting of sections	Mounting sections : max 1h at 60°C

Validation & verification : How ?

Practical example : HER-2 conc Ab (Agilent A0485)

- Select appropriate number of cases/controls
- Prepare slides/cases/controls
- Selection of method/protocol to be used for verification

Antilichaam	Kloon	Fabrikant	Referentienummer	☒ Nieuw	☐ Gewijzigd, reden
HER-2	c-cb-32 <i>Poly</i>	Jako	A0485 (picom-Ab) <i>c-cb-2</i>	<i>Omhu</i>	

STANDAARDPROTOCOL BORST Uitvoerder :*mv. l. p. l.*..... Datum : *17.10.12* Controleblok : *HER-2*
MCB/2013-06

Default protocol (IFU)

Antilichaam				Voor-behandeling			Detectie kit		Intensiteit (0-3)	Uniformiteit (0-1)	Specificiteit (0-1)(*)	Afwezigheid Achtergrond (0-2)	Tegenkleuring (0-1)	Totaal
Lotnummer	Vervaldatum	Verdunning	Tijd	Oplossing	Tijd	Temperatuur	Lotnummer	Vervaldatum						
<i>Leo 73783</i>	<i>10.1.12</i>	<i>1/1000</i>	<i>20'</i>	<i>TRIS High</i>	<i>30'</i>	<i>97°C</i>	<i>Leo 73770</i>	<i>2011/02/28</i>	<i>3</i>	<i>1</i>	<i>1</i>	<i>2</i>	<i>1</i>	<i>8</i>

Acceptance : score ≥ 7

Meets Acceptance criteria = method to be used for verification

Validation and Verification : How ?

POSITIEF	REK	Staalnr + MCB HER-2	Intensiteit (0-3)	Uniformiteit (0-1)	Specificiteit (0-2) (*)	Afwezigheid Achtergrond (0-2)	Tegenkleuring (0-1)	TOTAAL	Initiële beoordeling	HER-2 score Initieel	HER-2 score patholoog 1	HER-2 score patholoog 2	Correlatie
1	20	18B1051	Stain quality evaluation						2	2			OK
2	20	18B11251	3	1	1	2	1	8	AVC	2	2		OK
3	20	18B11382	1-3	1	1	2	1	8	DA	2	2		
4	19	18B206611	3	1	1	2	1	8	AVC	3	3		
5	19	19B728	1-3	1	1	2	1	8	DA	3	3	3	OK
6	25	18B4440	3	1	1	2	1	8	AVC	3	3		OK
7	19	18B10322	1-3	1	1	2	1	8	DA	3	3		OK
8	19	18B8433	3	1	1	2	1	7	AVC	3	2		OK
9	27	19B3153	1-3	1	1	2	1	8	DA	3	3		OK
10	27	18B5782	3	1	1	2	1	8	AVC	3	3		OK
11	25	19B5909	1-3	1	1	2	1	8	DA	3	3	3	OK
12	25	18B8292	1-3	1	1	2	1	8	AVC	3	3		OK
13	25	19B4281	1-3	1	1	2	1	8	DA	3	3		OK
14	27	19B7113	1-3	1	1	2	1	8	DA	2	2		OK
15	28	20B2941	1-3	1	1	2	1	8	DA	2	2		
16	27	19B7531	3	1	1	2	1	8	DA	3	3		
17	21	19B7029	1-3	1	1	2	1	8	DA	3	3		OK
18	20	18B10069	2	1	1	2	1	8	AVC	2	2		OK
19	20	18B6937	1-3	1	1	2	1	8	DA	2	2		
20	21	18B8490	3	1	1	1	1	8	AVC	2	2		OK

Verification HER-2 Breast

Omnis HER-2 poly
CE-IVD according to IFU
Reference Roche HER-2 (4B5)

Readout validation pathologists

True positive (TP)

Comparator/reference

Validation and Verification : How ?

