METABOLOMIC
DIAGNOSTICS

Pathway To Regulation & Market
Diarmuid Cahalane Metabolomic Diagnostics

The Importance of Accurate Diagnosis:

"Rapid pulse, sweating, shallow breathing ... According to the computer, you've got gallstones."

Definition Of A Medical Device (US FDA)

"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

intended for use in the **diagnosis of disease** or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

intended to affect the structure or any function of the body of man or other animals, and which **does not achieve its primary intended purposes through chemical action within or on the body of man or other animals** and

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and **which is not dependent upon being metabolized** for the achievement of its primary intended purposes."

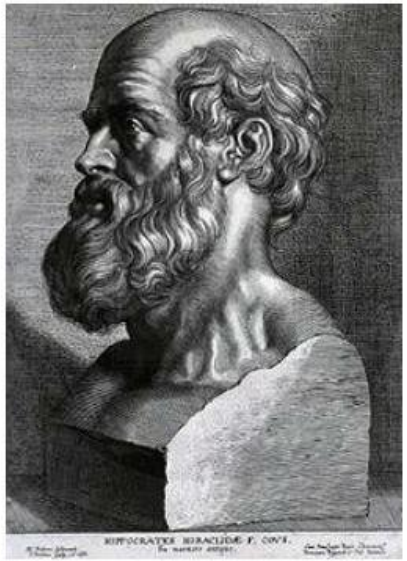
Definition of an IVD (HPRA)

An IVD medical device includes any medical device (such as a reagent, reagent product, calibrator, control material, instrument, apparatus) that is used alone or in combination and that is intended by the manufacturer to be used in vitro to provide information on, for example, a physiological or pathological state or **to monitor therapeutic measures**.

"It is more important to know what sort of person has a disease than to know what sort of disease a person has."

-Hippocrates

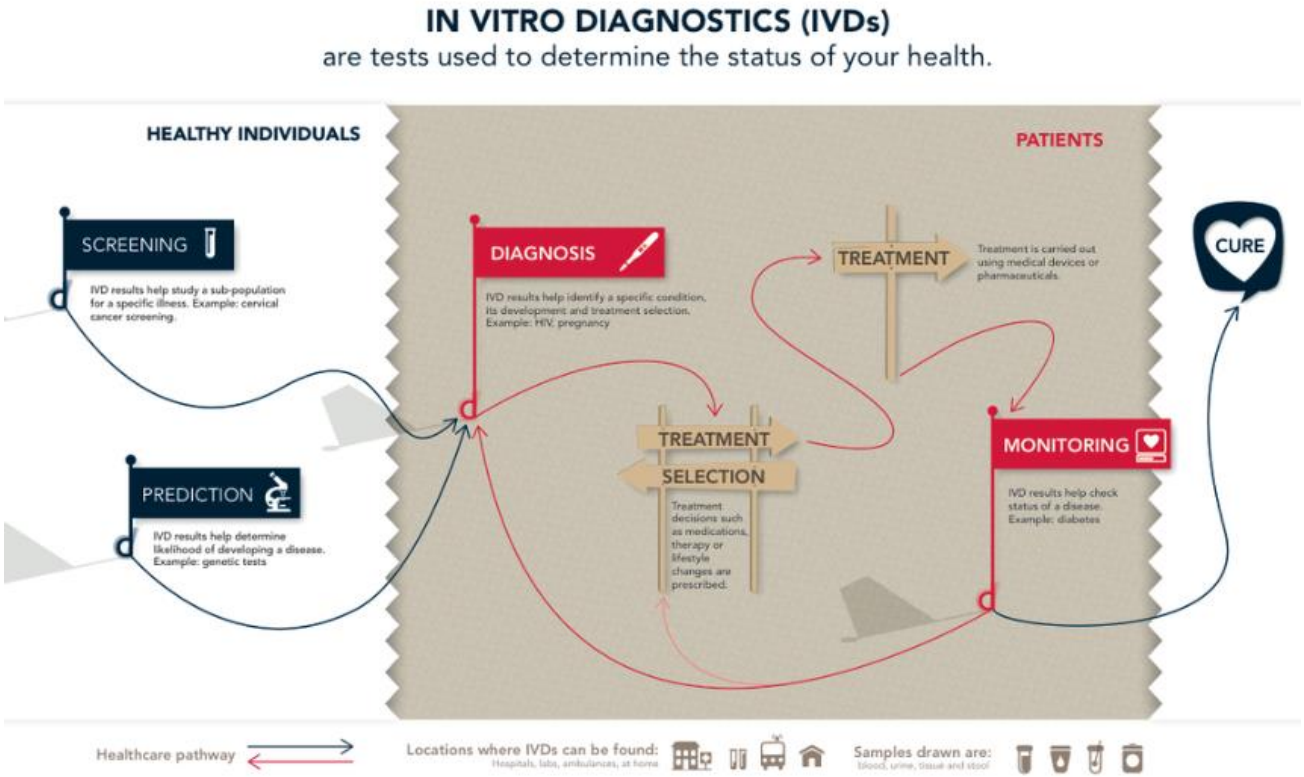
(460 BC – 370 BC)



