
**Performance Testing for IVDs
in Europe, USA and China**

Dr. Hubert Bayer



Aspects included in this presentation:

- Guidance documents and other supportive references

- Classification of IVDs
 - Requirements for Performance Testing

 - Examples for Performance Testing

Current Regulations for IVD Medical Devices define

the requirements for Performance testing:

- Europe: Directive 98/79/EC and 28 transpositions into national laws

- USA: Pre Market Notification process (21CFR 807) and
Pre Market Approval process (21CFR 814)

- China: Order 650 and IVD Regulations No 5

Europe

- Europe (1):
 - *Directive 98/79/EC*
 - Annex I: „Essential Requirements“ describes in chapter 8.7 requirements for performance specifications in device descriptions
 - Annex III: „EC Declaration of Conformity“ describes in chapter 3 the performance specifications as part of the technical documentation for each product
 - *Common Technical Specifications* 2002/364/EC are relevant for products of the highest risk class as listed in Annex II List A

- **Europe (2):**

- Harmonized Norms (excerpts)

Performance of IVDs

- EN 13612:2002 „Performance Evaluation of in vitro diagnostic reagents“
- EN13640:2002 (also ISO 23640) „Stability Testing for in vitro diagnostic reagents“
- EN 13532:2002 „General requirements for in vitro diagnostic medical devices for self testing“
- EN ISO 15197:2003 „In vitro diagnostic test systems – Requirements for blood-glucose monitoring systems for self –testing in mamaging diabetes mellitus“

Europe (4):

Performance Evaluation

- Is a requirement of the Quality Management System:
 - ISO 13485:2003
 - "Design Validation":
 - show evidence ... **by results of a performance evaluation that the IVD MD performs as claimed**
 - CEN ISO/TR 14969:2005 (= guidance on application of ISO 13485)

- Europe (5):
 - *EN 13612:2002 „Performance Evaluation of in vitro diagnostic reagents“*
 - *EN 13532:2002 „General requirements for in vitro medical devices for self testing“*
 - Responsibilities
 - Organization
 - Experimental Design
 - Report
 - Evaluation of data
 - Safety of test persons

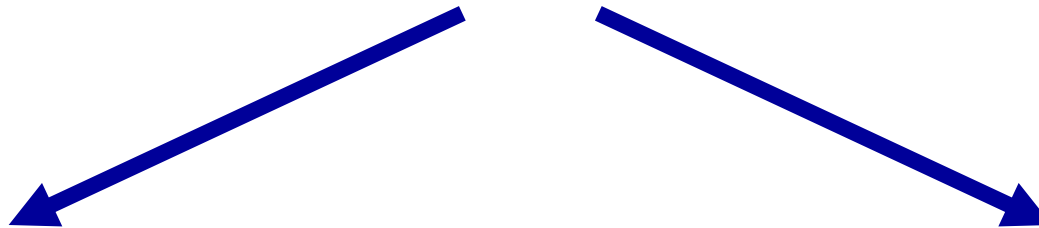
- Europe (5):

Impact of IVD Classification:

- Annex II
 - List A (Hepatitis B, C, D, HIV and major blood groupes)
 - » Common Technical Specifications apply
 - List B (Infectious markers, PSA, minor blood groupes, blood glucose self monitoring, ...)
 - » ISO 15197 applies for blood glucose testing
- Lay user products
 - » EN 13532 applies (device for self testing)
- General IVDs
 - » EN13612 (performance evaluation) and EN 13640 (Stability testing) apply for all IVDs.