NEGATIEF	REK	Staalnr + MCB HER-2	Intensiteit (0-3)	Uniformiteit (0-1)	Specificiteit (0-3) (*)	Afwezigheid Achtergrond (0-2)	Tegenkleuring (0-1)	TOTAAL	Initiële beoordeling	HER-2 score Initieel	HER-2 score patholoog 1	HER-2 score patholoog 2	Corelatie
Stain quality evaluation													
1	19	19B3991	2-3	1	1	2	1	8	IDA	1	1		OK
2	27	19B338	2-3	1	1	2	1	8	IDA	1	1-2		OK
3	22	19B5998	2-3	1	1	2	1	8	IDA	2	1-2		OK
4	23	19B1324	2-3	1	1	2	1	8	IDA	1-2	2	1-2	OK
5	22	19B4689	2-3	1	1	2	1	8	IDA	2	2	2	OK
6	23	19B4685	2	1	1	2	1	7	AVC	2	1-2		OK
7	23	194439	2-3	1	1	2	1	8	IDA	2	2(3?)	2	OK
8	23	19B3445	3	1	1	2	1	8	AVC	2	2		OK
9	23	19B3479	2-3	1	1	2	1	8	IDA	2	2	2	OK
10	22	19B2441	2-3	1	1	2	1	8	AVC	2	2		OK
11	18	19B2582	2-3	1	1	2	1	8	IDA	1	1	1	OK
12	21	18B9620	3	1	1	2	1	8	AVC	1	1		OK
13	15	18B10825	2-3	1	1	2	1	8	IDA	1			OK
14	15	18B11493	2	1	1	2	1	7	AVC	1			OK
15	15	19B11067	2-3	1	1	2	1	8	IDA	1	1		OK
16	15	18B9210	3	1	1	2	1	8	AVC	1	1		OK
17	21	18B9579	2-3	1	1	2	1	8	IDA	1	1	1	OK
18	15	18B9346	2	1	1	2	1	7	AVC	1	1		OK
19	21	18B10120	2-3	1	1	2	1	8	IDA	1	1		OK
20	22	19B9304	2-3	1	1	2	1	8	IDA	2	2		OK

Verification HER-2 Breast

Omnis HER-2 poly
CE-IVD according to IFU
Reference Roche HER-2 (4B5)

Readout validation pathologists

Comparator/reference

True negative (TN)

Validation and Verification : How ?

	Positie/slide	Op basis van MCB HER-2 nr uiter pos en neg reeks	Intensiteit (0-3)	Uniformiteit (0-1)	Specificiteit (0-4) (*)	Afwezigheid Achtergrond (0-2)	egenkleuring (0-1)	TOTAAL	Initialen beoordeler	
Stain quality evaluation										
Rack 1	WITHIN									
	REK1 (19)	1	19B2066	3	1	1	2	1	8	AVC
		2	18B10322	2-3	1	1	2	1	8	IDA
		3	19B3396	2-3	1	1	2	1	8	IDA
		4	18B8433/1	3	1	1	1	1	7	AVC
Rack 2		5	19B728	2-3	1	1	2	1	8	IDA
	REK2 (20)	1	18B10069	2	1	1	2	1	8	AVC
		2	18B1382	2-3	1	1	2	1	8	IDA
		3	18B11252	3						
		4	18B11057	2-3						
Rack 3		5	18B6938	2-3						
	REK3 (21)	1	18B10100	2-3						
		2	18B9579	2-3						
		3	18B9620	3	1	1	2	1	8	AVC
		4	19B7029	2-3	1	1	2	1	8	IDA
BETWEEN		5	18B21400	3	1	1	2	1	8	AVC
	REK4 (22)	1	19B7431	3	1	1	2	1	8	IDA
		2	19B5782	3	1	1	2	1	8	AVC
		3	19B7113	2-3	1	1	2	1	8	IDA
		4	19B3153/2	2-3	1	1	2	1	8	IDA
		5	19B33872	2-3	1	1	2	1	8	IDA

Tip!

On slide control

Within run within 1 rack

Tip!

On slide control

In between run over 3 racks

Verification HER-2 Breast

Omnis HER-2 poly
CE-IVD according to IFU
Reference Roche HER-2 (4B5)

Validation & verification : How ?

	Omnis HER-2 Poly (+)	Omnis HER-2 Poly (-)
Roche HER-2 4B5 (+)	TP	FN
Roche HER-2 4B5 (-)	FP	TN

	Omnis HER-2 Poly (+)	Omnis HER-2 Poly (-)
Roche HER-2 4B5 (+)	20	0
Roche HER-2 4B5 (-)	0	20

	Stain Quality Mean
20 (+)	7,95
20 (-)	7

Acceptance min 7 OK

Other : robustness, etc

	Reproducibility
Within run	100%
In between run	100%

Acceptance $\geq 95\%$ OK

Verification HER-2 Breast

- Omnis HER-2 poly
- CE-IVD according to IFU
- Reference test Roche HER-2 (4B5)

Evaluation :

Sensitivity : $TP / (TP + FN)$

$$20 / (20 + 0) = 1 = 100\%$$

Acceptance $> 90\%$ OK

Specificity : $TN / (TN + FP)$

$$20 / (20 + 0) = 1 = 100\%$$

Acceptance $> 90\%$ OK

Validation & verification : How ?