Primum non nocere – First Do No Harm

A Risk Based Approach To Patient Safety And Product Development

IVDs Are Medical Devices



Three Critical Criteria For A Successful IVD

1. **Unmet Medical Need**

   Simple Blood Test For Preeclampsia

2. **Demonstrated Clinical Utility**

   Proven Analytical Validity: Clinical Study Data, Published Papers

3. **Support and Endorsement of Key Opinion Leader(s)**

   If Such A Test Was Available, I Would Recommend It Be Used

"...'unmet medical needs' means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected."

Commission Regulation (EC) No. 507/2006

(EC Regulation on the conditional marketing authorisation for medicinal products for human use)

The Importance Of Intended Use Statement

- Submitting an application for a narrow, unmarketable intended use statement (IUS) simply to obtain regulatory approval can result in a commercial dead end. The product may lawfully be sold, but the ability to promote it would be fatally constrained.

- IUS should not be drafted solely with the input of regulatory personnel. Sales and marketing personnel should provide guidance, as well. Companies must **consider the potential impact** of the intended use **on the commercial success** of the product.
- *Jeffrey n. Gibbs*

Device “Intended Use” Claims

- Intende[illegible] drivin[illegible] and
  [illegible]fic[illegible]

Indication For Use

Intended Population

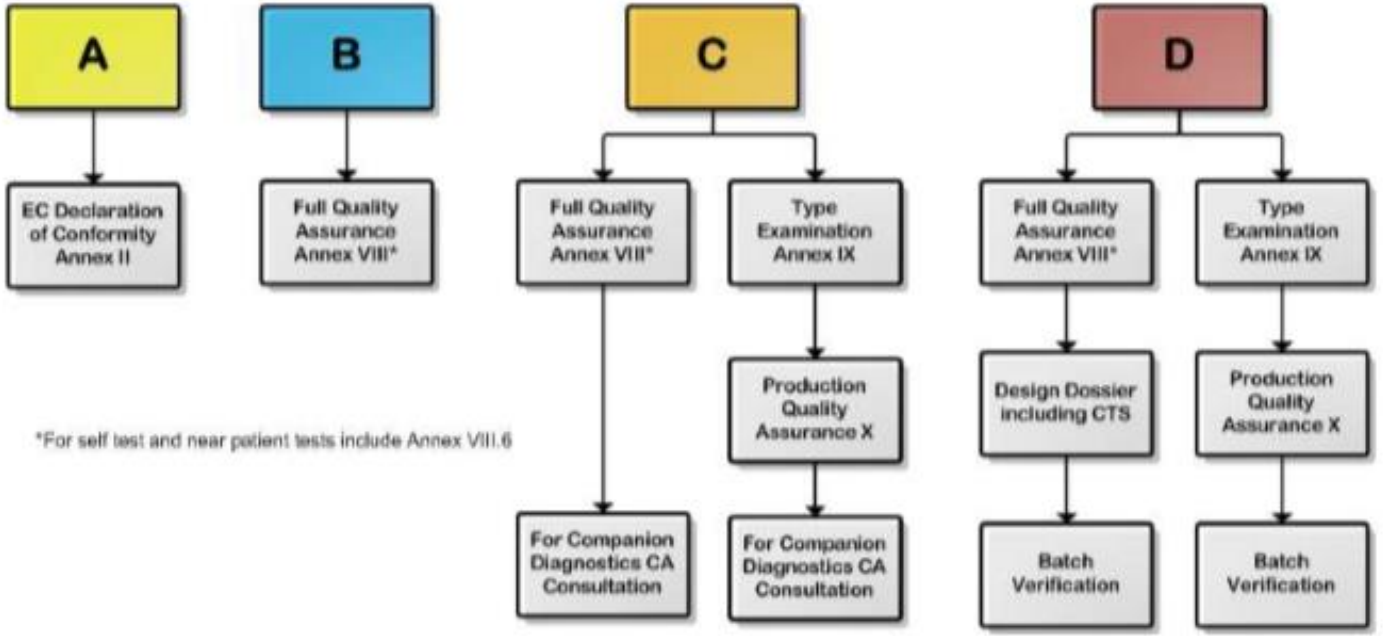
Analyte

The **XYZ** Assay is a multiplex Real Time RT-PCR *in vitro* diagnostic test for the rapid and qualitative detection and discrimination of **Influenza A Virus, Influenza B Virus, and Respiratory Syncytial Virus (RSV) nucleic acids** isolated and purified from **nasopharyngeal (NP) swab specimens obtained from symptomatic patients**. This test is **intended for use** to **aid in the differential diagnosis of Influenza A, Influenza B and RSV viral infections in humans** and is not intended to detect Influenza C.

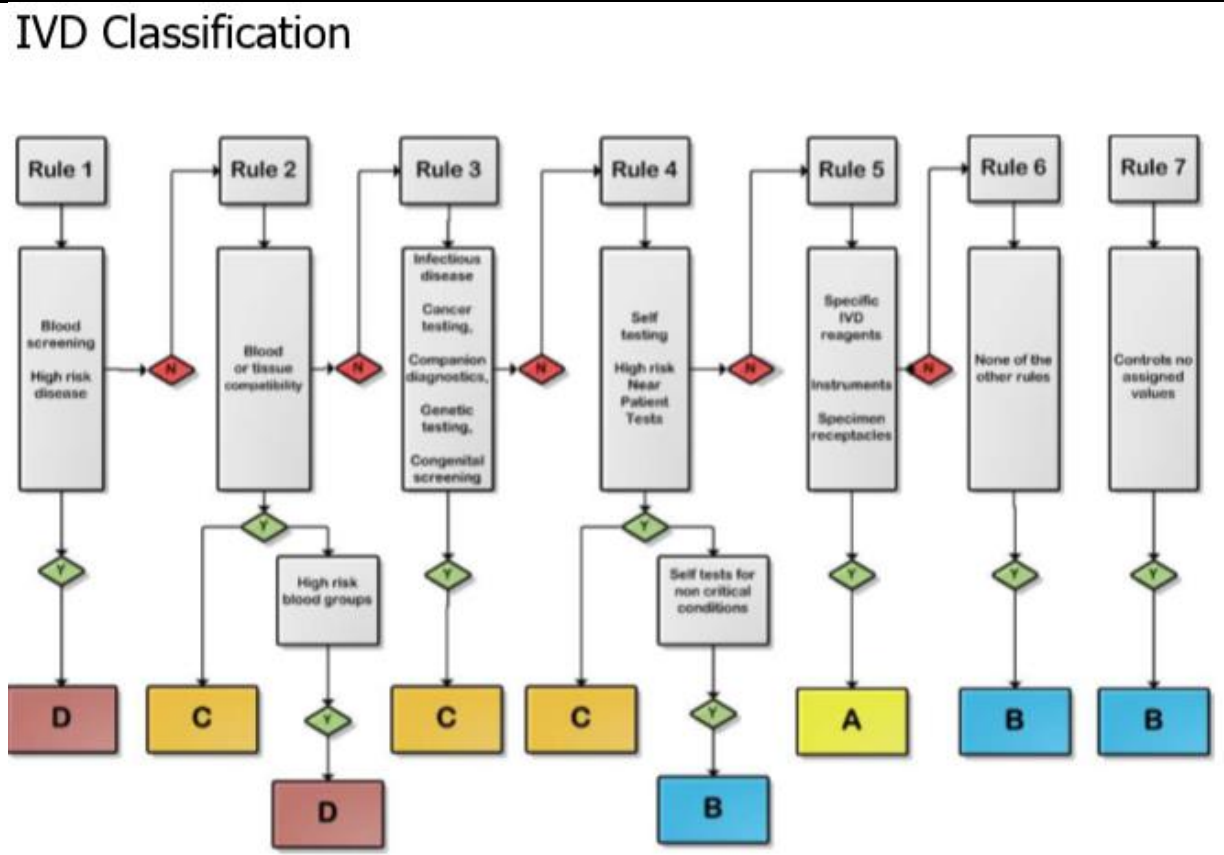
A negative test is presumptive and it is recommended these results be confirmed by cell culture. Negative results do not preclude influenza or RSV virus infection and should not be used as the sole basis for treatment or other management decisions.

