
به نام خدا

Quality and Performance Evaluation of In Vitro Diagnostic Medical Devices at National Level -Iran

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Definition

IVDs are a subset of medical devices which are “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”(21 CFR 809.3)

- Used in:
  - Clinical laboratories
  - Point-of-Care
  - Over-the-Counter

تعریف در ضوابط جاری کشور

شناساگرها، محصول شناساگرها، کالیبراتورها، مواد کنترلی، کیت‌ها، ابزارها، دستگاه‌ها، ملزومات، یا سیستم‌ها، چه بصورت منفرد و چه بصورت ترکیبی، که بوسیله سازنده با هدف انجام آزمایش نمونه هایی نظیر خون، بافت، مایعات بدن و سایر نمونه های بالینی با منشاء بدن انسان ، در خارج از بدن (in Vitro) تولید شده و برای بدست آوردن اطلاعات در یکی از موارد زیر مورد استفاده قرار گیرد:

-وضعیت فیزیولوژیک یا پاتولوژیک

-وضعیت ناهنجاری مادرزادی

-تعیین ایمنی و سازگاری گیرنده بالقوه

-پایش درمان

توجه :

- ظروف نمونه گیری، نگهداری و انتقال نمونه، از هرنوعی که باشد، با یا بدون نگهدارنده یا افزودنی وسیله تشخیص آزمایشگاه پزشکی محسوب می‌شود.
- وسایل و تجهیزات عمومی آزمایشگاه وسیله تشخیص آزمایشگاه پزشکی محسوب نمی‌شوند مگر اینکه با توجه به خصوصیاتشان توسط سازنده، بطور خاص، با هدف انجام آزمایش تشخیصی در خارج از بدن ساخته شده باشند.

Risk based classification of IVDs

- **The risk associated with IVD whe**

1- To public health

Spread of infectious diseases

Unsafe blood transfusion

2- To individual health

Misdiagnosis/delayed diagnosis

Delayed or inappropriate treatment

Incompatible tissue transplantation

Risk class	Risk to Individual Health	Risk to Public Health
A	**Low**	**No or Minima**
B	**Moderate**	**Low**
C	**High**	**Moderate**
D	**High**	**High**

Risk is determined considering :

- **Intended use/Indication for use**
- **Intended user (technical/scientific/medical expertise)**
- **Role of the result in diagnosis (key determinant or one of several)**
- **Impact of the result to individual and/or public health**

Classification dictates the premarket process and amount of regulatory oversight

Overview of IVD classes according to the GHTF format, and notified body involvement in corresponding conformity assessment procedures.

Class	Risk Level	Examples	Notified Body involvement In Conformity Assessment Procedure?
D	High individual risk and high public health risk	HIV testing, major blood-group typing	Yes for both quality management system and premarket review of technical documentation.
C	High individual risk and/or moderate public health risk	PSA screening, prenatal screening, blood glucose self-testing, HLA typing, sexually transmitted microbes, infectious agents in blood and cerebrospinal fluid, cancer markers, companion diagnostics, congenital disorders, etc.	Yes for both quality management system and premarket review of technical documentation.
B	Moderate individual risk and/or low public health risk	Vitamins, pregnancy self-testing, antinuclear antibody, urine test strips, hormones, etc.	Yes for quality management system. No for premarket review of technical documentation.
A	Low individual risk and low public health risk	Prepared selective culture media, instruments, specimen receptacles, etc.	No.

