



UMC Utrecht

# Erfahrungsbericht aus den Niederlanden zur IVDR-Umsetzung

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# Impact IVDR – many questions, few answers

- The impact for laboratories is potentially enormous
- No insight into consequences for laboratories



# Dutch IVDR task force



Clinical Chemistry



Laboratory specialists from all disciplines



Genetics



Medical Immunology

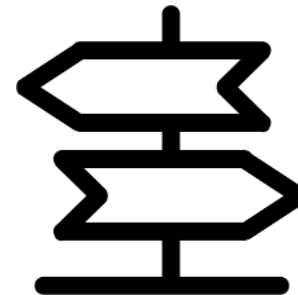


Pharmacy



# AIMS task force

- Raise awareness among decision makers (Ministry of Health, Welfare and Sport; Health and Youth Care Inspectorate; Management Boards, health insurance companies)
- Create sense of urgency among laboratory specialists
- **Provide tools/ develop guidelines (article 5, section 5) for (laboratory) professionals**



# How do we work?

- Meet and discuss IVDR
- Communication with / ask for input from professionals via professional associations
- Participate in meetings organized by Ministry of Health
- Participate in meetings organized by other stakeholders (Federation of Dutch Universities, National NEN committee, patient organizations)



# Create sense of urgency

- September 2019 flyer to all laboratory specialists:
- Take home messages:
  - Laws state WHAT to do – not HOW to do!
  - Don't expect that the IVD regulation will be postponed
  - Don't expect that The Dutch Government will not strictly follow European Regulations
  - You are yourself responsible for compliance to IVDR
- Task force will develop tools and guidelines to help you



# Guideline for interpretation

- Focus on **Lab-Developed Tests**
- IVD Regulation 2017/746, article 5, section 5 and Annex I:

*“With the exception of the relevant general safety and performance requirements set out in Annex I, the requirements of this Regulation shall not apply to **devices manufactured and used only within health institutions** established in the Union, provided that all of the following conditions are met...”*



# Guideline for interpretation

IVD Regulation 2017/746, article 5, section 5 and Annex I

- *Only applicable to devices NOT produced on industrial scale*
- In general, lab-developed tests are not applied on an industrial scale
  - Precise definitions of the scope / criteria regarding 'industrial scale' are currently not clearly specified in the law





# Definition of lab-developed test

1. In-house developed and manufactured
2. Research-use only test used for in-vitro diagnostics
3. IVD certified test used with modification



# Definition of lab-developed test

- Minor modification to IVD certified test should be possible without losing IVD mark i.e.:
  - Dilutions
  - Reaction time
- Modifications shall be justified and documented according to ISO 15189
  - i.e. additional validation
- Exception for modification made to individual samples necessary to answer clinical question
  - i.e. different matrix
  - Document that test has not been performed under ISO 15189



# Tools

Laboratory	Test	Subtest/reagent	Reagent / kit/ software/ hardware	Manufacturer	Order number	IVD (CE)	Categorie	What type of modification if 2
						Yes	1	
						Yes	2	
						No	3	
						No	4	

Take stock of laboratory tests currently in use (IVDR compliant?)

1. IVD, used according to manufacturer's instruction ✓
2. IVD, used with major modifications -> switch to IVD /  
potentially lab-developed test
3. Not IVD (home made/RUO), IVD alternative available -> switch  
to IVD / potentially lab-developed test
4. Not IVD (home made/RUO), no IVD alternative available -> lab-  
developed test



# Guideline

- IVD Regulation 2017/746, article 5, section 5 and Annex I
- *“With the exception of the relevant general safety and performance requirements set out in **Annex I**, the requirements of this Regulation shall not apply to devices manufactured and used only within health institutions established in the Union, provided that all of the following conditions are met:...”*
- Annex I:
  - General requirements
  - Requirements regarding performance, design and manufacture
  - Requirements regarding information supplied with the device



