Companion Diagnostics (CDx) and personalized Medicine

Rolf Thermann
TÜV Rheinland LGA Products GmbH

LISAvienna Business Treff:
Regulatory Konferenz für Medizinprodukte und IVD
Wien, 06.11.2018

TÜVRheinland®
Precisely Right.

Companion Diagnostics, topics to speak about…..

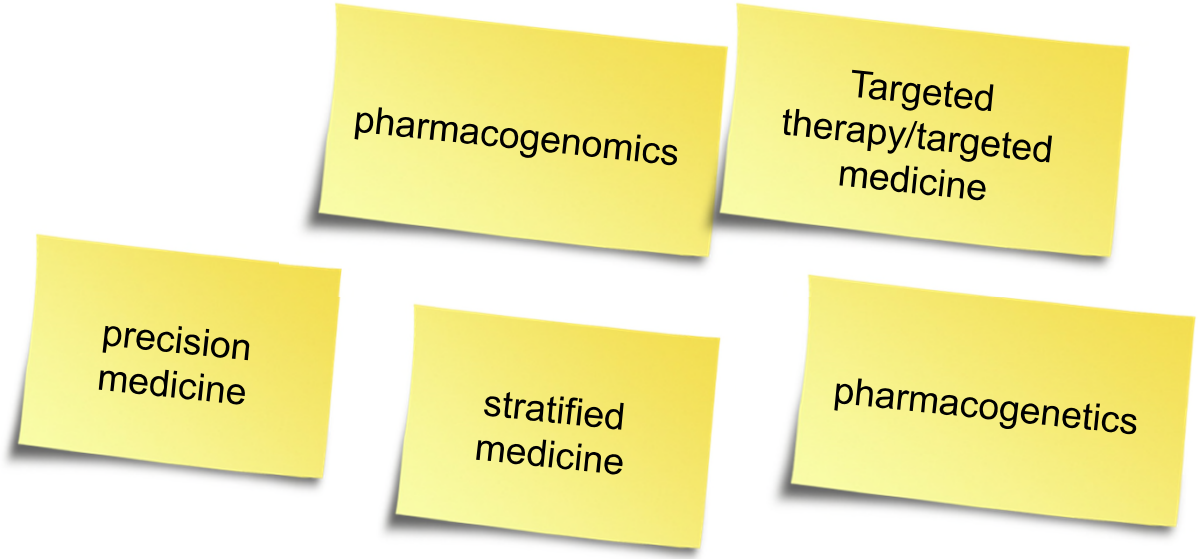
- A brief introduction about personalized medicine
- Companion Diagnostics under IVDR, how is it defined ?
- Risk classification, conformity assessment, clinical evaluation and some CDx specialities
- Rx + CDx: Routes to compliance

TÜVRheinland®
Precisely Right.

A brief introduction about personalized medicine

TÜVRheinland®
Precisely Right.

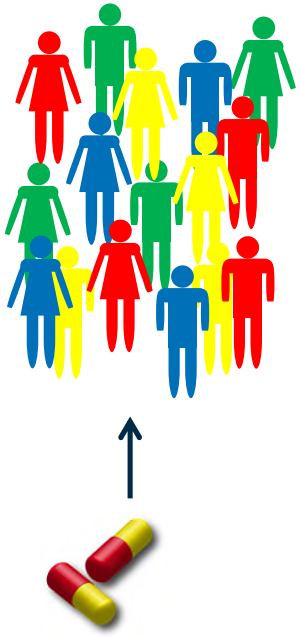
Personalized Medicine



TÜVRheinland®
Precisely Right.

Personalized Medicine

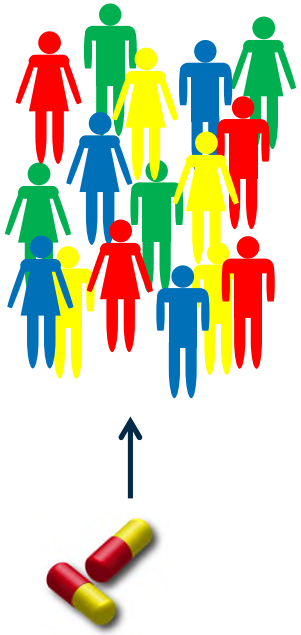
One-size-fits-all medicine



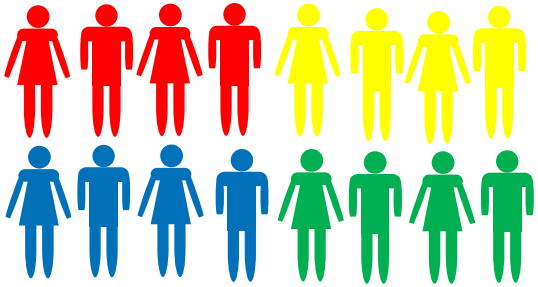
TÜVRheinland®
Precisely Right.

Personalized Medicine

One-size-fits-all medicine



Stratification medicine

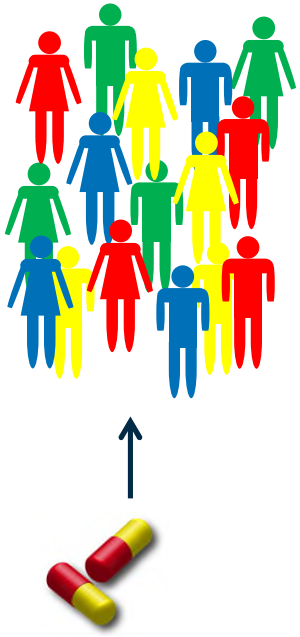


Grouping:
- **Disease Subtypes**
- **Biomarkers**

TÜVRheinland®
Precisely Right.

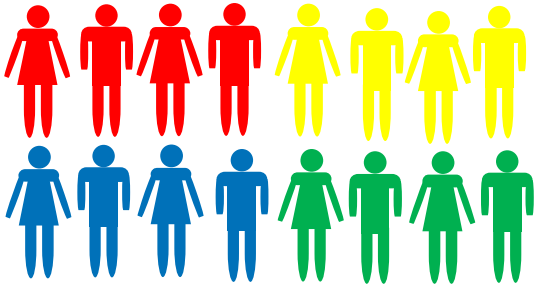
Personalized Medicine

One-size-fits-all medicine



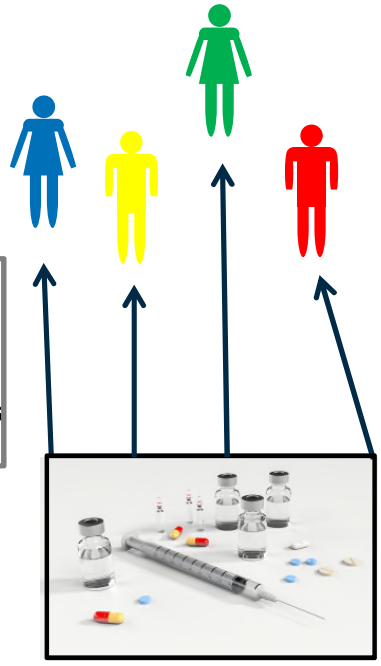
Grouping:
- **Disease Subtypes**
- **Biomarkers**

Stratification medicine



Individual Patient:
- **Clinical History**
- **Medication**
- **Biomarker**
- **Indiv. Preferences**
- **Habits/Lifestyle**

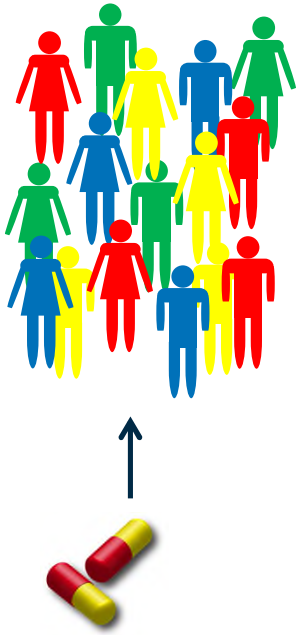
Personalized medicine



TÜVRheinland®
Precisely Right.