Clinical Evidence for an IVD

Ref: GHTF SG5/N6:2012



Scientific Validity

- Literature
- Expert opinions
- Feasibility studies

→ unique for a specific measurant (analyte)

Device Performance

- Analytical and technical Performance
= “Non clinical” Performance

- Clinical Performance

→ unique for the specific device

Purpose of Performance Evaluation Studies:

- **Technical performance**
 - » Precision
 - » Stability
 - » Accuracy
 - » Interference
 - » Lower detection limit

Purpose of Performance Evaluation Studies:

– **Clinical Performance**

- » To establish Reference Ranges for a defined population
- » Sensitivity and Specificity in defined collectives
- » to verify the established "Intended Use" (in comparison to an established Device)
- » to demonstrate a new "Intended Use" (additional clinical information needed)

Performance Testing for IVDs

Results using clinically defined samples:

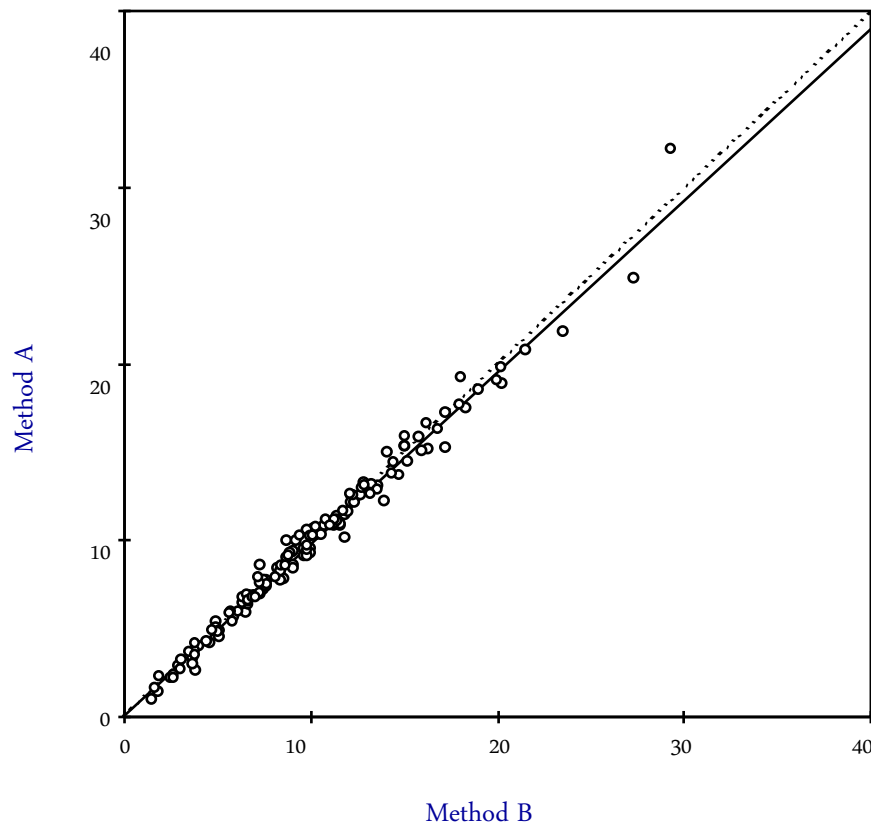
Method comparison

„qualitative“

		specificity sensitivity	
		-	+
new device	+		+++ +++++ +
	-	++ +++++ +++ ++	++
		established device	

