Paul-Ehrlich-Institut

Neues Konzept der EU Referenzlaboratorien

Anforderungen, Stand der Umsetzung und Perspektiven für das PEI

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Content

- IVD classification
- EURL concept
  - Scopes
  - Criteria and tasks
  - Current status
  - Gaps
- PEI as EURL candidate

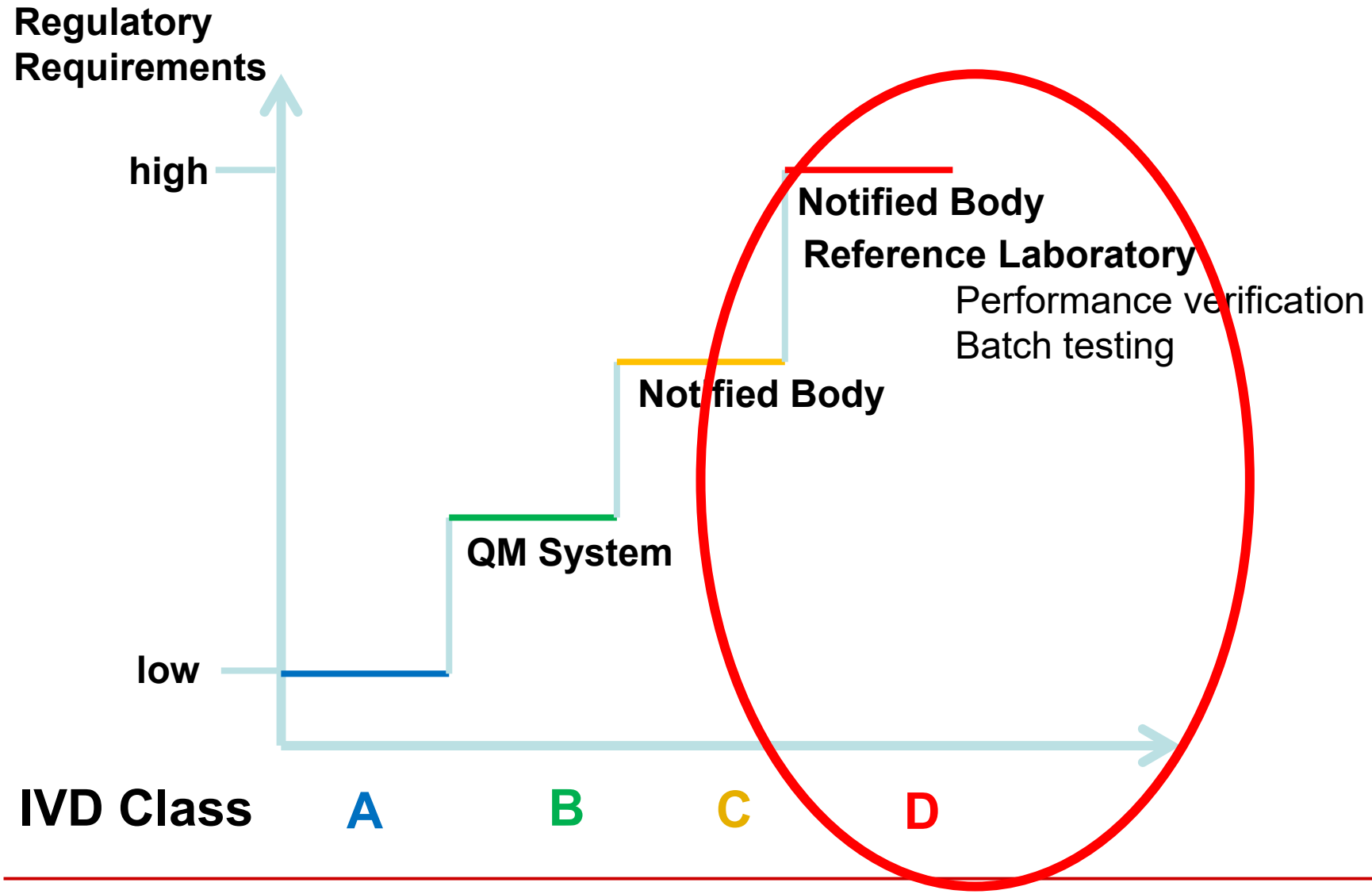
New Elements of IVD Regulation (EU) 2017/746