Personalized Medicine

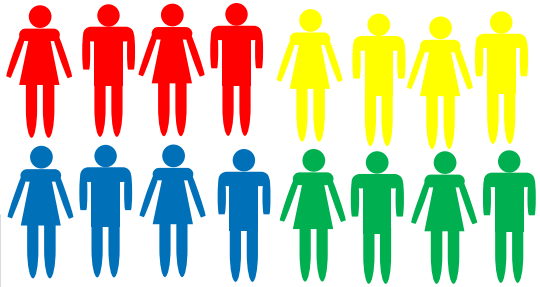
One-size-fits-all medicine



CDx

Grouping:
- Biomarkers

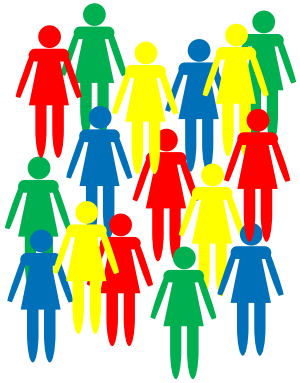
Stratification medicine



TÜVRheinland®
Precisely Right.

Companion Diagnostics/IVD‘s

What is a Companion Diagnostic (CDx) ?

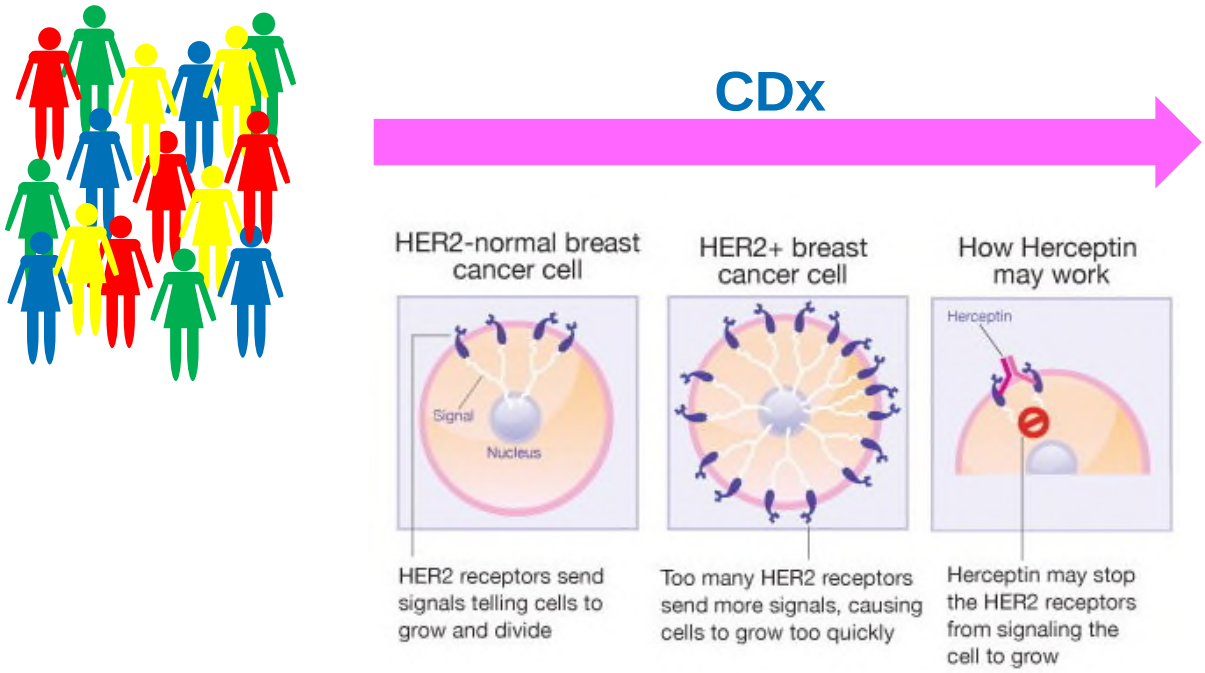


TÜVRheinland®
Precisely Right.

Companion Diagnostics/IVD‘s

What is a Companion Diagnostic (CDx) ?

First simultaneous approval of CDx (HER2 Assay) and Rx (Herceptin) 1998 in the US.

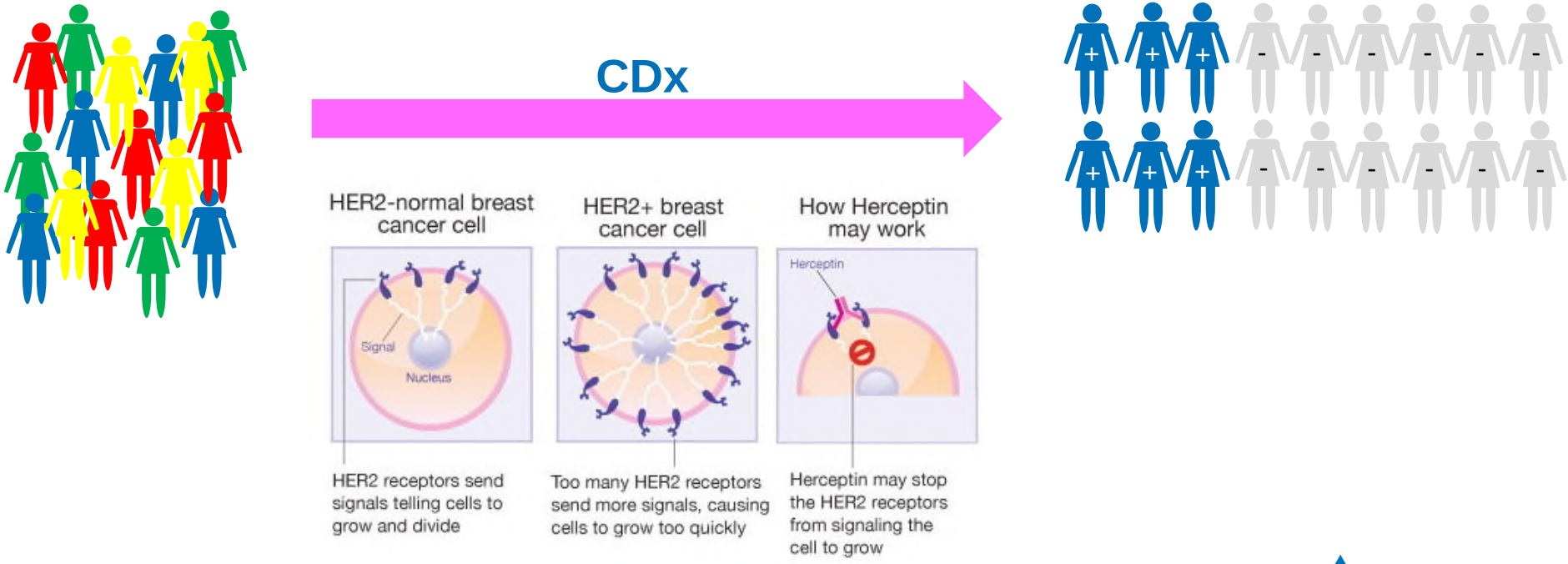


TÜVRheinland®
Precisely Right.