Performance Testing for IVDs

Quantitative Method comparison using clinical samples

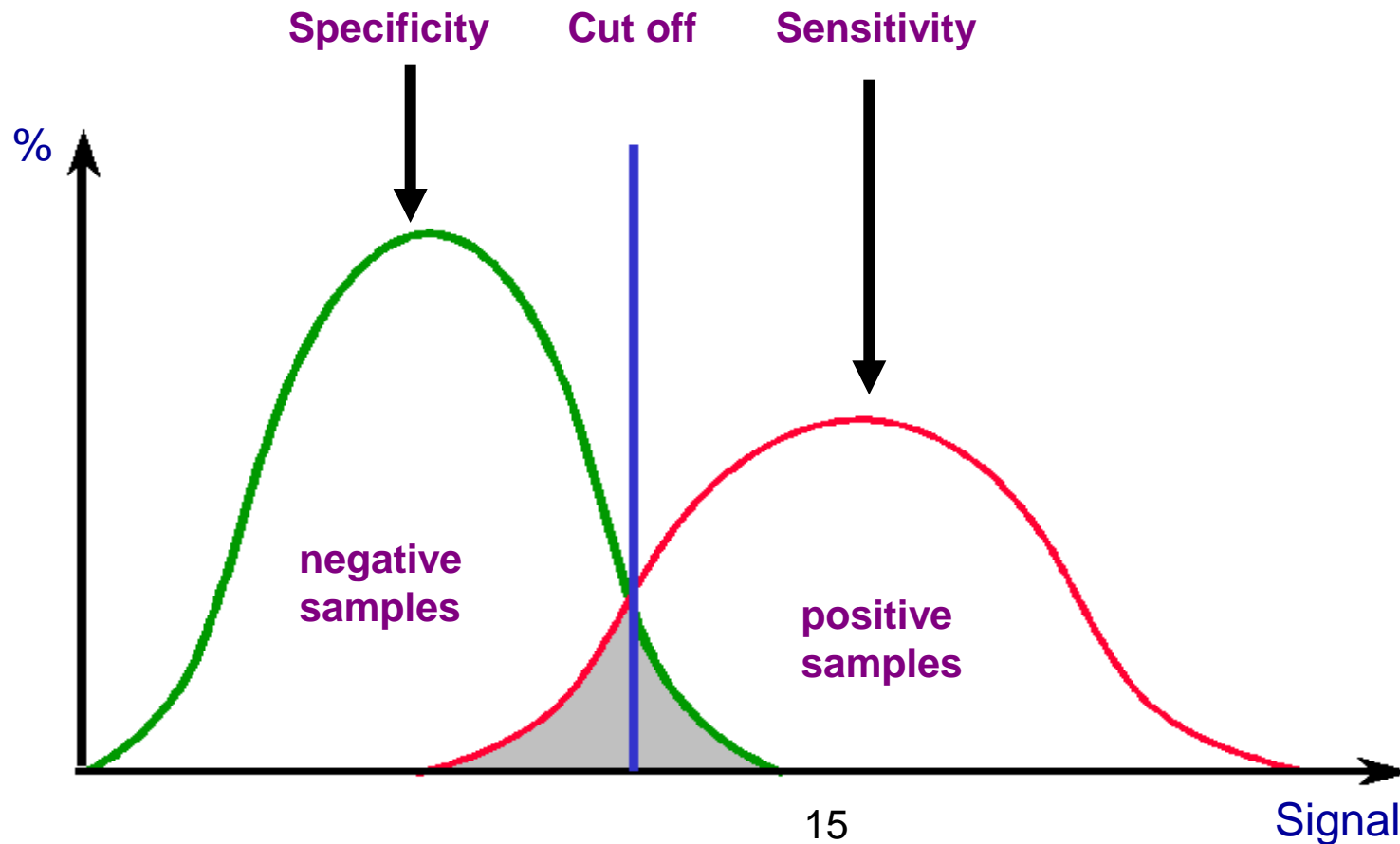


- linear regression

- correlation

Performance Testing for IVDs

"Cut-off" Verification for qualitative assays



COMMISSION DECISION

of 3 February 2009

amending Decision 2002 / 364 / EC on **Common Technical Specifications for
in vitro-diagnostic medical devices**

((notified under document number C(2009) 565))

(Text with EEA relevance)

(2009 / 108 / EC)

Common Technical Specifications (CTS) 2002/364/EC

Are developed for

- Performance evaluation for serological assays and Acid Amplification Techniques (NAT) for HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C, D. Nucleic
- Performance evaluation assays for blood grouping
- Manufacturer's Quality Control release testing

CTS: Content

- General principles for performance evaluation
- Specification for sensitivity and specificity
- General principle for manufacturers lot release
- Define minimal number of samples to be tested during performance evaluation.

CTS: Positive Specimens

- Positive specimens used in the performance evaluation shall be selected to reflect different stages of the respective disease(s), different antibody patterns, different genotypes, different subtypes etc.
- All true positive samples shall be identified as positive (sensitivity 100 %). Exception Anti HBc and HBsAg.
- Diagnostic test sensitivity during the early infection phase (seroconversion) has to represent the state of the art.



