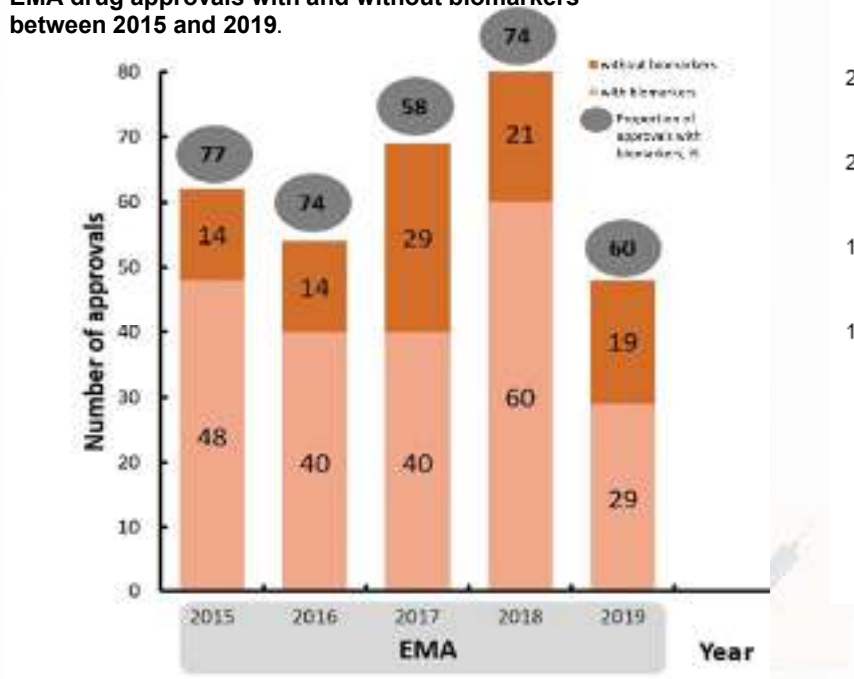
Biomarker Development and Optimisation
Regulatory Perspective

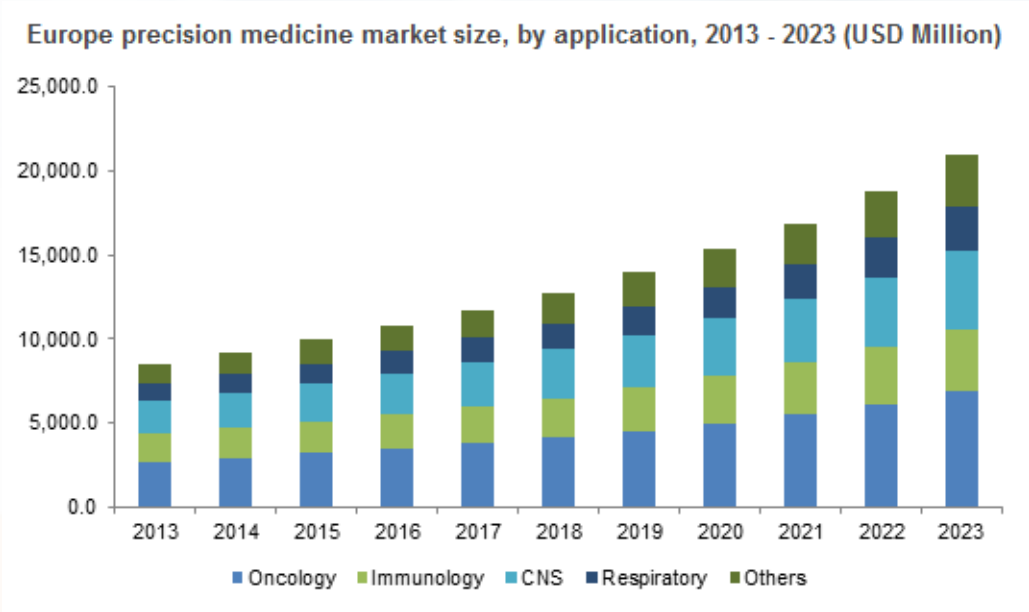
Hilke Zander
Paul-Ehrlich-Institut, Germany

Personalized medicine based on predictive biomarkers

EMA drug approvals with and without biomarkers between 2015 and 2019.