Companion Diagnostics/IVD‘s

What is a Companion Diagnostic (CDx) ?

First simultaneous FDA-approval of CDx (HER2 Assay) and Rx (Herceptin) 1998 in the US by Roche.



TÜVRheinland®
Precisely Right.

Companion Diagnostics under IVDR, how is it defined ?

TÜVRheinland®
Precisely Right.

Companion Diagnostics definition

CDx definition IVDR (article 2 (7))

„companion diagnostic' means a device which is essential for the safe and effective use of a **corresponding medicinal product** to:

- identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product;

or

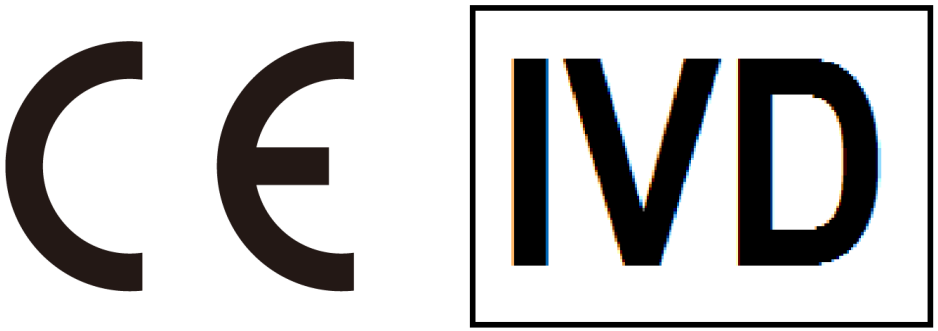
- identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product;

- Devices that are used with a view to monitoring treatment with a medicinal product in order to ensure that the concentration of relevant substances in the human body is within the therapeutic window are not considered to be companion diagnostics.

Companion Diagnostics/IVD‘s

CDx definition (IVDR, Preamble, 10)

“It should be made clear that all tests that provide information on the predisposition to a medical condition or a disease, such as genetic tests, and tests that provide information to predict treatment response or reactions, such as companion diagnostics, are ***in vitro* diagnostic medical devices**”.



TÜVRheinland®
Precisely Right.

Companion Diagnostics definition EU/US

CDx definition IVDR (article 2 (7))/FDA (2014)

„companion diagnostic' means a device which is essential for the safe and effective use of a corresponding medicinal product to:

- identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product;

  (Identify patients who are most likely to benefit from the therapeutic product)

or

- identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product;

  (to identify patients likely to be at increased risk of serious adverse reactions as a result of treatment with the therapeutic product)

- Devices that are used with a view to monitoring treatment with a medicinal product in order to ensure that the concentration of relevant substances in the human body is within the therapeutic window are not considered to be companion diagnostics.

  (to monitor response to treatment with the therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness)

Companion Diagnostics definition EU/US

„Complementary Diagnostics“ (FDA, 2015)

“A test that identify a biomarker-defined subset of patients that respond particularly well to a drug and aid risk/benefit assessments for individual patients, but that are not pre requisites for receiving the drug.”

A complementary test is not required, but it’s recommended (regulating LDTs, first pass metabolism, i.e. CYP 450)

Risk classification, conformity assessment, clinical evaluation and some CDx specialities

TÜVRheinland®
Precisely Right.

Companion Diagnostics risk classification

Classification of devices (Annex VIII)

„Devices shall be divided into classes A, B, C, and D, taking into account the intended purpose of the devices and their inherent risks. Classification shall be carried out in accordance with Annex VIII.“ (IVDR, Article 47)

Class	Risik	Examples
A	Low individual risk and low risk to public health	General lab supply, media, sample containers
B	Moderate individual risk and/or low risk to public health	Pregnancy self-tests, urine test strips, Vitamine B12
C	High individual risk and/or medium risk for public health	HLA typing, PSA, Rubella, Cancer diagnostics, -staging, CDx
D	High individual risk and high risk for public health	Blood donor screening (HIV/HCV), blood grouping (A,B,O)

IVDR, Annex VIII, Rule 3

Companion Diagnostics risk classification

Classification of devices (Annex VIII)

Class	Risik	Examples
A	Low individual risk and low risk to public health	General lab supply, media, sample containers
B	Moderate individual risk and/or low risk to public health	Pregnancy self-tests, urine test strips, Vitamine B12
C	High individual risk and/or medium risk for public health	HLA typing, PSA, Rubella, Cancer diagnostics, -staging, CDx
D	High individual risk and high risk for public health	Blood donor screening (HIV/HCV), blood grouping (A,B,O)

For products in classes B-D inclusion of Notified Body is mandatory!

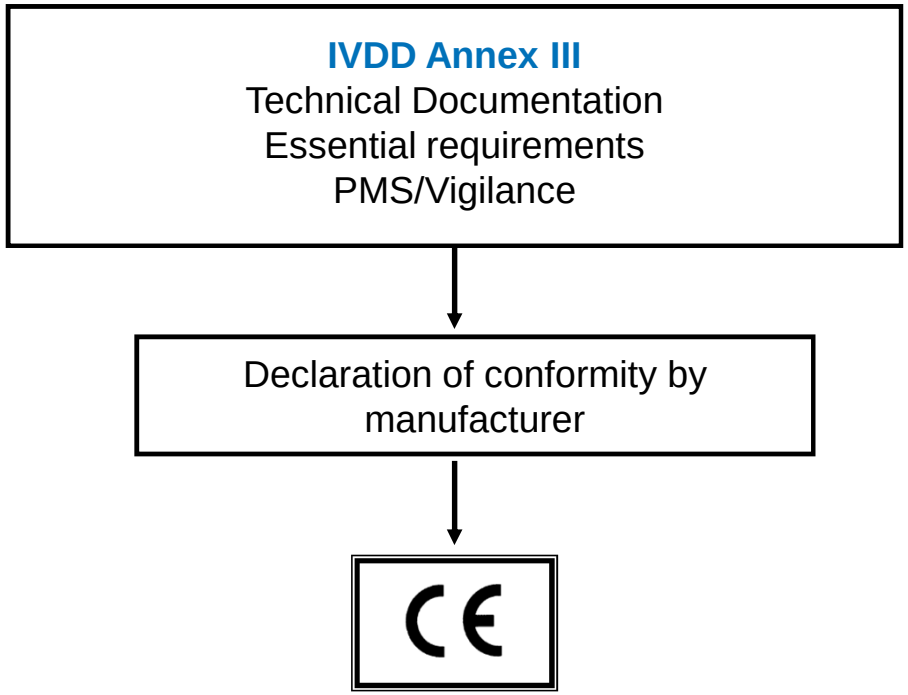
TÜVRheinland®
Precisely Right.

