EUROPEAN MEDICINES AGENCY
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Evolving framework for the co-development of medicinal products with companion diagnostics

3rd Industry Stakeholder Platform on R&D support, 18 May 2018

Presented by Falk Ehmann and Armin Ritzhaupt
Human Medicines Research and Development Support Department and Human Scientific and Regulatory Management Department

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Status update on the developments in the implementation activities of the MDR/IVDR

Presented by Armin Ritzhaupt
Regulatory Affairs Office, Human Medicines Evaluation Division

Outline

- Recap
- EMA's new role
- Implementation activities related to CDx
- Outlook

Recall EMA stakeholder platform meeting 25 April 2017

- ✓ Revision of the EU Medical Devices Legislation – adopted 5 April 2017
  - ➢ Regulation on medical devices (Regulation (EU) 2017/745)
  - ➢ Regulation on in vitro diagnostic medical devices (Regulation (EU) 2017/746)
- ✓ Impact Assessment of new MDR and IVDR on EMA and network
  - ➢ e.g. new consultation procedures, clinical trial regulation
- ✓ Drafting of implementation plan
  - ➢ Involvement of different and new stakeholders within and outside network
  - ➢ Establishing (new) relationships, cooperation and exchange of information

EMA's future role in review of medicinal product and medical device combinations

- Consultation on borderline products
- Consultation on devices that are composed of substances or of combinations of substances that are absorbed by or locally dispersed in the human body
- Consultation on companion diagnostics
- Medicinal products with an integrated device will need Notified Body opinion /certificate for MAA (Article 117)
- Mandatory to consult EMA on ancillary substances exclusively within the scope of the Annex to Regulation 726/2004 (e.g. biotech products)

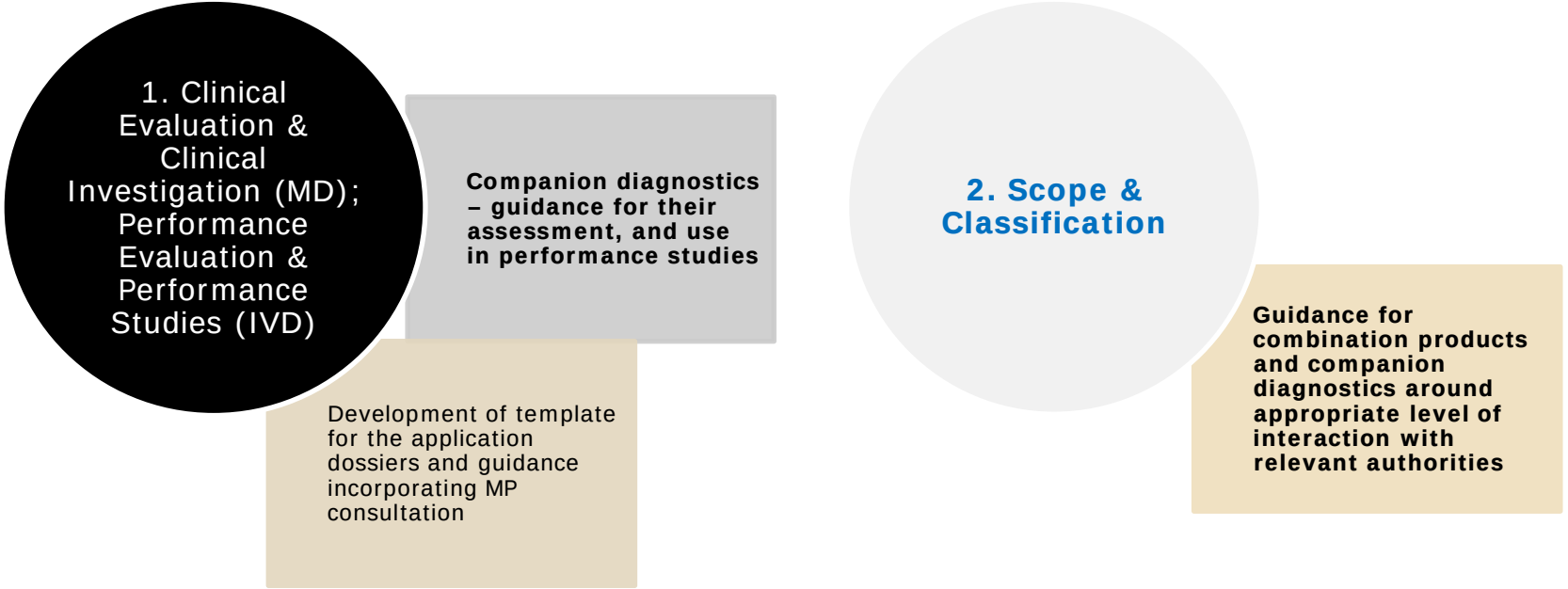
Nov 2017 - EC and CAMD implementation roadmap