Code	Expected result	Result	Evaluation
FLEX – 15	Stain quality - accuracy	Results accurate (equal to reference technique)	OK
FLEX – 16	Precision : Correlation within en between run >95%	HER-2 poly - Omnis : precision 100%	OK
FLEX – 17	Sensitivity : >90 % (diagnostic positive vs false negative)	HER-2 poly – Omnis : sensitivity = 100%	OK
FLEX – 18	Specificity : >95% (diagnostic negative vs false positive)	HER-2 poly – Omnis : specificity = 100%	OK
FLEX – 19	Stain quality score ≥ 7	Stain quality mean score 7,95 (positive) and 7 (negative)	OK
FLEX – 20	Readout – interpretation >90%	Correlation with reference technique = 100%	OK
FLEX – 21	Interobserver tuning	Correlation between pathologists = 100%	OK
FLEX – 22	Available internal qualitycontrol (IQC)	System for IQC available and operational	OK
FLEX – 23	Instructions For Use available (IFU)	IFU online available	OK
FLEX – 24	Cold ischemic time <1h	Cold ischemic time < 1u in >90% of cases	OK
FLEX – 25	Fixationtime between 6 – 72h	Verified fixationtime >90% of cases between 6-72h	OK
FLEX – 26	Robustness technique for fixationtime >72u	Technique can handle >72u fixation	OK
FLEX – 27	Storage of parafin sections	Storage of prepared parafin sections limited to 1 week at RT°.	OK
FLEX – 28	Mounting sections	Drying time and temperature max 1u op 60 °C (or overnight at RT°)	OK

Verification HER-2

Breast

- Omnis HER-2 poly
- CE-IVD according to IFU
- Reference Roche HER-2 (4B5)

Signed of for clinical use in daily practice



Validation & verification : How ?

- Validation and verification process : completion !?
 - Performed stains and compared results with comparator test
 - Acceptance criteria for performance characteristics are met
 - Implemented the validated method successfully



Job done ?



What have we proven so far ?

Validation & verification : what has been proven so far ?

- Validation : captures a moment in time **when limited to the initial validation**
- It only proves a test fulfills the requirements
 - At a certain point in time
 - Using certain lotnumbers of reagents
 - Performed on a staining platform in a certain condition (e.g. new)
 - Performed and evaluated by certain staff
 - etc

Validation & verification : what has been proven so far ?

- HOWEVER :

- Reagent lotnumbers vary
- Staining platforms evolve over time (impact maintenance, wear, defects, etc)
- Change in samples : pre-analytics, fixation, processing
- Change in staff, pathologists
- Etc

➡ These changes may impact IHC quality

NO 100% guarantee on daily quality if limited to the initial validation !

Validation & verification : what has been proven so far ?

- THEREFORE :

- Implementation of ongoing validation (maintaining a validated state): safeguards daily quality to a higher degree (= continuous monitoring on daily basis)

- Internal quality control : daily – on slide (batch)
- Participation in EQA programs
- Inter observer tuning – especially for typ 2 IHC
- Correlation studies with other methods : e.g. HER-2 IHC vs HER-2 ISH

- Acceptance testing for critical reagents & consumables
- Acceptance testing for instruments after repair, maintenance

Changes in validated methods?

Which changes require a re-validation/verification ?

Changes in an already validated method ?

- IHC Ab/method that are verified/validated and **used in daily practice** (Quality Management System) :
 - IQC : Acceptance criteria defined & evaluated
 - EQC : Score/evaluation from EQA provider (+ comments if applicable)
Acceptance criteria defined by lab for EQA participation
- Acceptance testing reagents (e.g.new lotnumber/shipment) : defined & evaluated
- Acceptance testing instruments (e.g. after repair) : defined & evaluated