Engage Early And Often With Regulatory Bodies (European Commission, Competent Authorities, FDA, etc.)

Risk Based Approach To Classification



Risk Based Approach To Classification



HPRA Classification Table:

- *"the Classification system for IVD medical devices is a **risk based** classification system based on the intended use as **specified by the manufacturer**"*

Class	Risk Level	Examples
A	Low individual risk and low public health risk	Clinical chemistry analyser, prepared selective culture media
B	Moderate individual risk and/or low public health risk	Vitamin B12, Pregnancy self testing, urine test stips
C	High individual risk and/or moderate public health risk	Blood glucose self testing, HLA typing, PSA screening
D	High individual risk and high public health risk	HIV blood donor screening, HIV blood diagnostic

Patient Safety Based On Risk

Governments are responsible for protecting the safety of their citizens. In order to ensure that citizens are not subjected to unnecessary risk, governments regulate products and activities that could cause harm

This is done by means of legislation.

It is important to remember that all regulatory and legislative requirements governing how we develop, test, manufacture and distribute medical devices including IVDs are based purely on the basis of patient safety. The greater the risk, the more rigorous the regulatory framework. We, or our relatives will all be patients one day. We will assume that the products used to treat us have been produced to the highest possible standards

The Regulatory Environment (European Union)

In the European Union, medicines are regulated by the national competent authorities (CA), in conjunction with the EMA

Medical Devices (Including IVDs) are regulated by the European Commission. The directives published by the EC are passed into law by the member states by way of a “Statutory Instrument, “ or S.I. Depending on the classification of the medical device it may require the involvement of a notified body to certify that the manufacturer is operating in conformance with the regulatory requirements.

https://ec.europa.eu/growth/sectors/medical-devices_en

The Regulatory Environment United States of America

In the United States, the regulatory authority responsible for both pharmaceuticals and medical devices is the Food & Drug Administration, (FDA).

Within the FDA, the division that regulates medical devices, including IVDs is the Center for Devices & Radiological Health, (CDRH).

Since it's establishment in 1906, the FDA has become one of the US' most trusted federal agencies.

https://www.fda.gov/medical-devices/ivd-regulatory-assistance/overview-ivd-regulation

EMA's future role for companion diagnostic development

IVDR Article 48(3)

For **companion diagnostics** the **notified body** shall **consult** the concerned **competent authority** designated in accordance with Directive 2001/83/EC or the European Medicines Agency (**EMA**), as applicable

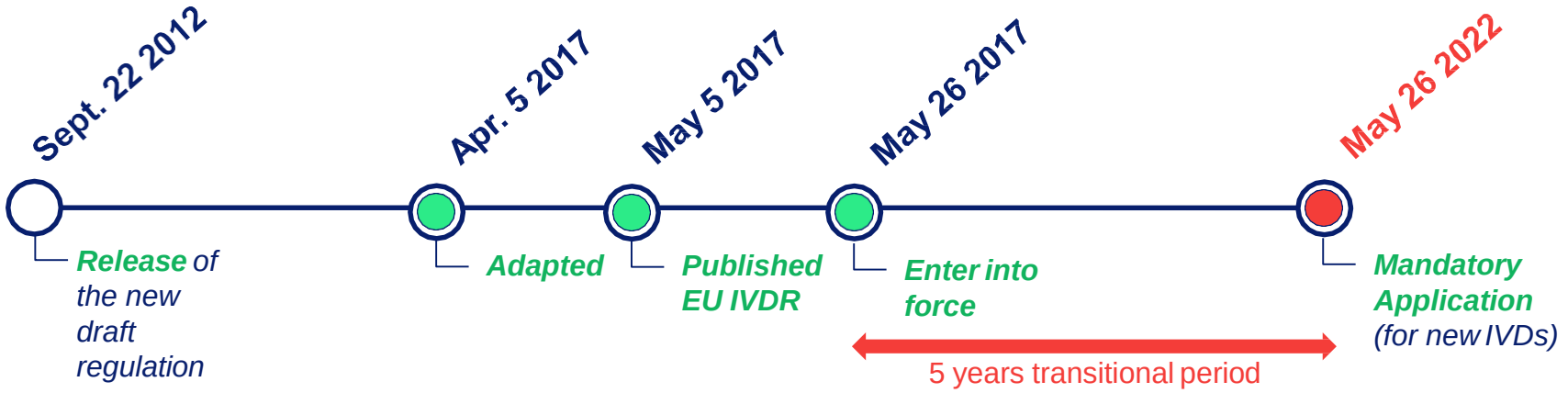
ANNEX IX, Chapter II - 5.2. Assessment of the technical documentation of companion diagnostics