8 road map priority clusters

- Clinical Evaluation & Clinical investigation (MD); Performance Evaluation & Performance Studies (IVD)
- Scope & Classification
- Notified Bodies
- Post-Market Surveillance & Vigilance
- Eudamed & UDI
- Market Surveillance
- IVD specific issues
- Over-arching &Cross-cutting Priorities

- Establishment of MDR/IVDR implementation task force to facilitate collaboration and cooperation within the medical devices network during the implementation phase of the new Regulations
- Practical guide for regulatory authorities and EC to work together towards implementation
- Envisaged that additional guidance and information will be needed in advance
- EMA specifically identified as responsible party for CDx and combination products

CAMD priorities for implementation relevant to EMA



Companion Diagnostic specific activities

Developing guidance for CDx (Joint CIE and IVD TG on performance studies)

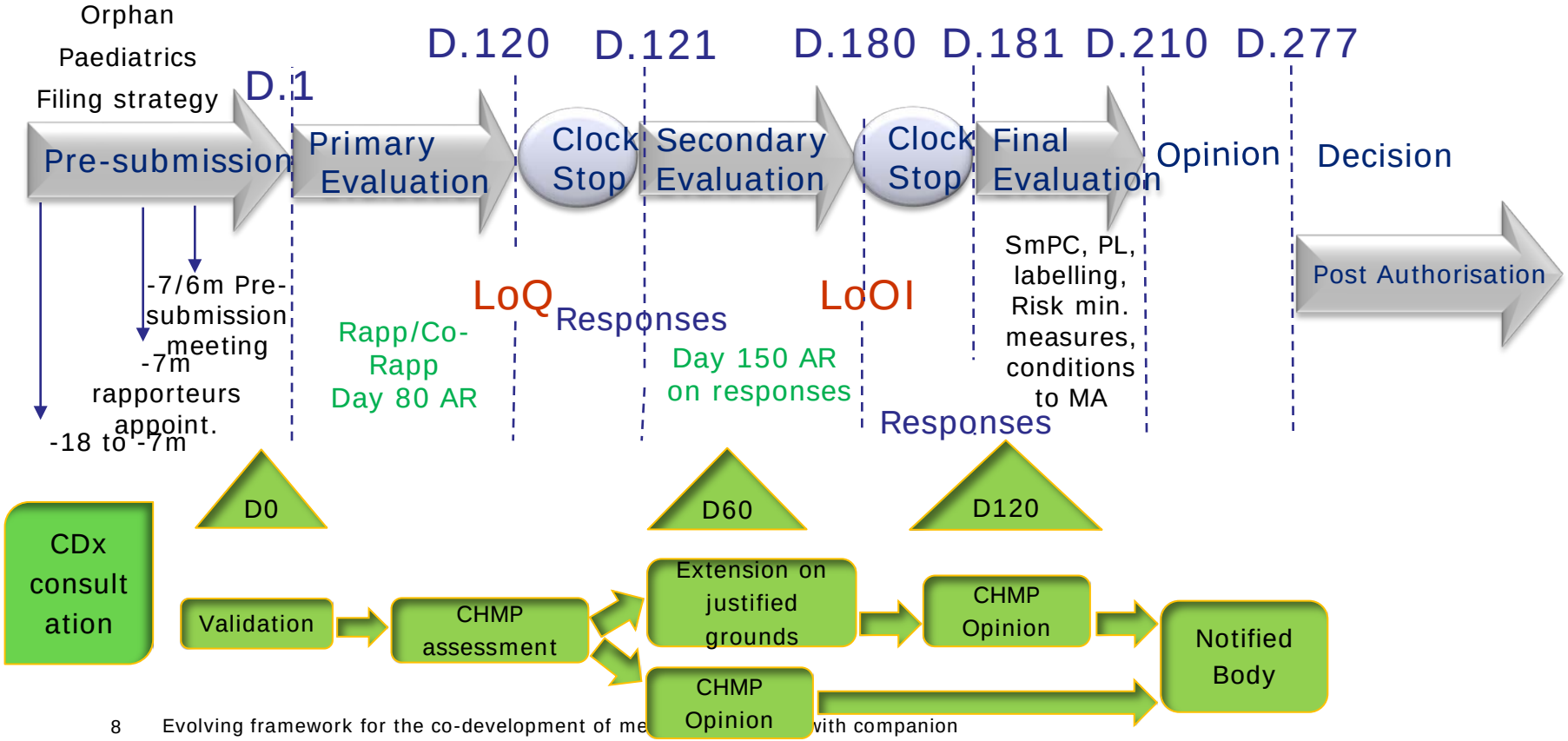
Aligning requirements for clinical trials (medicine) and clinical performance studies (CDx)