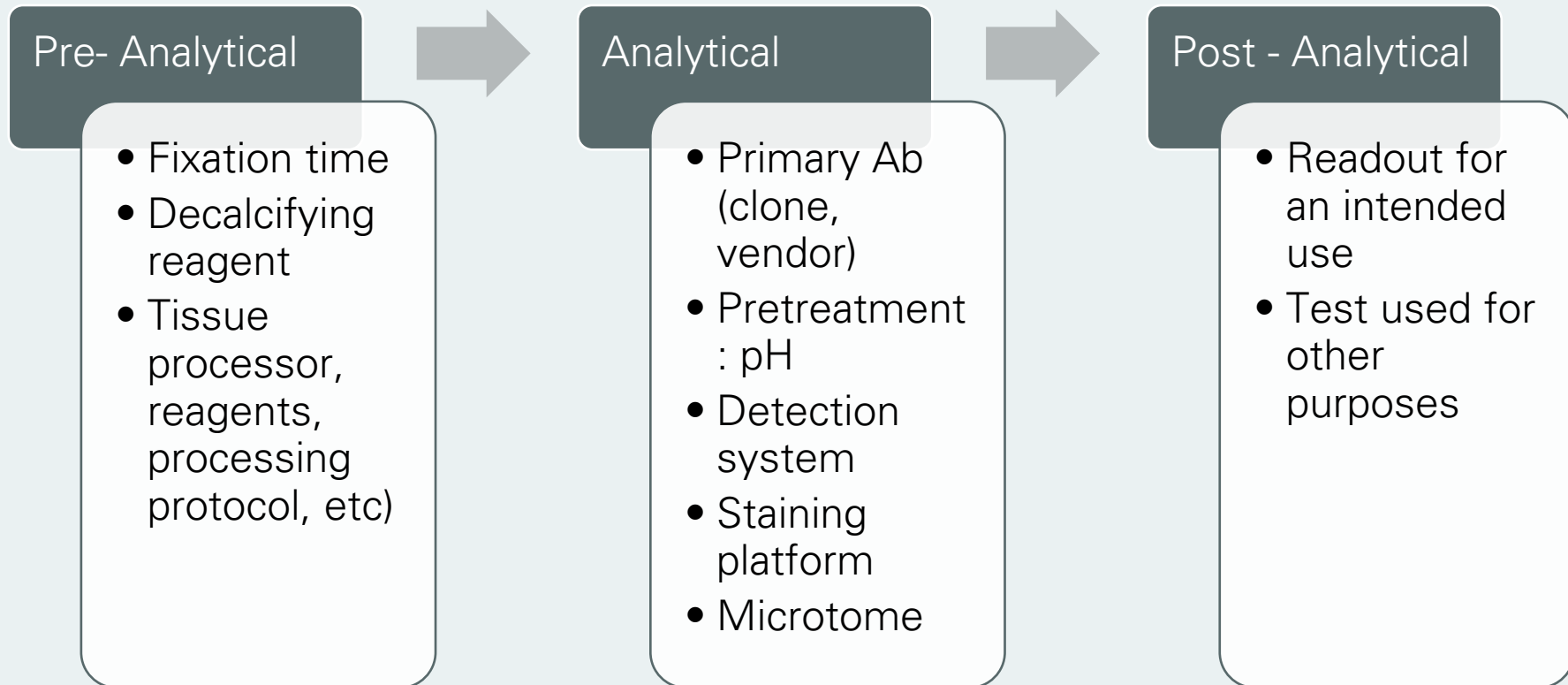
 Fail to meet acceptance criteria



Analyse possible cause  new optimization  Verification/validation

Changes in an already validated method ?

- Process/method changes that can trigger additional verification/validation :



Changes in an already validated method ?

- IHC Ab/method re- validation : guidelines ?
 - E.g. CAP guidelines for number of samples in re-validation set :

Change	Verification - Validation
New reagent lot for existing validated assay (*)	Confirm assay performance using 1 (+) and 1(-)
Antibody dilution, antibody vendor (same clone), Incubation or retrieval times (same method)(* *)	Confirm assay performance using at least 2 (+) and 2(-)
Fixation type, antigen retrieval method (change pH, different buffer, different heat platform), detection system, tissue processing or testing equipment, relocation, water supply	Confirm with sufficient number of cases to ensure assay consistently achieves expected results Labdirector decides on how many predictive and non predictive markers, how many (+) and (-) tissues to test
Antibody clone	Full revalidation(equivalent to initial analytic validation)

(*) Equals acceptance testing (ISO15189)

(**) Ab vendor – same clone : Ab concentrations may vary !

Changes in an already validated method ?