The notified body shall, before issuing an EU technical documentation assessment certificate for the companion diagnostic and **on the basis of the draft summary of safety and performance** […] consult one of the competent authorities […] **regarding the suitability of the device in relation to the medicinal product concerned**.

Challenges in (co-)development of companion diagnostic and medicinal product

- No requirement of simultaneous development of CDx and medicine from beginning to end
- Co-development should generally facilitate contemporaneous marketing authorizations for the medicinal product and the associated IVD companion diagnostic - but not a requirement
- New IVDR specifies timeframe (max 120 days) for scientific opinion

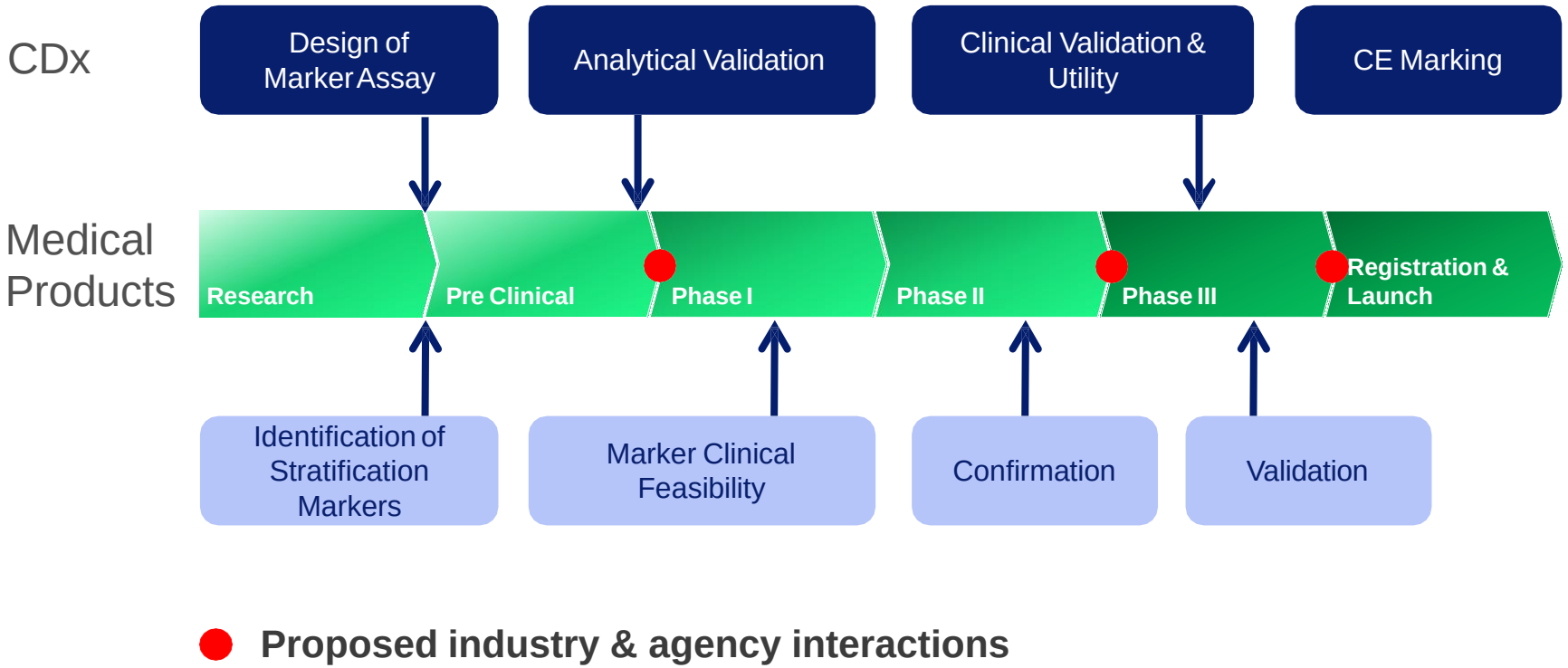
Key Dates


Sept. 22 2012
Apr. 5 2017
May 5 2017
May 26 2017
May 26 2022
Release of the new draft regulation
Adapted
Published EU IVDR
Enter into force
Mandatory Application (for new IVDs)
5 years transitional period

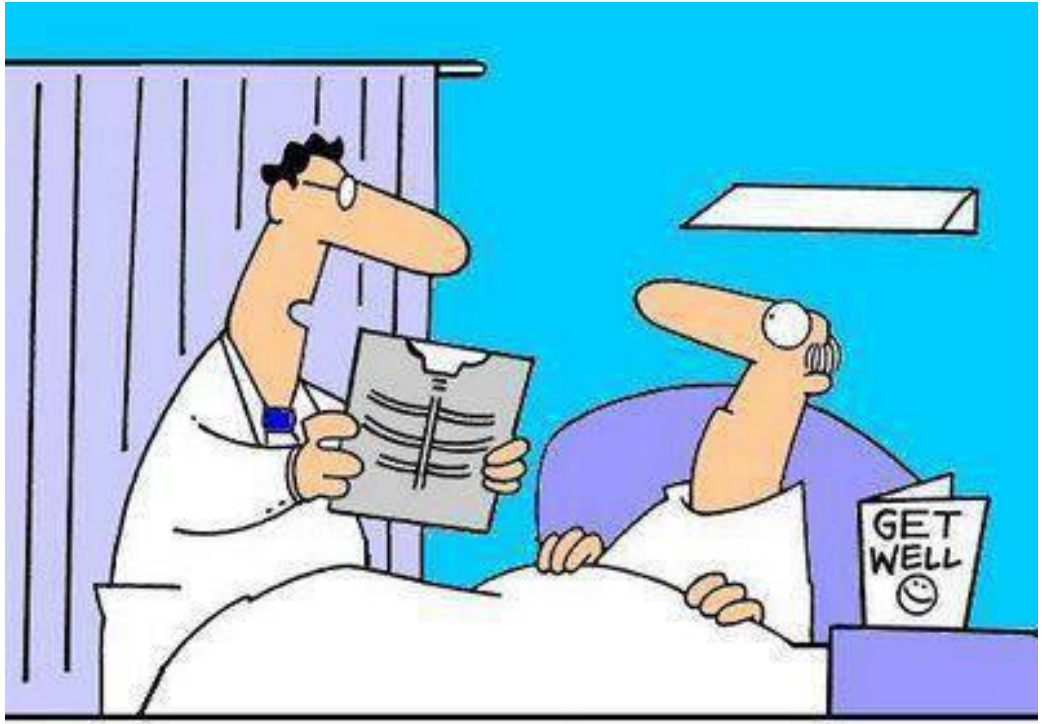
Summary of CE Marking Requirements for CDx

General CE Marking Requirements	Additional requirements for CDx
Compliance with general safety and performance requirements (+ clinical evidence)	Quality management system and technical documentation of representative samples assessed by the NB
Technical documentation and specific documentation on post-market surveillance	Summary of safety and performance characteristics of the device
Manufacturer's quality management system (ISO 13485)	At the request of a Member State, the Commission may designate EU reference laboratories to check the claimed performance of the device
Post-market requirements (Post-market surveillance, vigilance and market surveillance)	Regular surveillance assessment by NB in the post-market phase
All technical documentation made available upon request of any Competent Authority	Update of the performance evaluation report and the summary of safety and performance, as necessary
	Analyses of the gathered post-market surveillance data (Periodic safety update report)
Color code: *Reinforced requirements in green* *New requirements in blue*	EMA / NCA review

Coordination of CDx & Drug Developments



Digital Health



"Your x-ray showed a broken rib, but we fixed it with Photoshop."

Thank You
Any Questions?

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