- .....
- **IVD definition** covers also
  - genetic tests
  - companion diagnostic
- Risk based **classification rules** for IVD classes A – D
  - No longer lists of devices with cumbersome updating (Annex II, list A; list B)
- More stringent **pre-market review of high-risk devices** (class D)
  - EU Reference Laboratory
  - (pool of experts)

IVD Classification

Class	Health Risk		Examples
	individual	***public***	*Annex VIII, Classification Rules 1 - 7*
A	**low**	**low**	Clinical chemistry analyser, culture media
B	**moderate**	**low**	Vitamin B12, pregnancy self testing, anti-nuclear antibody, urine test strips
C	**high**	**moderate**	HLA typing, PSA, Rubella, cancer IVDs, genetic tests, companion IVDs,
D	**high**	**high**	HIV, HBV, HCV; CMV, EBV; Ebola; ABO, Rhesus

IVD Classification



Class D IVDs (1)

Annex VIII, Rule 1

Detection of

- transmissible agents
  - blood transfusion — ***EU Directives:*** *minimal testing* ***2002/98/EC*** HIV1/2, HBV, HCV
  - organ transplantation — ***2010/53/EU*** HIV, HBV, HCV
  - tissues and cells administration — ***2006/17/EC*** HIV1/2, HBV, HCV
    „optional“: CMV, EBV, HTLV-I, T pallidum, Plasmodium spp, Toxopl gondii, Tryp cruzii
- transmissible agents
  - life threatening disease — Ebola, Marburg, Lassa; vCJD
  - high risk of propagation — SARS CoV, MERS CoV, smallpox, highly virulent pandemic influenza

Monitoring of

- infectious load of life-threatening disease — HIV, HBV, HCV viral load

Class D IVDs (2)