Companion Diagnostics IVDD

Current legislation under IVDD (98/79/EC): Self-declaration (Annex III)

Companion Diagnostics = „other IVD“

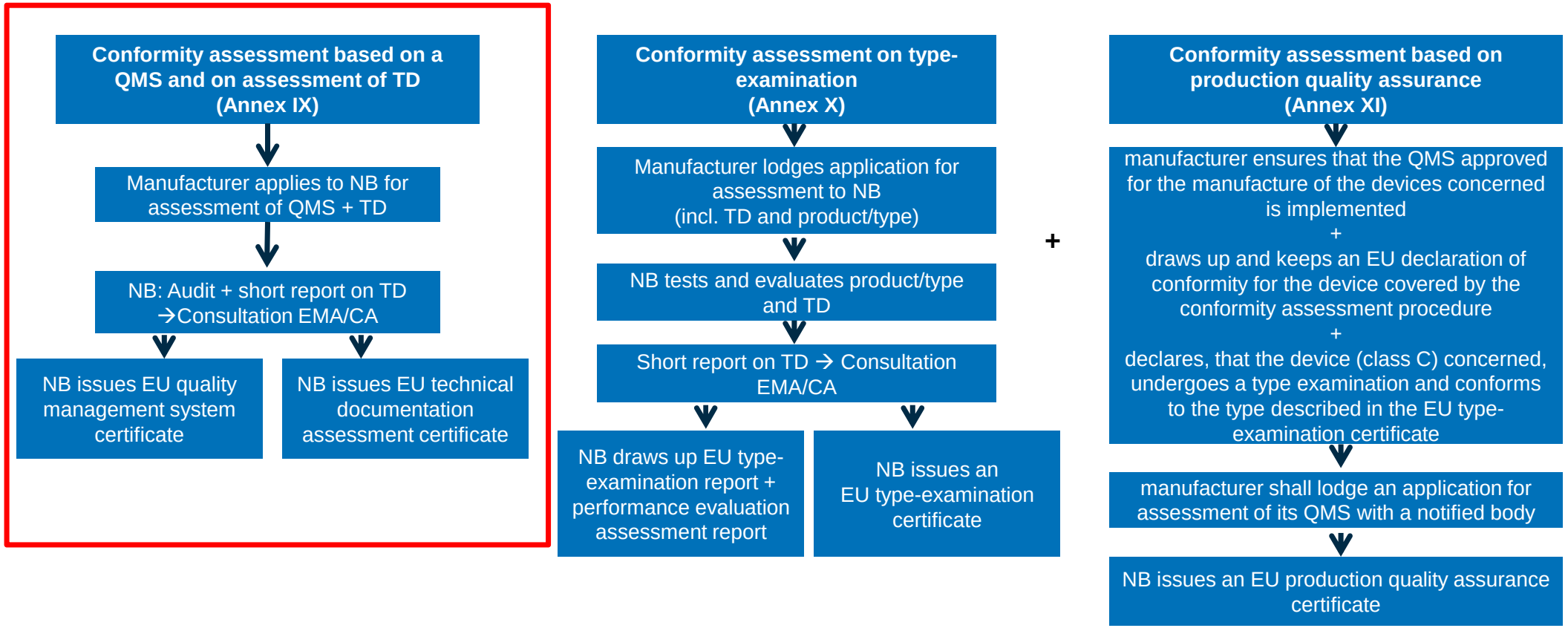
- “Self-declaration“ of conformity by manufacturer
- Inclusion of a third party (Notified Body) not necessary
- IVDD (98/79/EG) Annex III „EC declaration of conformity“
- Manufacturer ensures and declares that products concerned meet the provisions of the Directive
- Technical Documentation (IVDD Annex III.3) including
  - -general description of the product,
  - -documentation of the quality system
  - -results of the risk analysis
  - -test reports/performance evaluation
- Manufacturer ensures that the manufacturing process follows the principles of quality assurance (IVDD Annex III.4)
- systematic procedure to review experience gained from devices in the post-production phase



TÜVRheinland®
Precisely Right.

Companion Diagnostics conformity assessment

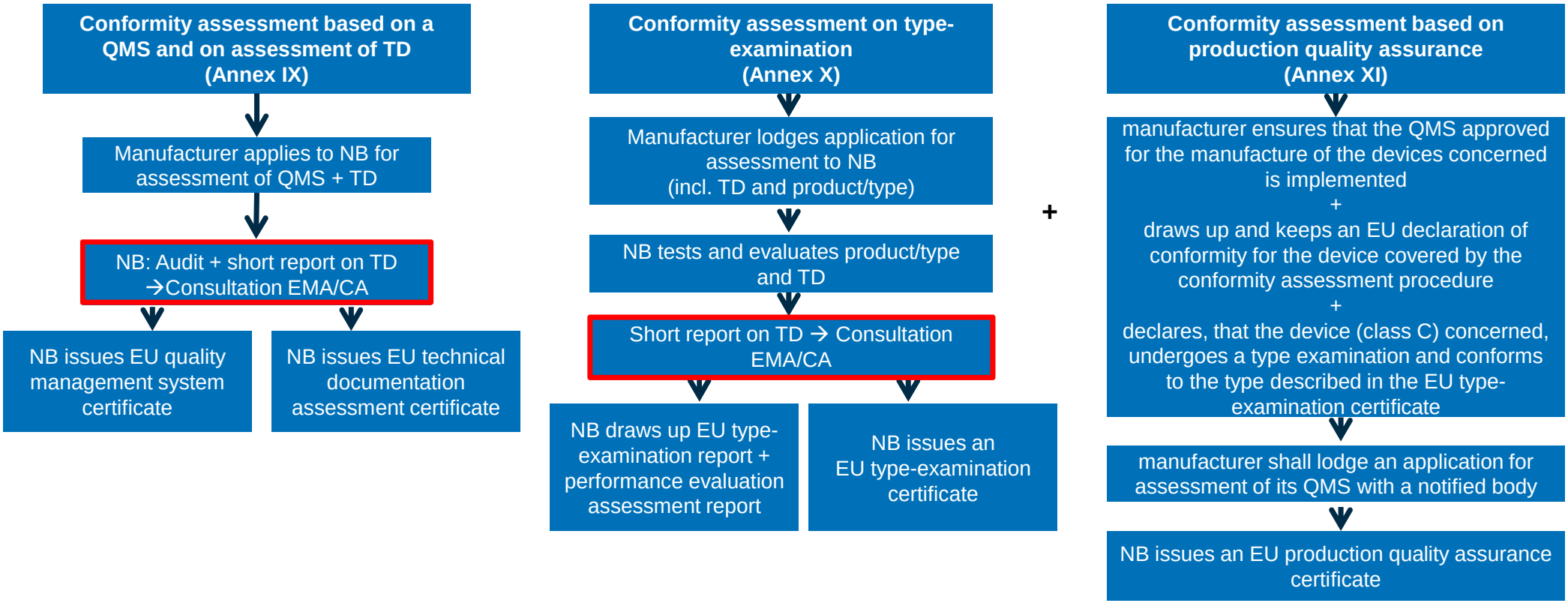
Routes of conformity assessment (IVDR, Article 48/Annex IX-XI)



TÜVRheinland®
Precisely Right.