Common technical specifications (CTS)



Performance evaluation Anti-HIV 1 / 2:

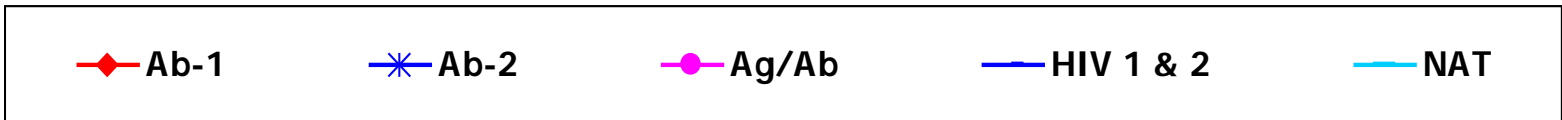
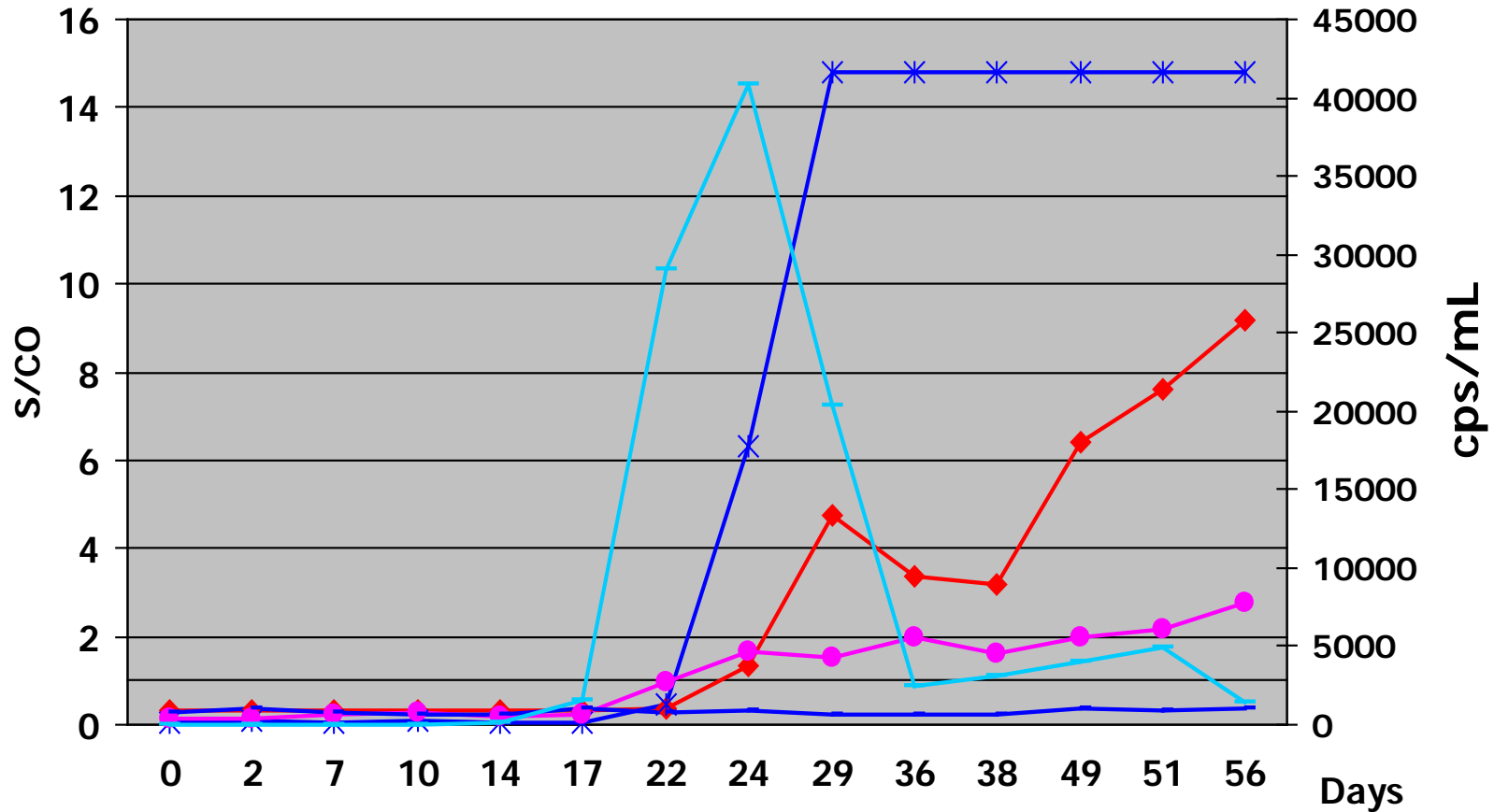
Diagnostic	positive	400 HIV-1
Sensitivity	specimens	100 HIV-2
		including: 40 non-B-subtypes, available HIV-1 subtypes represented by at least 3 samples per subtypes
Sensitivity	sero-conversion	20 panels (40 early samples) 10 further panels (at NB or manufacture)
Specificity	unselected donors	5000
	hospitalized patients	200
	potentially cross-reacting blood-specimens	100
	(RF+, related viruses, pregnant women etc)	