Annex VIII, Rule 2

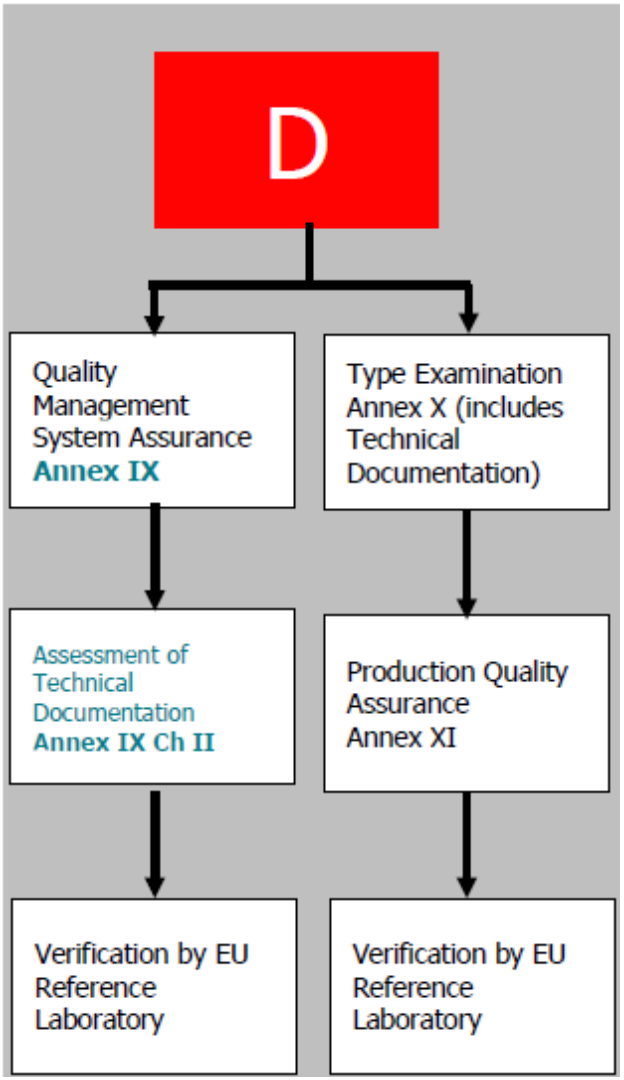
Blood grouping, tissue typing

- AB0 [A (ABO1), B (ABO2), AB (ABO3)]
- Rhesus System [RH1 (D), RHW1, RH2 (C), RH3 (E), RH4 (c), RH5 (e)]
- Kell System [KEL1 (K)]
- Duffy System [FY1 (Fya), FY2 (Fyb)]
- Kidd System [JK1 (Jka), JK2 (Jkb)]

Potential EURL Scopes (Competence Areas)

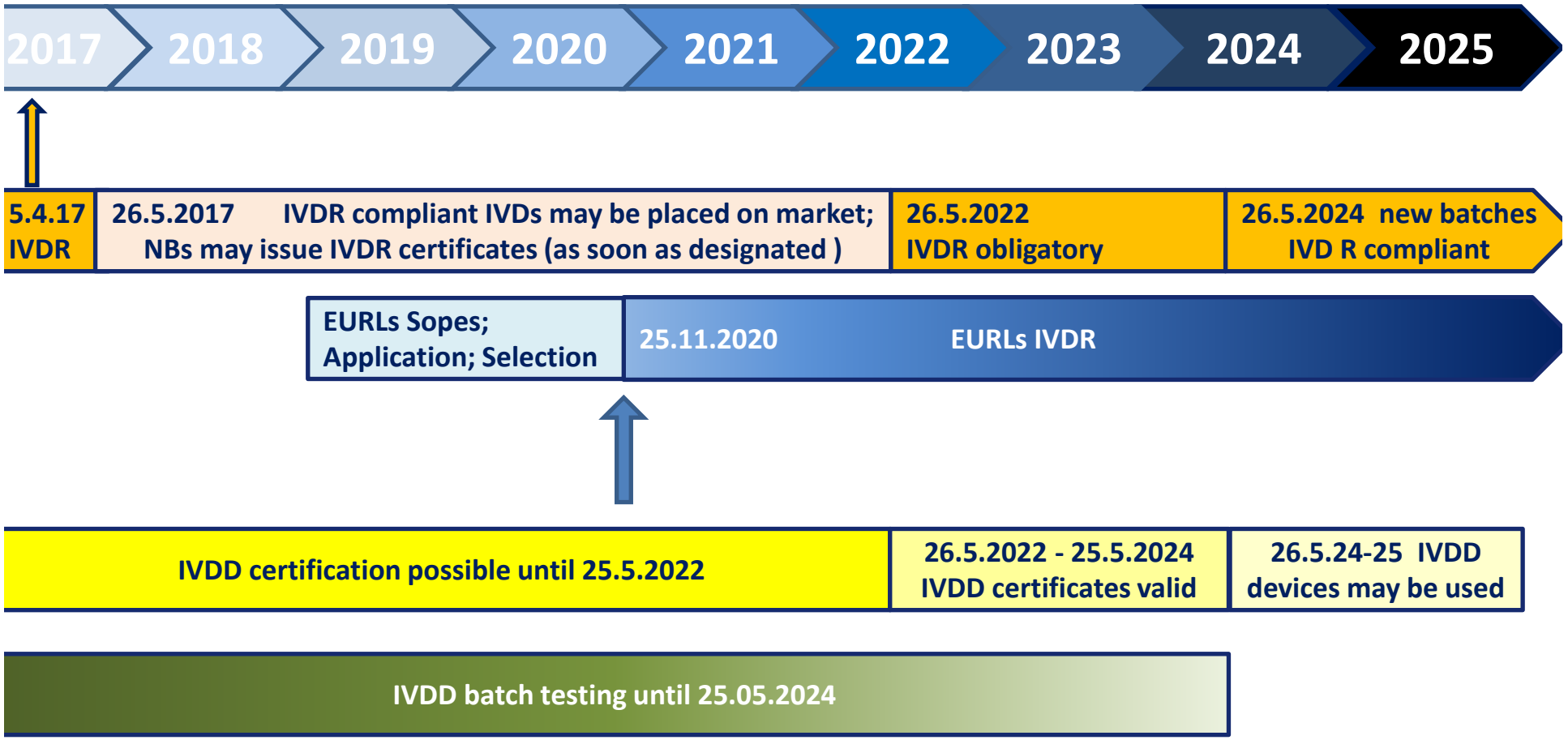
Pathogen detection (blood, cells, tissue, organs)	Virus monitoring	Respiratory viruses BSL3	Haemorrhagic fever BSL4	Parasites	Prions	Blood groups
HIV1/2 **HBV** **HCV** **HTLV-I, II** **CMV** **EBV** **Trep pallidum**	**HIV** **HBV** **HCV**	**SARS CoV** **MERS CoV** **Influenza** (pandemic, virulent)	**Ebola** **Marburg** **Lassa** **CCHF**	**Plasmodium spp** **Trypanosoma cruzi** **Toxoplasma gondii**	**vCJD (?)**	**ABO** **Rhesus** **Kell** **Kidd** **Duffy**
HEV ?	***CMV ?*** ***EBV ?***		***Smallpox ?***			