# Guideline – Link Annex I to ISO15189

ANNEX I		ISO-15189	Comments
	CHAPTER 1		
	GENERAL SAFETY AND PERFORMANCE REQUIREMENTS		
1	Devices shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose. They shall be safe and effective and shall not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety, taking into account the generally acknowledged state of the art.	General	
2	The requirement in this Annex to reduce risks as far as possible means the reduction of risks as far as possible without adversely affecting the benefit-risk ratio.	4.14.6	
3	Manufacturers shall establish, implement, document and maintain a risk management system.  Risk management shall be understood as a continuous iterative process throughout the entire lifecycle of a device, requiring regular systematic updating. In carrying out risk management manufacturers shall: a) establish and document a risk management plan for each device; b) identify and analyse the known and foreseeable hazards associated with each device; c) estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse; d) eliminate or control the risks referred to in point (c) in accordance with the requirements of Section 4; e) evaluate the impact of information from the production phase and, in particular, from the post-market surveillance system, on hazards and the frequency of occurrence thereof, on estimates of their associated risks, as well as on the overall risk, benefit-risk ratio and risk acceptability; and f) based on the evaluation of the impact of the information referred to in point (e), if necessary amend control measures in line with the requirements of Section 4.	4.14.6; not st	Additional risk management needed
4	Risk control measures adopted by manufacturers for the design and manufacture of the devices shall conform to safety principles, taking account of the generally acknowledged state of the art. To reduce risks, the manufacturers shall manage risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable. In selecting the most appropriate solutions, manufacturers shall, in the following order of priority:	Not applicable?	



# Guideline

*“With the exception ... set out in Annex I, the requirements of this Regulation shall not apply to devices manufactured and used only within health institutions established in the Union, provided that all of the following conditions are met:*

*(a) the devices are not transferred to another legal entity;*

The transfer of results (with or without clinical interpretation) is essential for good quality and accessibility of the Dutch healthcare system.

Transfer of lab-developed test itself **X**

Results **V**

Protocols/publications/etc. **V**





# Guideline

*(b) manufacture and use of the devices occur under appropriate quality management systems;*

ISO 15189 ✓

Caveat: additional requirements may be required (i.e. for software)



# Guideline

(c) the laboratory of the health institution is compliant with standard EN ISO 15189 or where applicable national provisions, including national provisions regarding accreditation;

ISO 15189 ✓





# Guideline

(d) the health institution justifies in its documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an equivalent device available on the market;

Lab developed test meets needs of specific patient population arguably better ✓

Arguments i.e.:

- performance characteristics (sensitivity, specificity, stability)
- turn-around time
- multiplex vs different single tests
- amount of material required
- type of material

Substantiation:

- National guidelines from professional associations / international guidelines
- Scientific literature
- Expert opinion



# Guideline

(e) the health institution provides information upon request on the use of such devices to its competent authority, which shall include a justification of their manufacturing, modification and use;

- All previously mentioned items must be documented
  - Follow Annex I and add justification
- Information available upon request of the competent authorities
  - No need to submit without request



# Tool

(f) the health institution draws up a declaration which it shall make publicly available,

...

<b>Documentation lab-developed tests</b>	
Institute / Laboratory	
Name:	
Department:	
Address:	
Contact person	
Name:	
Position:	
Phone:	
Email:	
Statement	
Above mentioned institution states for all tests listed in attachment A: i) This test is manufactured in house and under NEN ISO15189:2012 accreditation. ii) This test is compliant with relevant general safety and performance rules as depicted in Annex I of IVDR 2017/746. iii) Deviations from Annex I of IVDR 2017/746 are substantiated and documented in the quality management system. iv) Argumentation for use of lab-developed test is documented in quality management system.	
Signature	
Name:	
Date:	
Signature:	



# Template for documentation

- Statement

Above mentioned institution states for all tests listed in attachment A:

- i) This test is manufactured in house and under NEN ISO15189:2012 accreditation.
- ii) This test is compliant with relevant general safety and performance rules as depicted in Annex I of IVDR 2017/746.
- iii) Deviations from Annex I of IVDR 2017/746 are substantiated and documented in the quality management system.
- iv) Argumentation for use of lab-developed test is documented in quality management system.

- Attachment A

Description Lab-developed test		Identification
1		
2		



# Guideline

(g) as regards class D devices in accordance with the rules set out in Annex VIII, the **health institution draws up documentation** that makes it possible to have an understanding of the manufacturing facility, the manufacturing process, the design and performance data of the devices, including the intended purpose, and that is sufficiently detailed to enable the competent authority to ascertain that the general safety and performance requirements set out in Annex I to this Regulation are met. Member States may apply this provision also to class A, B or C devices in accordance with the rules set out in Annex VIII;

- Special request only for class D devices





# Guideline

(h) the health institution takes all necessary measures to ensure that all devices are manufactured in accordance with the documentation referred to in point (g);

(i) the health institution reviews experience gained from clinical use of the devices and takes all necessary corrective actions.

ISO 15189 ✓

- in particular on the basis of section 4.14 (Evaluation and Audits)



# Where are we now?

- A lot of unknowns (also for authorities)
- Dutch authorities want professionals to be involved in setting up guidelines for IVDR interpretation
- Task force is seen as important partner by authorities
- Guideline will be discussed broadly with national stake holders
- Guideline will be discussed with European committees via Dutch representatives
- Task force will join forces with patient organizations that are experienced in European Union lobby work