Companion Diagnostics conformity assessment

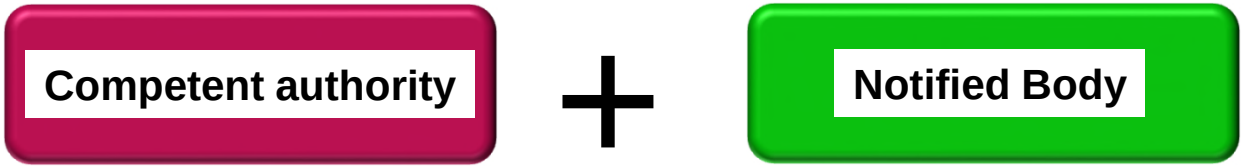
Routes of conformity assessment (IVDR, Article 48/Annex IX-XI)



TÜVRheinland®
Precisely Right.

Companion Diagnostics conformity assessment: Players

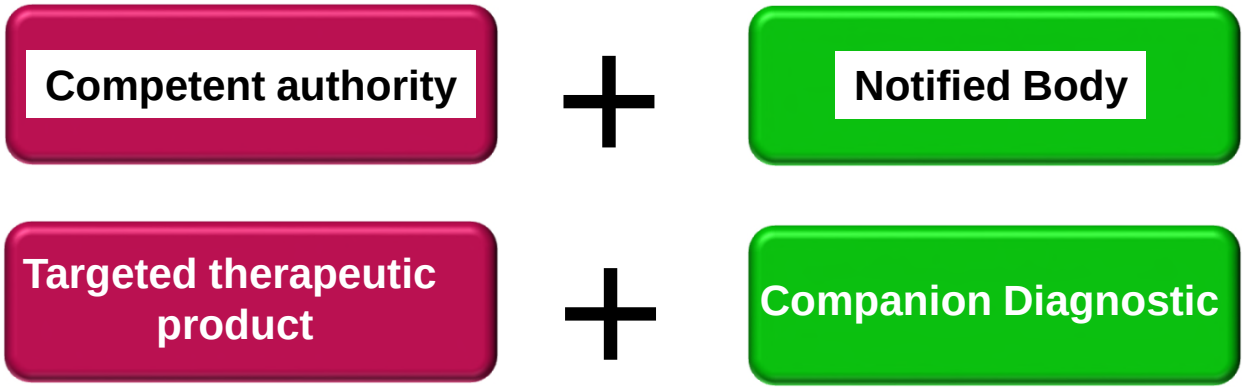
The EU situation



TÜVRheinland®
Precisely Right.

Companion Diagnostics conformity assessment: Players

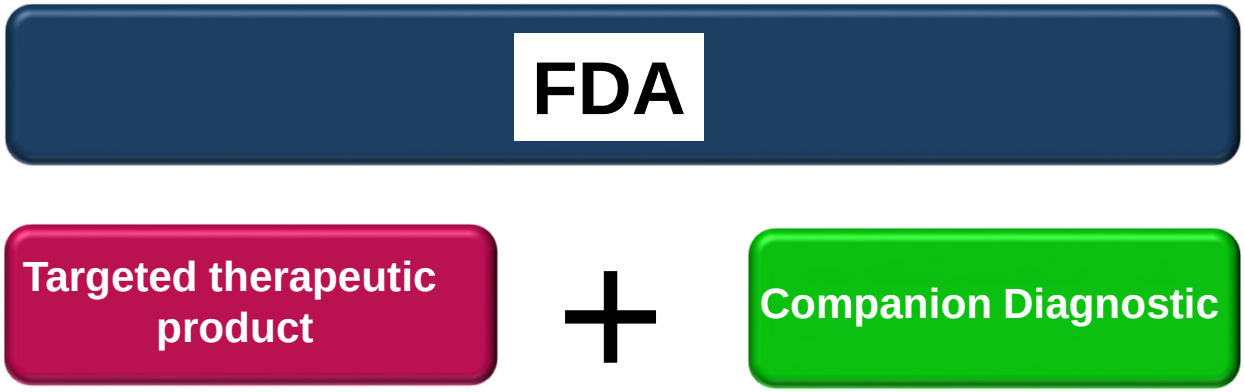
The EU situation



TÜVRheinland®
Precisely Right.

Companion Diagnostics conformity assessment: Players

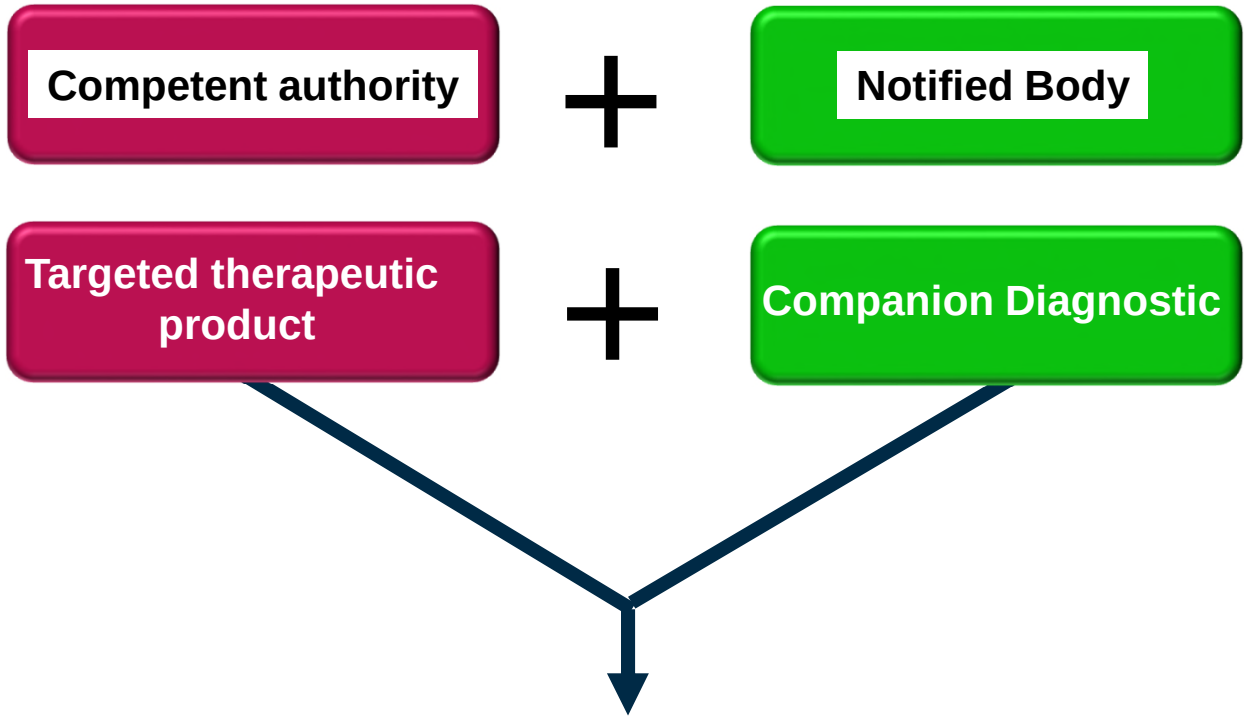
The US situation



TÜVRheinland®
Precisely Right.