The National process of IVD registration

- **Registration of manufacturer/supplier**

  Legal and Qualification issues

- **Registration of Product**

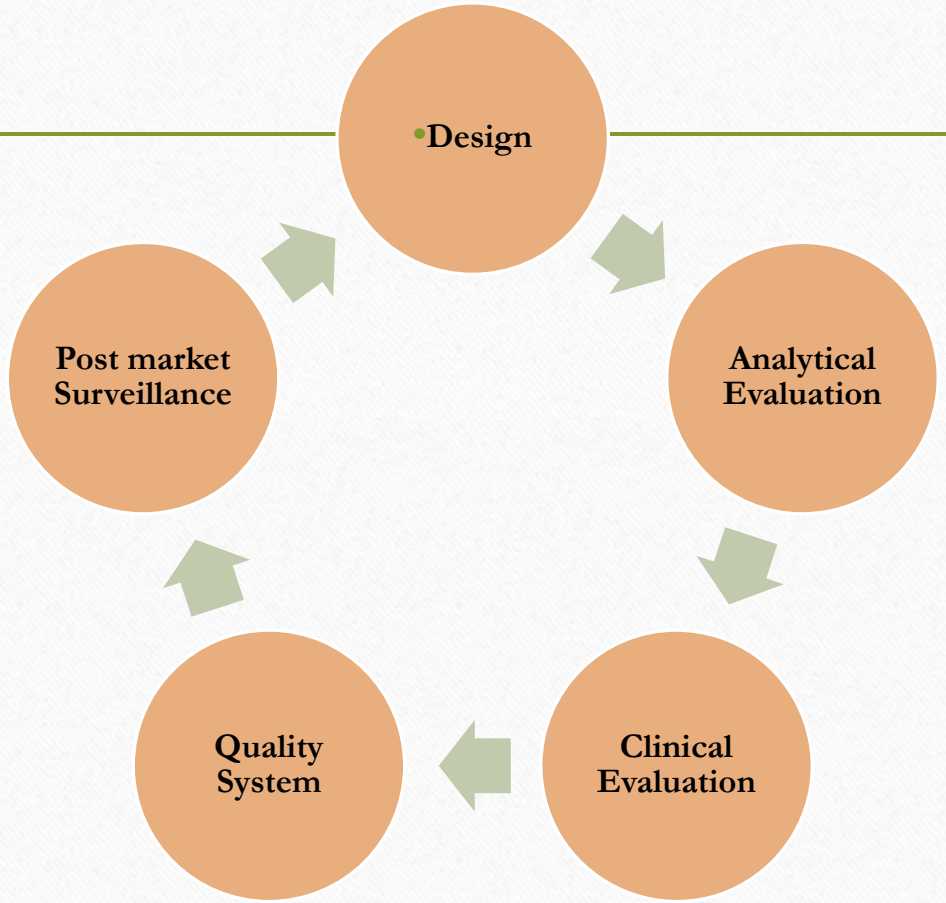
  Submission of application form

  Technical file review

  Site inspection (Assessment of manufacturer's QMS)

  Laboratory evaluation of operational and performance characteristics of the product (if applicable)