CE-marked Tests: SC Panel Zeptometrix 9032

Acute Infection



WB - - - - - +/ - +/ - +/ - +/ - + +



CTS: Negative Specimen

- blood donors (Specificity of at least 99.5%)
- hospitalised patients,
- pregnant women etc.
- **Potential interferences:**
 - related infections, samples from multipara,
 - rheumatoid factor positive patients, Anti E.coli or anti-yeast positive samples

CTS: upcoming changes and updates

parameter	status
vCJD included	Desided and in process
HIV NAT: assay design and sensitivity for types and variants	Wording agreed change process started
HIV Saliva „home assay“	in discussion; products do not fullfill CTS for rapid assay
HCV Antigen and Antibody+Antigen combination	Proposed by Paul-Ehrlich-Institute
Syphilis immunoassay	Proposed by EDMA
Chagas immunoassay	Proposed by EDMA

EN 13640:2002 (now ISO 23640) Stability testing of in vitro diagnostic reagents

- Scope
 - determine shelf life of an IVD under storage conditions
 - Check transportation stability
 - determine stability when “in use “ ("on board stability")
 - monitor stability of lots on the market

EN 13640:2002 (now ISO 23640):

- General Requirement
 - Protocol
 - final report or certificate

- In total three batches are required:
 - 1 batch for transport stability testing
 - 1 batch for "in-use"
 - 1 batch for "modifications"
 - 3 batches for extension of "shelf life"

Stability Testing Protocol:

- Define testing intervals and period
- fixed claims (i.e. +/- 15 % recovery)
- defined test samples
- accelerated testing to predict of shelf life

Performance Testing for IVDs

Real-time stability (4 °C to 8 °C) : range 85 % - 115 %

		fresh	3 months	6 months	9 months
Lot 1	PC 1	100 %	95 %	90 %	92%
	PC 2	105 %	98 %	92 %	90%
Lot 2	PC 1	102 %	98 %	92 %	
	PC 2	101 %	101 %	95 %	
Lot 3	PC 1	97 %	98 %		
	PC 2	95 %	92 %		

Incomplete data because of consecutively manufactured batches are accepted by

US FDA for 510 k and EU Notified Bodies

Accelerated stability testing : EN 13640

4.3.3 Interpretation of results:

"In the absence of sufficient real-time data, this shall be done on the *basis of experience with similar IVD-reagents* and / or by using the Arrhenius equation or other stated models"

(Models may be 37 °C stress for several weeks)

Comment: This approach is accepted only by few authorities (e.g. Health Canada gives conditional licenses)