Companion Diagnostics conformity assessment: Players

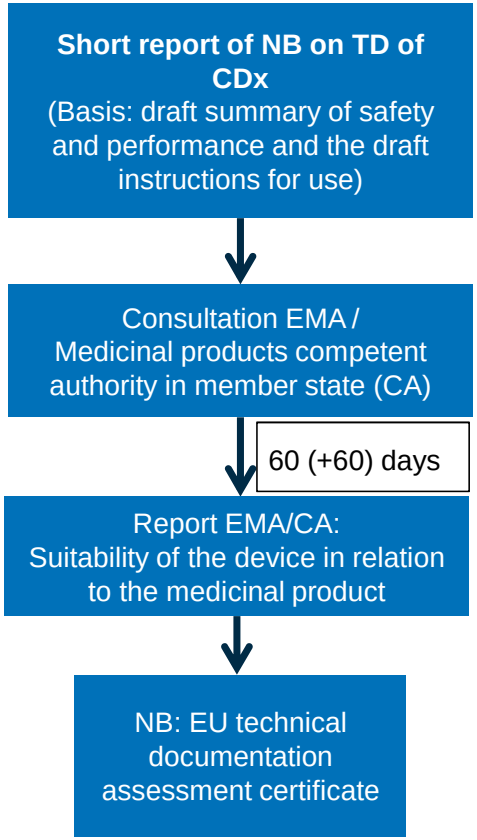
The EU situation



TÜVRheinland®
Precisely Right.

Companion Diagnostics consultation process

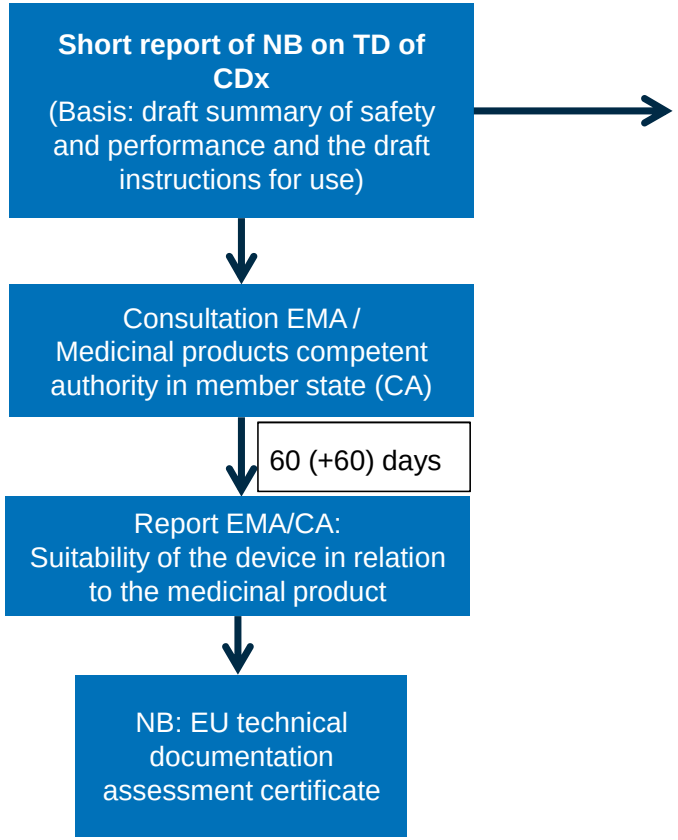
Consultation process EMA / Medicinal products competent authority (CA)



TÜVRheinland®
Precisely Right.

Companion Diagnostics consultation process

Consultation process EMA / Medicinal products competent authority (CA)



- **Article 29** („Summary of safety and performance“)
- **Annex XIII** („Performance evaluation, performance studies and post-market performance follow up (PMPF))
- **Annex I, Chapter III** (“Requirements regarding information supplied with the device”)

TÜVRheinland®
Precisely Right.

Companion Diagnostics: Miscellaneous

Assessment of the technical documentation of companion diagnostics: TD-file sampling

Article 48 (7):

Manufacturers of class **C devices**, other than devices for performance study, shall be subject to a conformity assessment as specified in Chapters I and III of Annex IX, including an assessment of the technical documentation as specified in Sections 4.4 to 4.8 of that Annex of **at least one representative device per generic device group.**

In addition to the procedures referred to in the first and second subparagraphs, for **companion diagnostics** the notified body shall for **every device follow the procedure for technical documentation assessment** laid down in Section 5.2 of Annex IX, and shall apply the procedure for technical documentation assessment laid down in Sections 4.1 to 4.8 of Annex IX……..

No sampling of TD-files for CDx products !

Companion Diagnostics: Miscellaneous

Specific and relevant requirements for CDx

- Information in the instructions for use:

  „The instructions for use shall contain ….. its function (e.g. companion diagnostic)…and for companion diagnostics, **the International Non-proprietary Name (INN, i.e. *-azepam* for Diazepam-derivatives) of the associated medicinal product for which it is a companion test**

  (Annex I, Chapter 3: Requirements regarding information supplied with the device)

EMA: Assignment of CDx on the basis of a result (Summary of product characteristics, SmPC)

FDA: Assignment of CDx on the basis of a brand name

- Device description and specification:

  „…the intended purpose of the device which may include information on … its function such as Companion Diagnostic…in addition, for companion diagnostics, **the relevant target population and the associated medicinal product(s)**.

  (Annex II: Technical Documentation)

TÜVRheinland®
Precisely Right.

Companion Diagnostics: Miscellaneous

Additional requirements for certain performance studies (Article 58, IVDR).

- Performance studies / interventional clinical performance studies (Article 58)

  "**Performance studies involving companion diagnostics** shall….in addition to meeting the requirements set out in **Article 57** and **Annex XIII**, be designed, authorised, conducted, recorded and reported in accordance with **Article 58** and **Articles 59 to 77 and Annex XIV**."

  "This **does not apply to performance studies involving companion diagnostics using only left-over samples**. Such studies shall however be notified to the competent authority."

  "in the case of interventional clinical performance studies, the analytical performance and scientific validity has been demonstrated, taking into consideration the state of the art. **Where, for companion diagnostics, the scientific validity is not established, the scientific rationale for the use of the biomarker shall be provided**"

TÜVRheinland®
Precisely Right.

Companion Diagnostics: Performance evaluation

Clinical evidence (Article 2 and 56, Annex XIII)

„Scientific validity of an analyte" means the association of an analyte with a clinical condition or a physiological state.