Conformity Assessment Procedures



„Pre-Market Testing" by EURL →

IVDD / IVDR Transition Timeline



EU Reference Laboratories (EURL) for IVDs

2017 / 746, Art 100 (2)

- **Tasks**
  - **Class D IVDs**
    - **Verification of performance claims**
    - **Compliance with Common Specifications (CS)**

EURL laboratory testing is part of conformity assessment
Focus on analytical and diagnostic sensitivity
NB takes into account EURL report **60 days**

- **Batch testing**

EURL batch testing; batch release by NB **30 days**

EU Reference Laboratories (EURL) for IVDs

2017 / 746, Art 100 (2)

- **Tasks**

  - **Support** of European Commission, Medical Device Coordination Group, Competent Authorities, Notified Bodies

    - Scientific and technical assistance
    - Testing and analysis methods, best practices
    - Advice „state of the art“ IVDs
    - Reference materials and reference procedures

    - Development of Common Specifications

  - **Management** of network of national reference laboratories

EU Reference Laboratories (EURL) for IVDs

Several EURLs per scope necessary

- manage work load
- reduce risks of work overload
- compensate potential bottlenecks
- prevent monopoly

2017 / 746, Art 100 (5)

- **EURL network**
  - harmonised methods, procedures, SOPs
  - common reference materials
  - uniform interpretation criteria and reports
  - peer review system

EU Reference Laboratories (EURL) for IVDs

EURL preconditions

2017 / 746, Art 100 (4)

- qualified staff, IVD expertise
- appropriate structure and organisation
- equipment, reference materials
- public interest, independant, confidentiality, no conflicts of interest

Implementation Act „Tasks and criteria EURL“ (draft)

- ISO 17025 accreditation
- financial and economic standing
- details for staff qualification
- preference criteria for selection of EURLs

Implementation Act „EURL fees“ (draft)