- IHC Ab/method re- validation : guidelines ?
 - E.g. CAP guidelines for number of samples in re-validation set :

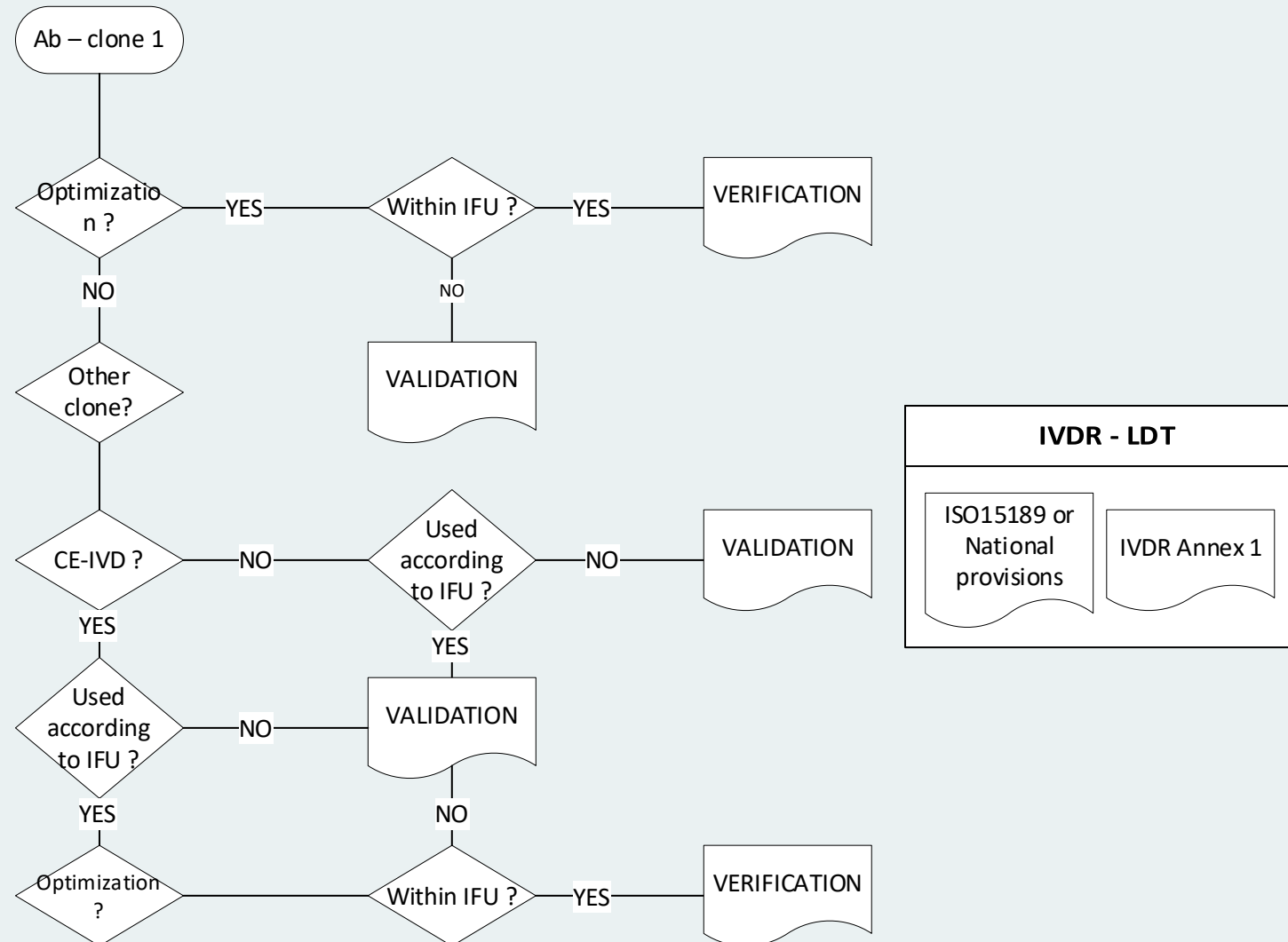
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Fixation type, antigen retrieval method (change pH, diferent buffer, different heat platform), detection system, tissue processing or testing