Performance Testing for IVDs

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Lot 2	PC 1	102 %	98 %	92 %	94%
	PC 2	101 %	101 %	95 %	92%
Lot 3	PC 1	97 %	98 %	96 %	94%
	PC 2	95 %	92 %	90 %	91%

Conclusion: The shelf life of this product is at least 8 months

Shelf life is usually part of the registered product features

- Some authorities (customs) require a „**remaining shelf life**“ in % of the registered shelf life when the product enters the country.
 - e.g. Vietnam and India require 60% remaining shelf life)
 - 6 weeks if a products has 10 weeks shelf life
 - 12 months if a product has 20 months shelf life
 - Proposal: Remaining Shelf life should rather consider logistic aspects and user requirements.
 - Time to distribute + time to consume
 - e.g. > 3 months

Shelf life is usually part of the registered product features

- Critical findings:
 - IVD reagent kits consist of multiple components:
 - Shelf life of a batch is defined by the expiry of the component which expires first.
 - » The shelf life of a batch may deviate from the registered shelf life (packaging of a batch to expiry)
 - » Shelf of a product is determined using newly manufactured components

Registered self life > shelf life of a batch

Shelf life and product labelling

- Regulations require to give information on the time where the **manufacturer guaranties the safe use of a product**.
 - Most countries require an **expiration date**
 - India require the **manufacturing date**
 - China requires **manufacturing date** plus either shelf life or expiration date
 - Custom problems in certain countries because of deviations to the registered shelf life
 - IVD instruments do not have a shelf life or expiration date
 - » Time for Safe use depends on service and intesity of use

USA

United States of America: Requirements for IVD

- Pre Market Notification process (21CFR 807)
 - Class II products

- Pre Market Approval process (21CFR 814)
 - Class III products

USA: Requirements for IVD

<http://www.fda.gov/MedicalDevices/default.htm>

- In Vitro Diagnostic (IVD) Device Studies-
Frequently asked Questions (June 25, 2010)

- Parameter Guidance documents
 - For class II and class III IVDs

- CLSI Standards describe non- clinical performance experiments

USA: Requirements for IVD

<http://www.fda.gov/MedicalDevices/default.htm>

- The 510 (k) Program: Evaluating Substantial Equivalence in Premarket Notifications
- Class II Special Guidance Document
 - Performance Characteristics
 - Analytical Studies with reference to CLSI standards
 - Prevalence and expected values
 - Method comparison
 - Sample Selection, inclusion and exclusion criteria

US FDA: **Guidance for Industry and Food and Drug Administration Staff**

“Class II Special Controls Guidance Document: Herpes Simplex Virus Types 1 and 2 Serological Assays

Document issued on: August 9, 2011”

This document supersedes “Herpes Simplex Virus Types 1 and 2 Serological Assays” dated April 3, 2007. .

USA: Requirements for IVD

<http://www.fda.gov/MedicalDevices/default.htm>

- **Pre Market Approval** of medical devices starting July 1986
 - Parameter specific guidance documents
(often only in draft versions)

- IDE Process:
 - Includes the approval of the study protocol
before start of the testing

Comparison of Performance Studies in Europe and USA

Item	HCV-AB* „CE“	HCV-AB* „US“
In use stability	+	+
Precision within run	5 samples	6 samples
Precision between runs	5 samples	6 samples
Potential cross reactions	774 samples	345 samples
Genotype detection	+	+
Sero- conversions	50 panels	20 panels
Sensitivity for genotypes	+	+
Clinical specificity	2230 samples	1640 samples [°]
Clinical sensitivity	818 samples	459 samples [°]