- transparent fee structure
- cost recovery, no profit

EU Reference Laboratories (EURL) for IVDs

Current gaps

- Finalisation of Implementing Acts („Tasks and Criteria“, „Fees“)
- Definition of final scopes for individual EURLs
- Application (through NCAs)
- Selection and designation (by Europ Commission)
- Establishment of EURL Network
  Performance verification; compliance with Common Specifications
  - Definition of evaluation panels
  - Harmonisation of evaluation procedures and criteria
  - Peer review
  - Common (Technical) Specifications (CS) for class D IVDs as precondition

Common (Technical) Specifications

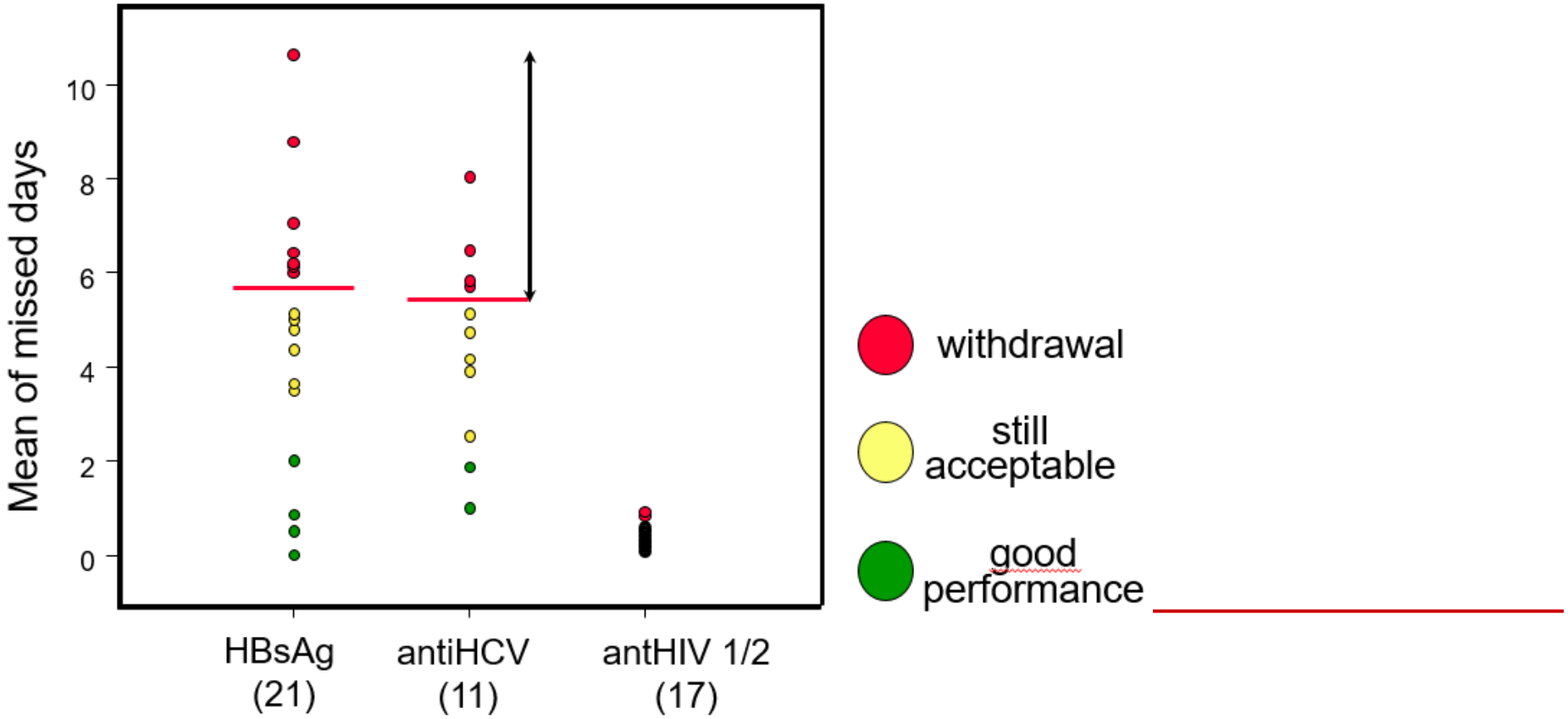
- defined
- in preparation
- not initiated