equipment, relocation, water supply	Confirm with sufficient number of cases to ensure assay consistently achieves expected results Labdirector decides on how many predictive and non predictive markers, how many (+) and (-) tissues to test
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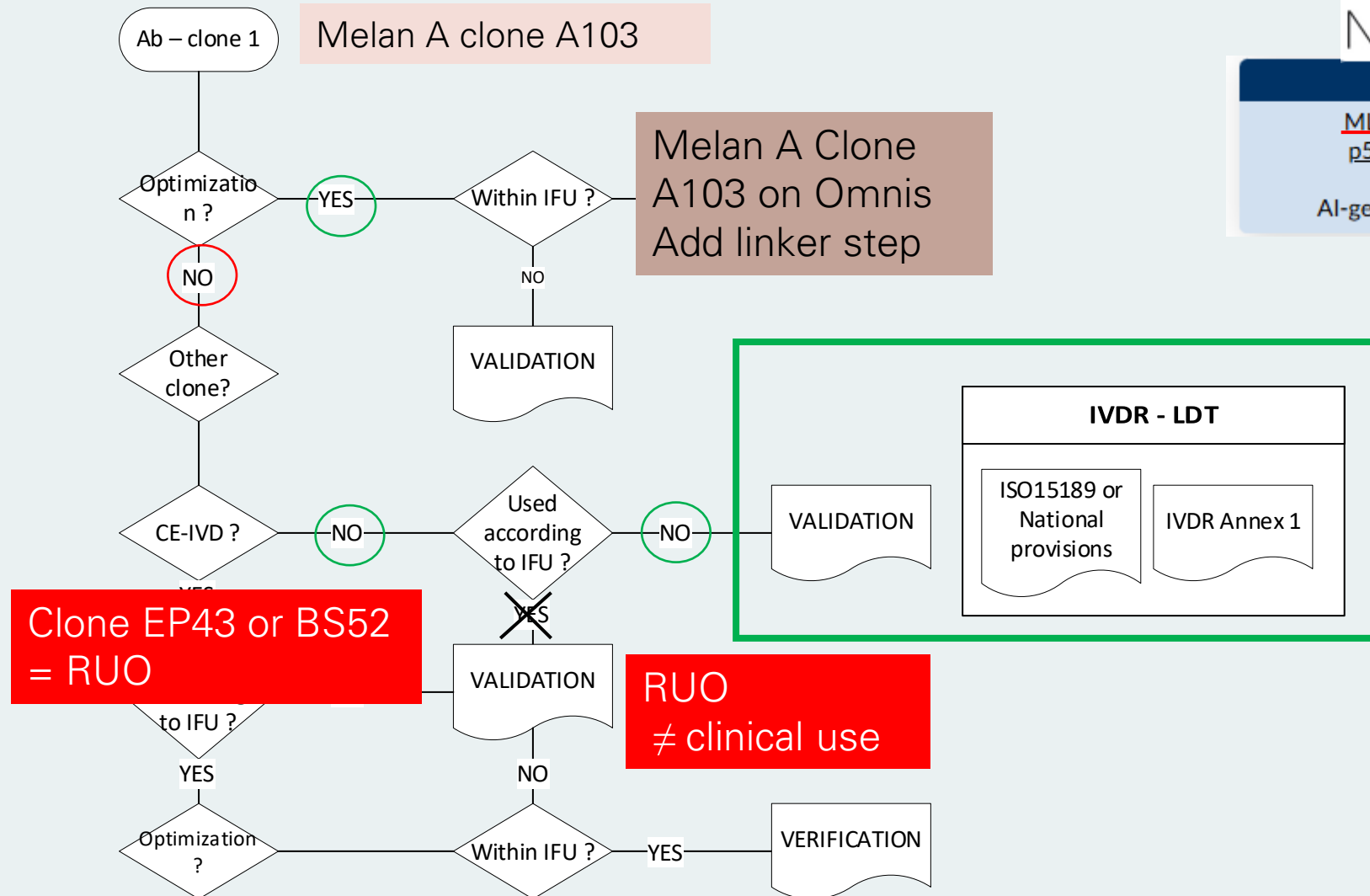
Changes in an already validated method ?