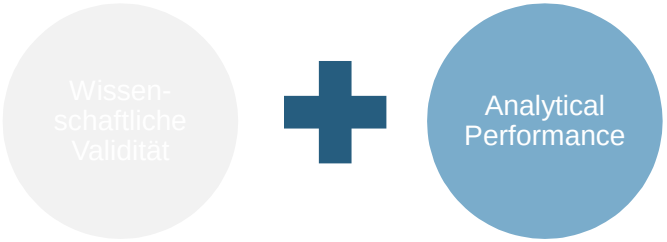
- relevant information on the scientific validity of devices measuring the same analyte or marker;
- scientific (peer-reviewed) literature;
- consensus expert opinions/positions from relevant professional associations;
- results from proof of concept studies;
- results from clinical performance studies.

TÜVRheinland®
Precisely Right.

Companion Diagnostics: Performance evaluation

Clinical evidence (Article 2 and 56, Annex XIII)

„Analytical performance" means the ability of a device to correctly detect or measure a particular analyte.



- As a general rule, the analytical performance shall always be demonstrated on the basis of analytical performance studies.
- For novel markers or other markers without available certified reference materials or reference measurement procedures, it may not be possible to demonstrate trueness.
  - Composite reference standard (CRS)
  - Clinical performance studies

TÜVRheinland®
Precisely Right.

Companion Diagnostics: Performance evaluation

Clinical evidence (Article 2 and 56, Annex XIII)

„Clinical performance'" means the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended user.

- clinical performance studies;
- scientific peer-reviewed literature;
- published experience gained by routine diagnostic testing.
- Clinical performance studies shall be performed unless due justification is provided for relying on other sources of clinical performance data

TÜVRheinland®
Precisely Right.

Companion Diagnostics: Performance evaluation

Clinical evidence (Article 2 and 56, Annex XIII)

„Clinical evidence" means clinical data and performance evaluation results, pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer.

Annex XIII, 1.3.2. Performance evaluation report
The clinical evidence shall be documented in a performance evaluation report. This report shall include the scientific validity report, the analytical performance report, the clinical performance report and an assessment of those reports allowing demonstration of the clinical evidence.

TÜVRheinland®
Precisely Right.

Companion Diagnostics: Performance evaluation

Clinical evidence (Article 2 and 56, Annex XIII)

"Clinical benefit" means the positive impact of a device related to its function, such as that of screening, monitoring, diagnosis or aid to diagnosis of patients, or a positive impact on patient management or public health;

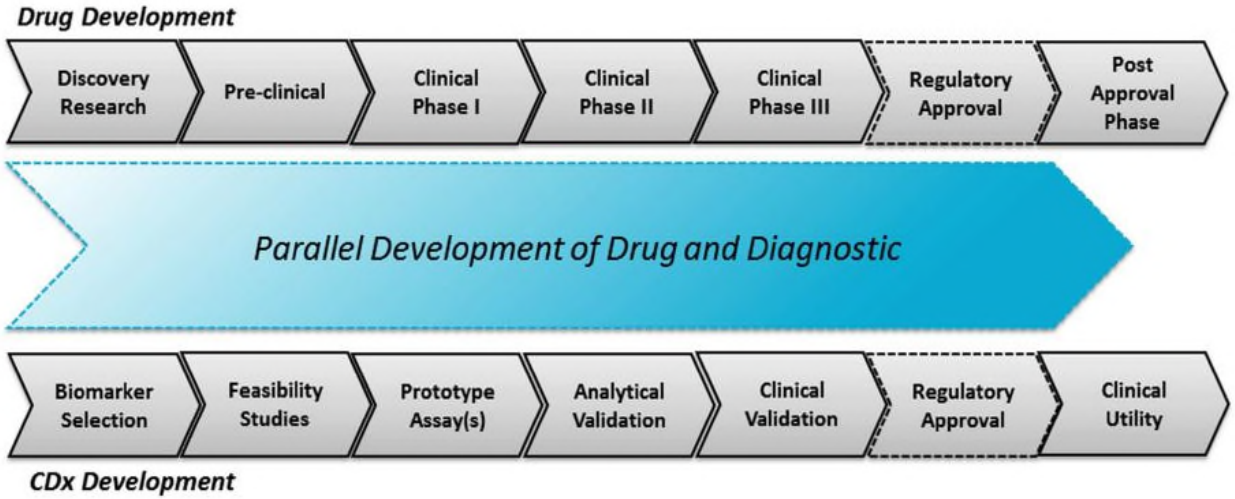
TÜVRheinland®
Precisely Right.

Rx + CDx: Routes to compliance

TÜVRheinland®
Precisely Right.

Companion Diagnostics: Routes to compliance

Regulators opinion on CDx developmental strategies

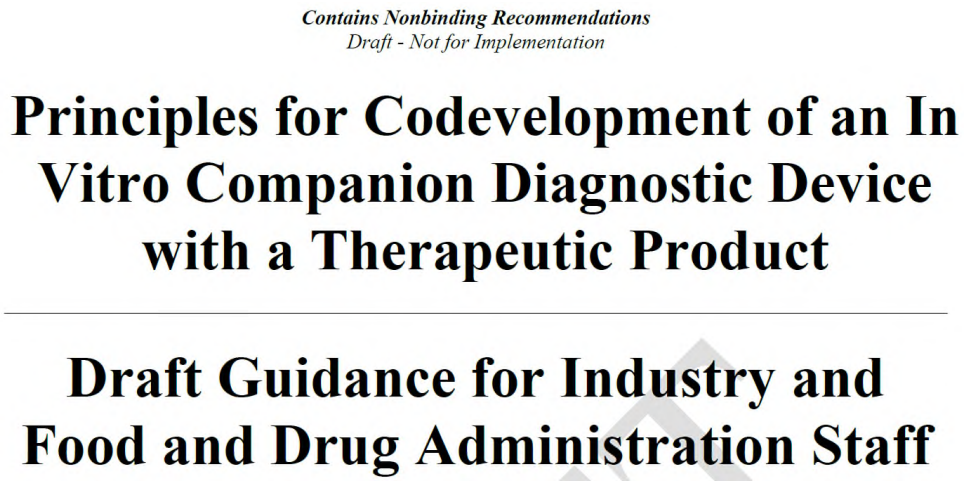


Dana Olsen1 and JanTrøst Jørgensen, Companion diagnostics for targeted cancer drugs – clinical and regulatory aspects, Frontiers in Oncology, pages 1-8, Vol. 4, May 2014.

TÜVRheinland®
Precisely Right.

Companion Diagnostics: Routes to compliance

Regulators opinion on CDx developmental strategies: **FDA**



Contains Nonbinding Recommendations
Draft - Not for Implementation

Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

---

Draft Guidance for Industry and Food and Drug Administration Staff

"This guidance document is intended to be a practical guide to assist therapeutic product sponsors and IVD sponsors in developing a therapeutic product and an accompanying IVD companion diagnostic, a process referred to as *codevelopment*. This guidance is also intended to assist FDA staff participating in the review of candidate IVD companion diagnostics or their associated therapeutic products.

TÜVRheinland®
Precisely Right.