Pathogen detection (blood, cells, tissue, organs)	Virus monitoring	Respiratory viruses BSL3	Haemorrhagic fever BSL4	Parasites	Prions	Blood groups
HIV1/2 HBV HCV HTLV-I, II CMV EBV Trep pallidum	HIV HBV HCV	SARS CoV MERS CoV Influenza (pandemic, virulent)	Ebola Marburg Lassa CCHF	Plasmodium spp Trypanosoma cruzi Toxoplasma gondii	*vCJD ?*	ABO Rhesus Kell Kidd Duffy
HEV ?	*CMV ?* *EBV ?*		*Smallpox ?*			

PEI as potential EURL Candidate

PEI with history of IVD expertise

- **1975 – 2003 Governmental approval of IVDs (German Drug Law)**
  - Performance evaluation study
  - Batch testing
  - Regular re-evaluation of „state of the art“



PEI as potential EURL Candidate

PEI with history of IVD expertise

- **since 2001**
  - **PEI-IVD: IVD testing laboratory for Directive 98 / 79 / EC**
    - Batch testing on behalf of NBs
      - Annex 2 list A products
        - » HIV, HBV, HCV, HTLV; blood groups
        - » Serology, NAT and blood group laboratories
    - Recognition by ZLG, based on ISO 17025

Anerkannt durch/Recognized by
Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten
www.zlg.de
ZLG-AP-304.10.33

PEI as potential EURL Candidate

PEI with history of IVD expertise

- **„Federal Institute for Vaccines and Biomedicines“**
  - Responsible for e.g. blood and blood products; cells and tissues
    - Investigation of adverse events, e.g. virus transmissions
      - sometimes IVD related
      - definition of regulatory measures
  - **Competent Authority for Annex II list A, (B) IVDs**
    - IVD vigilance

- **WHO Collaborating Center for Quality Assurance of Blood Products and in vitro Diagnostic Devices“** (since 2005)
  - Standardization of IVDs
    - Characterization and establishment of WHO International Standards (ISs) and WHO International Reference Panels (IRPs)
    - Custodian for WHO ISs and WHO IRPs

WHO International Standards
WHO International Reference Panels

Established by PEI

➢ WHO 1st IS antiHBc	NIBSC 95/522
➢ WHO 1st IS anti-HBe	129095/12
➢ WHO 1st IS HBeAg	129097/12
➢ WHO 1st IRP HBsAg (HBV genotypes)	6100/09
➢ WHO 1st IRP HBV DNA (HBV genotypes)	5086/08
➢ WHO 1st IS HCV core Ag	129096/12
➢ WHO 1st IS HDV RNA	7657/12
➢ WHO 1st IS HEV RNA	6329/10
➢ WHO 1st IRP HEV RNA (HEV genotypes)	8578/13
➢ WHO 1st IS anti-CMV IgG	136616/17
➢ WHO 1st IS Chikungunya virus RNA	11785/16
➢ WHO 1st IS Zikavirus RNA	11468/1
➢ WHO 1st IS Mycoplasma DNA	8293/13

➢ 3 WHO Repositories Bacteria (Platelets, Erys)

Potential EURL Scopes

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HEV ?	*CMV ?* *EBV ?*		*Smallpox ?*			

Conclusions

- **Risk-based classification of IVDs**
  - More flexible
  - Current approach for class D inclusion scientificly justified ?

- **EURLs**
  - Conformity assessment (class D)

  - Scopes definition as precondition for application
  - EURL network !!
  - National reference laboratories ?
  - Common Specifications ?

  - PEI potential EURL candidate

VIELEN DANK FÜR IHRE AUFMERKSAMKEIT!

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