- My Ab clone fails on EQA ?



Changes in an already validated method ?

- My Ab clone fails on EQA ?



Podcasts

MLA run 74 podcast
p53 run 70 podcast

AI-generated by NordiQC

Changes in an already validated method ?

- My Ab clone fails on EQA ?
 - EU - IVDR : CE-IVD = first choice reagent !
 - Re-validation of test with change from CE-IVD to RUO
 - Used in clinical setting $\neq$ Instructions For Use of RUO reagent
 Lab Developed Test according to IVDR
 - Requires validation and additional documentation & registration
- Validation : preferably on same cases/samples used for CE-IVD or split sample on both CE-IVD & RUO
 - Demonstrate performance RUO vs CE-IVD
 - Document

Changes in an already validated method ?

1 No transfer to another legal entity

IVDR Art 5. 5- LDT

- 2
- Used under **Quality Management System**
 - Fullfils **ISO15189** requirement or appropriate national guidelines regarding accreditation
 - Information of **manufacturing, modification, use** upon request to **competent authority**
 - Public **declaration** to competent authority
 - **Documentation** on manufacturing process, performance data, intended purpose to comply to **Annex 1 – for class D or C & D**
 - Review experience + corrective actions

Annex 1 (Class C or D)

- Risk management plan
- Risk management (risk/benefit ratio)
- Performance + follow up
- Documentation manufacturing process
- Labelling

-
- 3 **Justification** of the **use of LDT**
- Specific needs of patient population
 - No CE-IVD available that fullfils requirements of performance criteria
- Periodic **review of availability CE-IVD**
(EUDAMED database)

IVDR – LDT : PLAG-1 (RUO)

ISO 15189 : 2022 & National guidelines



Certificat d'Accréditation n° 580-MED

En application des dispositions de l'arrêté royal du 31 janvier 2006 créant BELAC, le Bureau d'Accréditation atteste avoir délivré une accréditation conformément aux exigences de la norme EN ISO 15189:2022 à:

A.Z. SINT-LUCAS vzw
Sint-Lucaslaan 29
8310 Brugge



Praktijkrichtlijn voor het opzetten van een
kwaliteitssysteem in de erkende laboratoria voor
pathologische anatomie werkzaam binnen het k
van het Erkeningsbesluit

(in toepassing van het KB van 5 december 2011)

Public declaration & registration competent authority

Mijn hulpmiddelen
Kennisgevingen van fabricage en herverwerking



Mijn hulpmiddelen beheren

Mijn hulpmiddelen

Gevalideerd 0 Gestopt 0 Te corrigeren 0 Te valideren 1

Toevoegen

FAGG notificatie code Marktdelnemer Naam hulpmiddel Notificatietype Risicoklasse
Zoek op identificatiecode FAG Zoek op marktdelnemer Zoek op naam van het hulpmi
A.Z. SINT-LUCAS PLAG1 Antilichaam (kloon 3B... In-house IVDR Klasse IVDR C

1 resultaat(en)

Validation (performance) + Art 5.5 requirements (summary)

Risk management plan + risk/benefit assessment

Code	Processtap	Falen	Gevoig	Kans*	Effect*	Risico graad	Detectie*
	Wijziging beoogd gebruik/doel						
	❖ Ander beoogd gebruik dan vermeld in bijsluiter						
IVDR 1A	Uitbereiding met referentie						
IVDR 1B	Uitbereiding zonder referentie						
IVDR 1C	Beperking met referentie						
IVDR 1D	Beperking zonder referentie						

Justification use LDT

FORMULIER Pathologische anatomie

IVDR sjabloon - motivering gebruik LDT Middelen

Naam reagens	Fabrikant	Referentie
❖ MDCG 2022-6 classificatie wijziging		
☐ Beoogd doel	☐ Beperking ☐ Uitbereiding ☐ Andere (specimen type)	JA NEE
		☐ NS ☐ NS ☐ S ☐ NS ☐ S ☐ NS
☐ Ontwerp	☐ Testprincipe gewijzigd ☐ Negatief effect op veiligheid/performance of risico/voordeel verhouding	JA NEE
		☐ S ☐ NS ☐ S ☐ NS
☐ Ingrediënten of materialen	☐ Essentieel voor testprincipe ☐ Negatief effect op veiligheid/performance of risico/voordeel verhouding	JA NEE
		☐ S ☐ NS ☐ S ☐ NS
☐ Software	Besturingssysteem, database (geen bugfix, security update, etc)	JA NEE
		☐ S ☐ NS ☐ S ☐ NS
☐ Steriliteit of verpakking	☐ Impact op steriliteit van het product ☐ Gewijzigde verpakking met impact op steriliteit product	JA NEE
		☐ S ☐ NS ☐ S ☐ NS
☐ Gevolg van CAPA	☐ CAPA beoordeeld en geaccepteerd door competente autoriteit	JA NEE
		☐ NS ☐ S

☐ Significante/ majeure wijziging (minimaal 1 x JA (S)) ☐ Niet significante / mineure wijziging (alles NS)