Companion Diagnostics: Routes to compliance

Regulators opinion on CDx developmental strategies: **EMA**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2010
EMA/CHMP/641298/2008
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on co-development of pharmacogenomic biomarkers and Assays in the context of drug development

Draft

Draft Agreed by Pharmacogenomics Working Party	June 2010
Adoption by CHMP for release for consultation	24 June 2010
End of consultation (deadline for comments)	30 November 2010

Comments should be provided using this template. The completed comments form should be sent to PGWPSecretariat@ema.europa.eu

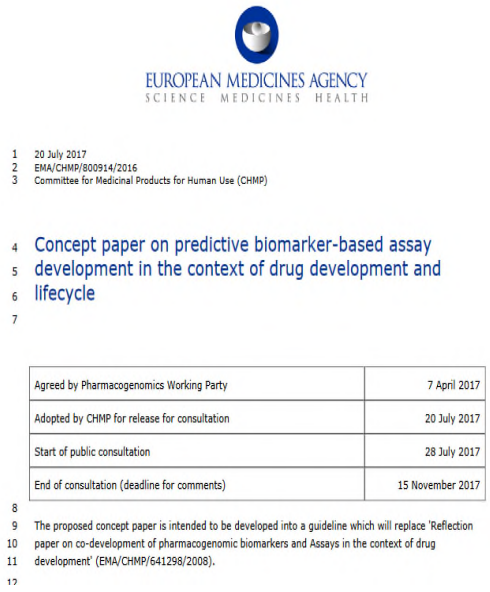
Keywords	*Genomic biomarkers, Pharmacogenetics, pharmacogenomics, assays, platforms, genetic testing, drug development*

"The scope of this paper is the co-development of a new PGBM and the relevant assay(s) in the context of either a drug development or for qualification purposes."

TÜVRheinland®
Precisely Right.

Companion Diagnostics: Routes to compliance

Regulators opinion on CDx developmental strategies: **EMA**



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2017
EMA/CHMP/800914/2016
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle

Agreed by Pharmacogenomics Working Party	7 April 2017
Adopted by CHMP for release for consultation	20 July 2017
Start of public consultation	28 July 2017
End of consultation (deadline for comments)	15 November 2017

The proposed concept paper is intended to be developed into a guideline which will replace 'Reflection paper on co-development of pharmacogenomic biomarkers and Assays in the context of drug development' (EMA/CHMP/641298/2008).

"The guideline will provide recommendations relating to the interface between predictive biomarker based assays including CDx, and the development and lifecycle of medicinal products."

TÜVRheinland®
Precisely Right.

Companion Diagnostics: Routes to compliance

Regulators opinion on CDx developmental strategies: Points to consider

Legacy products:

Retrospective review by NB and CA for each product:

- Technical documentation corresponds to the requirements of the IVDR ?

- Sufficient data for successful re-evaluation ? Need for more (clinical-) data ? Pharmacovigilance ?

TÜVRheinland®
Precisely Right.

Companion Diagnostics: Routes to compliance

Regulators opinion on CDx developmental strategies: Points to consider

New CDx, known Rx:

IVDR Annex IX, Chapter II, 4.5

“The notified body shall, in circumstances in which the clinical evidence is based partly or totally on data from devices which are claimed to be equivalent to the device under assessment, assess the suitability of using such data, taking into account factors such as new indications and innovation. The notified body shall clearly document its conclusions on the claimed equivalence, and on the relevance and adequacy of the data for demonstrating conformity.”

Generic devices (same test principle)

- check for equivalency
- head-to-head comparison with established test?
- demonstration of equal analytical, clinical performance by retrospective testing ?

Me too (different test principle)

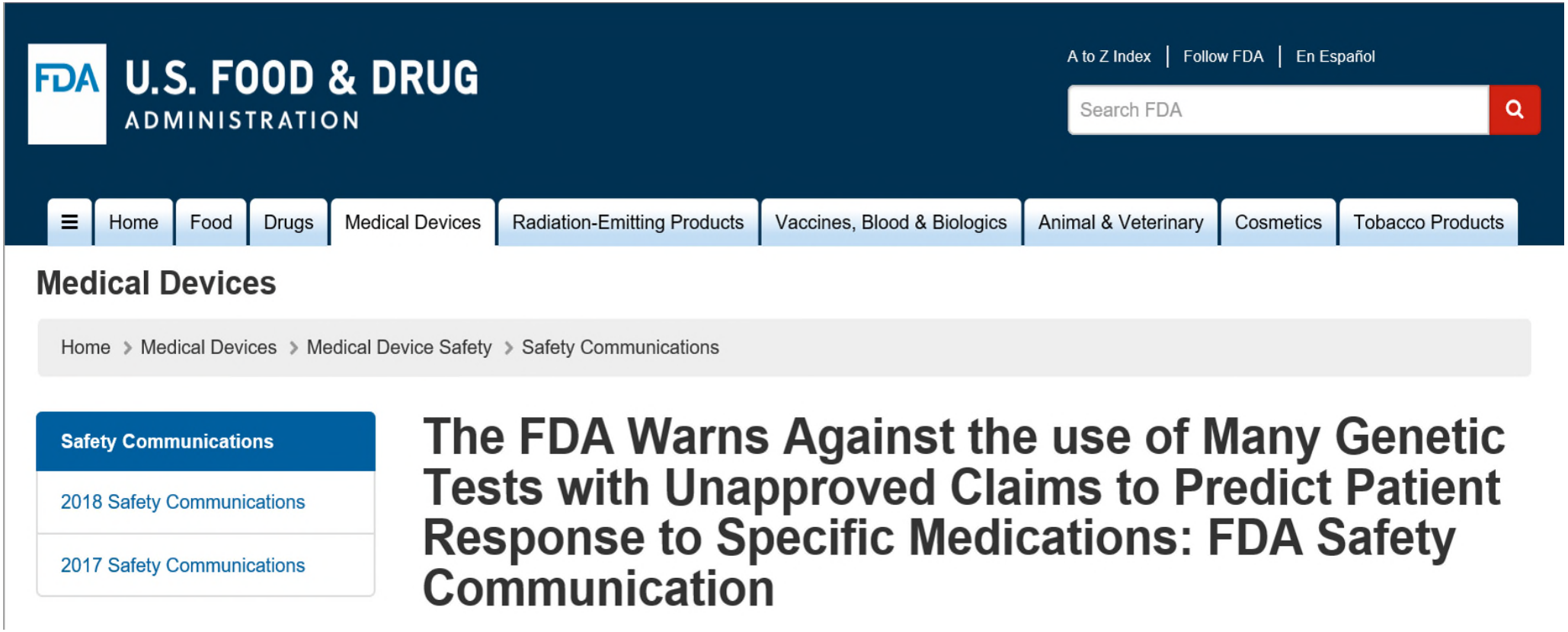
- head-to-head comparison with “gold” standard
- performance data/clinical evidence needs to be demonstrated
- different/same BM format?

TÜVRheinland®
Precisely Right.

Companion Diagnostics: Routes to compliance

Regulators opinion on CDx developmental strategies: Points to consider

FDA Approves Foundation Medicine's FoundationOne CDx™, the First and Only Comprehensive Genomic Profiling Test for All Solid Tumors Incorporating Multiple Companion Diagnostics



THANK YOU VERY MUCH FOR YOUR ATTENTION!

Rolf Thermann, PhD
TÜV Rheinland LGA Products GmbH
Am Grauen Stein 29
D-51105 Köln
rolf.thermann@de.tuv.com

TÜVRheinland®
Precisely Right.