Gromova M et al. Biomarkers: Opportunities and Challenges for Drug Development in the Current Regulatory Landscape; Biomarker Insights 2020, 15: 1–15



The French Platform for Personalised Medicine (F2PMed)http://precisionmedicine.tbiscientific.com/?p=825

Histology independent drug development

- Indication solely determined by biomarker

  -> Adequate selection of biomarker crucial

- Solid rationale that MoA independent of tumor histology

  Needs to be justified by
  - Preclinical data
  - Clinical data

- Adequate selection of patients based on biomarker crucial

  ->*biomarker validation important*

Histology independent drug development / CDx

- InVitroDiagnostics (IVD)-Regulation 2017/746 (IVDR) applied on 26 May 2022

  NEW:
  - Companion diagnostics (CDx) are legally defined (Art. 2(7) IVD)

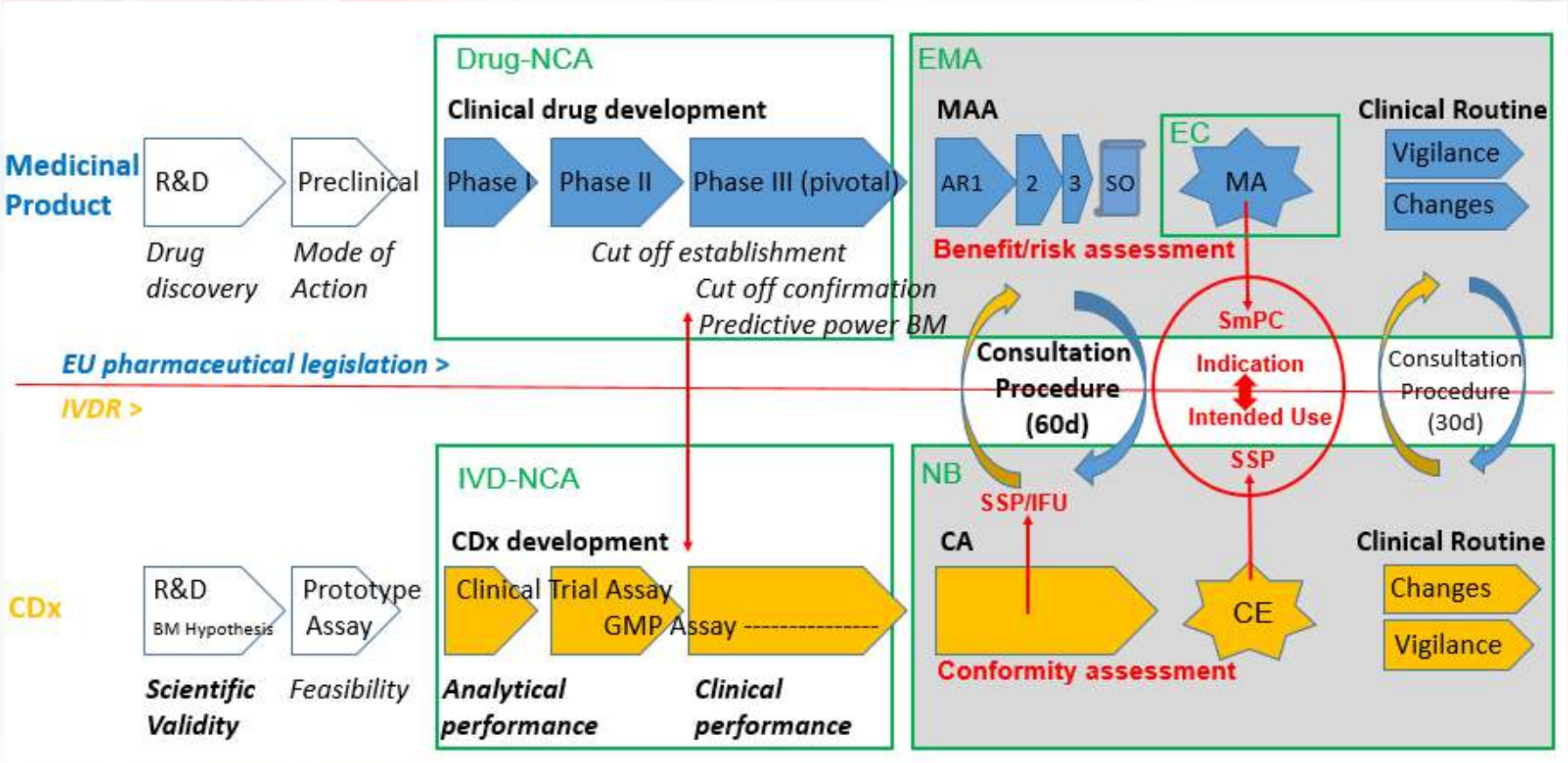
(7) '**companion diagnostic**' means a device which is **essential for the safe and effective use** of corresponding medicinal product to:
(a) Identify**, before** and/or during treatment, patients **who are most likely to benefit** from the corresponding medicinal product, or (b) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product.