❖ Wijziging beoogd doel of type staal

Beoogd doel volgens originele bijsluiter	Beoogd doel als LDT
Type staal volgens originele bijsluiter	Type staal als LDT
☐ FFPE ☐ Andere :	☐ FFPE ☐ Andere

Conformity IVDR Annex I

FORMULIER Pathologische anatomie

IVDR – Checklijst conformiteit Annex 1 Middelen

Reagens	Referentie	Fabrikant	Klasse
☐ A ☐ B ☐ C ☐ D			
❖ Algemene eisen			
Item	JA	NEE	Opmerking
Risicomanagement			
☐ Risico management plan			
☐ Risicobepaling			
Risico beheersende maatregelen			
☐ Risicobeperkende maatregelen			
☐ Mitigeren of veilig ontwerp/productie			
☐ Evaluatie bv IQC, EQC, etc			
☐ Bijkomende veiligheidsinfo of opleiding			
☐ Informatie voor gebruiker i.v.m. restrisico			
☐ Opvolging efficiëntie maatregelen			
☐ Restriscio aanvaardbaar ?			

IVDR – LDT : PLAG-1



ISO 15189 : 2022 & National guidelines 



Risk management plan + risk/benefit assessment 



Organisme belge d'Accréditation
Belgische Accreditatieinstelling
Belgische Akkreditierungsstelle
Belgian Accreditation

EA MLA Signatory

So

Risico - FMEA IVDR klasse C wijzigingen buiten bijsluiter Management

Some remarks with RUO and IVDR ...

- ❖ Lab : Switch from CE – IVD to RUO + additional requirements as to documentation, etc ?
Does performance for patient overcome additional documentary burden ?
Knowledge, dedicated staff, means to do so ?
- ❖ Manufacturer : Taking the effort of creating a CE-IVD certified reagent or go for RUO with less requirements or get the product out of the market ?
- ❖ EU – IVDR : IVDR still not fully operational
Many “grey areas”, uncertainties, etc
Still in line with initial goal to improve quality with IVD ?

Are we “over-regulating” , finally resulting in less quality instead of more ?
How much patient benefits are left in the current regulations/demands ?

FAGG notificatie code	Marktaandeelner	Naam hulpmiddel	Notificatietype	Risicoklasse	Acties
Zoek op identificatiecode FAG	Zoek op marktdeelnemer	Zoek op naam van het hulpmi	In-house IVDR	Klasse IVDR C	Acties
1 resulta(a)t(en)					

☐ Significant(e) majeure wijziging (minimaal 1 x JA (S))		☐ Niet significant(e) / <u>mineure</u> wijziging (alles NS)	
♦ Wijziging beoogd doel of type staal			
Beoogd doel volgens originele bijsluiter		Beoogd doel als LDT	
Type staal volgens originele bijsluiter		Type staal als LDT	
☐ EFBE, ☐ Andere		☐ EFBE, ☐ Andere	

☐ Evaluatie bv IQC, EQC, etc.			
☐ Bijkomende veiligheidsinfo of opleiding			
☐ Informatie voor gebruiker i.v.m. restrisico			
☐ Opvolging efficiëntie maatregelen			
☐ Restrisico aanvaardbaar?			

CG 2022-6.

Risico graad	Detectie

Klasse
☐ A ☐ B ☐ C ☐ D

[illegible]

Take home messages

Validation – Verification : WHAT ?

- ❖ Demonstrating a test performs as it needs to or is intended for
- ❖ Key elements : Comparator/reference – performance characteristics – acceptance criteria
- ❖ Difference verification – validation determined by :
Type of test – used according to IFU – for intended purpose

Validation – Verification : WHY?

- ❖ Legal/ISO15189 accreditation – IVDR - Technical

Validation – Verification : HOW?

- ❖ Staining platform : IQ – OQ – PQ (overlap method validation)
- ❖ Type of test – intended use : verification or validation
- ❖ Select cases/controls, prepare slides & perform staining
- ❖ Evaluate performance characteristics & acceptance criteria
- ❖ Signed off for use in daily practice + Practical implementation
- ❖ Ongoing validation (IQA, EQA, etc) = continuous monitoring

Validation – Verification : Changes?

- ❖ Pre-analytical – Analytical
- ❖ Additional optimization – verification/validation
- ❖ Additional documentation (IVDR – LDT)

Thank you !

I welcome any questions or
comments

Email : donald.vanhecke@stlucas.be