* Example of a Roche Diagnostics assay

[°] US studies have detailed demographic and age statistics

Comparison of Performance Studies in Europe and USA

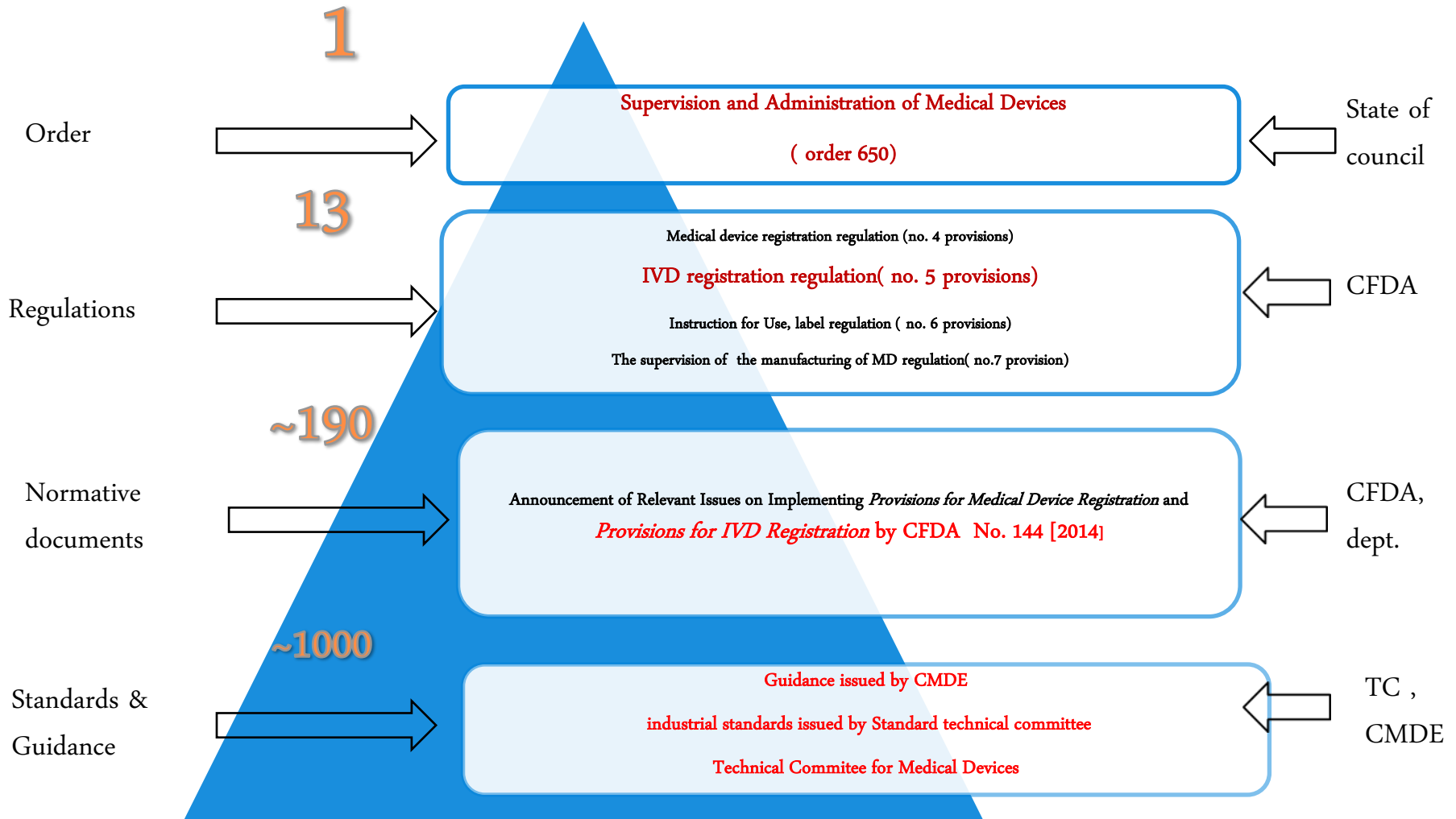
Item	T-PSA* „CE“	T-PSA* „US“
In use stability	+	+
Precision within run	5 samples	5 samples
Precision between runs	5 samples	5 samples
Interferences	+	+
Measuring range	+	+
Reference ranges	1121 samples [°]	1121 samples [°]
Lower detection limit	+	+
linearity	+	+
Benign/malign tumors	730/391	730/391

* Example of a Roche Diagnostics assay

[°] detailed demographic and age statistics

China

CFDA MD IVD Regulation Systems



IVD registration regulation(5th provisions)

– Article 23:

- “Class II and class III assays shall be subjected to registration testing of the samples in 3 successive batches.”
- The Medical Device Testing institute shall test relevant product according to the Product Technical Requirement.