IVD Life Cycle

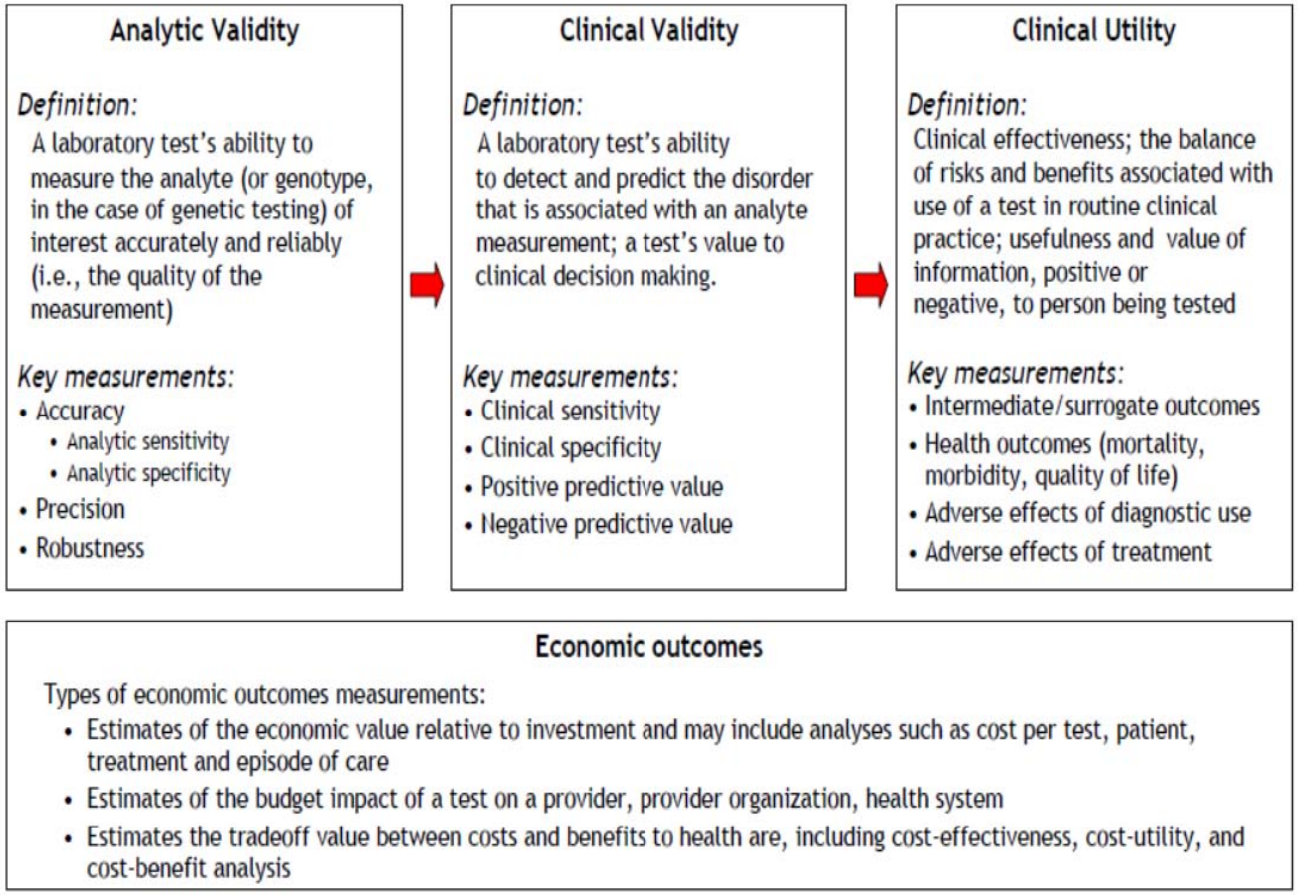


Assessable elements

WHO Prequalification of IVD

- **Technical documentation**
- **Performance and operational utility**
- **Quality management systems**
- **Post market surveillance**

Figure 1. Chain of inquiry for valuation of laboratory tests



Technical file review

- Assessing what is the design of product and how it performs
- Assessing the product manufacture and its consistent reproduction
- Efficiency of verification processes to ensure consistent quality of product

- Depth and detail of information in the technical file is dependent to :

Risk class, Complexity and Novelty of device

Principles considered in Device Review :

- **Safety**

Are there reasonable **assurance** based on valid scientific **evidence** that **probable benefits** to health from use of the device outweigh any **probable risks**

- **Effectiveness**

Is there reasonable **assurance** based on valid scientific evidence that the use of the device in the target population will provide **clinically significant results**

Analytical studies :

- Demonstrating evidences of **safety** : **Misdiagnosis and unsafe use**

  - Likelihood of false positives

  (cross reactivity , carry over, …)

  - Likelihood of false negatives

  (limit of detection, matrix effect, …)

Clinical studies :

- Demonstrating evidences of **effectiveness :**

Device has clinical indication and adds value to clinical management

(if well designed , controlled ,…)

Valid Scientific evidence

Requirements for Tech. file compilation

Product Technical file checklist

Requirements
General format of Technical file
1. completed product registration form
1. Brief introduction of Manufacturer activities
1. Certificates (FDA approval/ clearance , CE …)
1. Quality management system certifications
1. Iran Ministry of Health certificates
1. Conformity with recognized or other standards such as CTS(Common technical specifications) for high risk devices
1. Marketing history (including name of countries and amount of supply)
1. Price list
1. Recall (Adverse events / reports and field corrective actions in last 5 years)
1. GMP certificate
1. Flowchart of manufacturing process
1. Certificate of Analysis
1. Pages are numbered and signed by authorized person

Requirements
Device description/ Principle of technology
1. Product/Device description
1. Product/ Device Design
1. Risk analysis and control summary
Labeling
1-Instructions for use
2- Sample of advertisements
3-Labels

Requirements		
Performance specifications and associated validation & verification studies		
Analytical studies(including protocols, results and analytical methods)		
1-Accuracy	Precision	Repeatability &Reproducibility: ✓ Within- run (intra-batch) ✓ Between-run (inter-batch)
	Trueness	Comparison with reference materials
		Agreement between methods
		Recovery test *
2-Limit of Detection – Limit of Quantitation*		
3. Analytical specificity (Cross Reactivity , Interference)		
3. Metrological traceability of calibrators and control material values		
3. Linearity/Reportable range		

Requirements	
Hook effect	
Cut-off definition/ validation	
Stability studies	✓ Shelf-life (unopened()
	✓ In-use
	✓ stress (Accelerated test)*
Clinical studies – manufacturer	
Reference interval	
PPV,NPV, Likelihood ratio, Clinical sensitivity & specificity	
Clinical Researches and publications	
Independent studies (Reference Health laboratory)	
Analytical studies	
Clinical studies	

GMP inspection

- WHO definition: Good Manufacturing Practices or 'current Good Manufacturing Practice' is the aspect of quality assurance that ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the product specification
- Based on ISO 13485: 2003 / ISO 13485: 2016

Medical devices-Quality Management Systems-Requirements for regulatory purposes

Assessing the functionality of Quality Management System

Laboratory Evaluation

- **Design of evaluation mostly depends on :**

- Type of product/ Principle of assay

- Adequacy of information in presented Tech. file

- Risk class of product

Laboratory Evaluation (cont'd)

- Using control materials and biological specimens
- Against selected Comparative method
- Covering claimed analytical measuring range
- Interpretation : considering statistical analysis and clinical categorization

An important note of NGSP that should be remembered !!

- The NGSP certification evaluates agreement of each method at the manufacturing site using one lot of reagents and calibrators, one instrument, and one application under optimal conditions….For these reasons, it is important that laboratories review not only the certification status of HbA1c methods but also their performance in the CAP survey over time (a good indication of field performance) when selecting or evaluating HbA1c assay methods.


Thank you