  - IVDs (in-vitro-diagnostics) are risk classified (A - D)
  - CDx are mainly class C devices, i.e.
    - CE-marking through conformity assessment by a Notified Body (NB)
    - with consultation of a Competent Medicines Authority responsible for the corresponding medicine

European regulatory framework for CDx-based drug therapy

CDx: US (FDA)	CDx: Europe
Co-approval of a personalized medicinal product **(MP)** and a corresponding **specific CDx**	**Independent approval** of **MP** and corresponding **CDX** 2 different legal frameworks: IVD and MP regulation
CDx (trade name) is coupled via the **Full Prescribing Information**	**MP:** Drug approval / Biomarker section *MP and CDx not directly linked via SmPC* *Trade name normally not mentioned* **CDx**: Conformity assessment of the NB-(IVDR Article 48) *The name (INN) of the MP for which CDx is a companion test must be stated in the instructions for use (IFU) and Summary of Safety performance (SSP) for the CE-CDx*

Medicinal Product - Companion Diagnostics (Co)- Development



Co-developed CDx: Aspects for scientific validity (scientific rationale)

Important aspects:

- Scientific rationale for biomarker selection:

  -> Relationship between marker and (patho-)physiology
  -> Basis: MoA of the medicinal product

- Prevalence of the biomarker

- Evidence of scientific data

  -> Marker predictive, diagnostic, prognostic? Already established or new marker?

Co-developed CDx: Aspects for analytical performance

Important aspects:

- Performance and validation parameters of assay adequate?
  -> accuracy of measurement, sensitivity, specificity, measurement range (validation covering defined clinical cut-offs)

- Pivotal study: Diagnostics sufficiently analytically validated -> robust data for approval
  -> ideally GMP-Assay (CDx intended for conformity assessment / approval)

Co-developed CDx: Aspects for clinical performance

Important aspects:

- Biomarker assay (analytically fully validated -> if Clinical Trial Assay was used in pivotal study: demonstration of equivalent analytical performance (concordance studies)

- Pivotal study: confirmatory prospective randomized controlled trial
- Stratification (if applicable for different cut-offs)
- Prespecified cut-offs
- Adequate tumor material / central assessment
- Biomarker assessment for all study patients

Not applicable for Histology independent indications (basket trials)

Relevant publications

- **IVD-Regulation 2017/746 (IVDR)**
- **Questions & Answers** on the interface between Regulation (EU) 536/2014 on clinical trials for medicinal products for human use (CTR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR)
- **Guidance on the procedural aspects** for the consultation to the EMA by a notified body on companion diagnostics
- **Questions & Answers** on practical arrangements on the companion diagnostics consultation procedure to the EMA by notified bodies

- **Guideline on the clinical evaluation of anticancer medicinal products** EMA/CHMP/205/95 Rev.6 (draft) Revision section 5 Biomarkers