– Article 24:

- ...the applicant shall provide the Testing Institute with relevant technical data, samples for registration testing, **Product Technical Requirements and standard/reference material.**

- **China:**
- **IVD registration regulation (#5): Attachment “In Vitro Diagnostic Reagent Clinical Trial Technical Guideline”**
 - **I. General Requirements of clinical trials**
 - **II. Requirement for clinical trial institutions and personal**
 - **III. Design principles of clinical trials**
 - **IV. Compilation of clinical trial report**

- China:
- “In Vitro Diagnostic Reagent Clinical Trial Technical Guideline”
 - I. General Requirements of clinical trials
 - Comply with Helsinki Declaration
 - Consider safety and Health of subjects
 - Confidentiality of involved patients
 - Supported by preclinical results

China:

“In Vitro Diagnostic Reagent Clinical Trial Technical Guideline”

- **II. Requirement for clinical trial institutions and personal**
 - **Institutions must be certified by CFDA**
 - **Institutions must be equipped with personal and technology to support the intention of the CT**
 - **Responsibilities of involved parties must be specified**
 - **Pilot studies should support the clinical study**

China:

- **“In Vitro Diagnostic Reagent Clinical Trial Technical Guideline”**
 - **III. Design principles of clinical trials**
 - **Clinical Trial Protocol must contain**
 - » **Objectives and design**
 - » **Evaluation Method and Statistics**
 - » **Rules for revision of the protocol**
 - **Clinical trial method**
 - » **Comparative device and “Gold standard”**
 - » **Numers of samples required**

China:

- “In Vitro Diagnostic Reagent Clinical Trial Technical Guideline”
 - IV. Compilation of clinical trial report
 - Study Design
 - Details on selections of the Comparative method
 - Sample selection
 - Results and statistical analyses
 - Involved investigators

Performance Testing for IVDs: China



Classification	Description	example
Drug-IVD	Blood screening	HIV NAT or 96 well ELISA
Class III	Testing for pathogen antigen or antibody, NAT ; blood type, human genetic tests drug abuse, toxic drugs; therapeutic drug; tumor marker ; allergen	HBsAg, CEA, EGFR mutation
Class II	Assays for detection hormone, enzymes ester, vitamin, metabolites, autoantibody, microorganism identification and drug sensitivity test,	TSH, Glucose
Class I	Microbial media; diluents, staining solution	Universal diluent,

Performance Testing for IVDs: China



	Description	Site	Cases
Class II	Established marker	2	200
	New marker	3	1000
	1. Change the sample type 2. Change the reaction condition	2	100
Class III	1. NAT for infection disease 2. Flow cytometry 3. Narcotic, psychotropic, and toxic drugs, DAB	3	500
	Established Markers	3	1000
	Blood type	3	3000
	1. Change the sample type 2. Change the reaction condition	2	200

Summary:

- European requirements for Performance Testing of IVDs are based on Harmonized Standards and Common Technical Specifications
- Testing of reagent stability is essential for distribution and performance of IVDs. Requirements for „remaining Shelf Life“ in some countries hinder global distribution.
- US requirements for performance studies are based on the 510 (k) process showing substantial equivalence, CLSI standard, and the PMA process (including study protocol approval in IDE). Parameter specific guidance documents are available for some Class II and Class III products.
- Examples for performance testing of HCV Antibody and total PSA assays show that the testing volume is very similar in US versus European studies.
- Chinese requirements for local studies are based on the IVD regulations (order 5, July 2014). National product standards are tested with 3 batches in local Testing Institutions. The clinical study requirements are lower in volume than in EU and USA. For imported products the results are not included in the Chinese product labelling.

Doing now what patients need next