Timetables for CDx CE marking and medicine MAA

Engage with NBs to agree on data requirements for the consultation

PGWP Expert meeting on co-dev June 2018

Overview of Centralised Procedure Timetable



Outlook

- External procedural guidance based on 60 day TT with a maximum extension of another 60 days in collaboration with relevant stakeholders (including dossier requirements and expectations);
- Internal guidance documents;
- Scientific guidance (-> PGWP Concept paper)

Actions:

- Continue engagement with EC's Working Groups and other relevant stakeholders to prepare for consultation procedure;
- Interaction with notified bodies and other industry stakeholders (including conducting survey)

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Identified issues for the (co-)development of companion diagnostics and medicinal products - proposals coming into the regulatory system

Presented by Falk Ehmann
Science and Innovation Support Office, Human Medicines Research and Development Support Division

An agency of the European Union

Outline

- Background
- Analysis of Companion Diagnostic related questions discussed at Scientific Advice
- EMA multi-stakeholder meeting (18 June)
- Conclusion → Outlook and Aim

Background:

- The use of **companion diagnostics (CDx) measuring predictive biomarkers (BMs)** is well established for the selection of the right treatment for patients

  → **Analysis** of CHMP discussion on CDx in **scientific advices** and **MAA evaluations**

- Currently **majority of CDx** only **require self-declaration –** will change…

New IVD Regulation published May 2017 → will apply May 2022
Consultation with EMA / NCA on CDx required

- CHMP CDx–MP **Concept Paper** (July 2017)

  → **100 pages comments**

  → EMA multi-stakeholder workshop (18 June 2018)

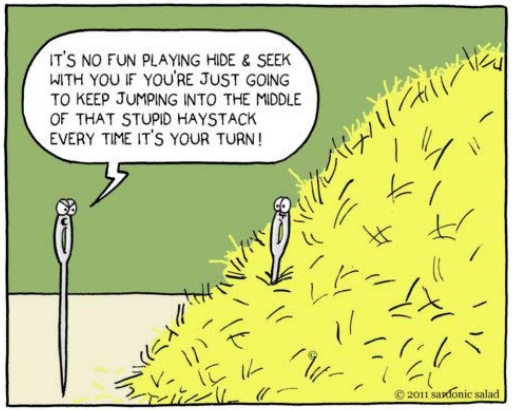
→

Analysis of CDx related questions discussed at Scientific Advice

EMA receives ~ 600 SA / year → ~ 10 include questions related to CDx…

- **Analytical validation** of the BM (data requirements),
- **Clinical validation** of **gene signature** BM
- Establishment of **clinical utility (rationale** for **biomarker panel)**
- **Cut-off values** defined, validated and used for assay
- **Classification / definition of patients** with altered tumors using **NGS**
- **Prospective retrospective analysis** (of tissue samples)
- **Concordance analysis** (retrospective)

- **NGS specific**: minimum coverage, central vs. decentral testing, CLIA and CAP accreditation, classification algorithm
- **Feasibility to implement this into practice in EU** (CDx capabilities)



Challenges to be discussed at workshop (18 June):

Data requirements for CDx (detail, overlap): **analytical / clinical**
(Cross-) Labelling considerations for CDx and medicinal product

Article | Full-text available

Pharmacogenomic information in drug labels: European Medicines Agency perspective

February 2015 · The Pharmacogenomics Journal 15(3)
DOI · 10.1038/tpj.2014.86
Source · PubMed

Future interactions between EMA/NCA and NBs (as in IVDR)

Post-authorisation and pharmacovigilance requirements for CDx

Data requirements and review process / regulatory oversight for “follow-on” assays (CDx)

Clinical trials including medicines and CDx

Conclusion, aim and outlook:

- Experience gained from CDx related questions discussed at Scientific Advice and MAA
- CDx related questions addressed by SA Coordinator from Agencies with CDx expertise

- Notified Bodies (NB) involvement to be explored
- We encourage more exposure to challenge the system and gain further experience

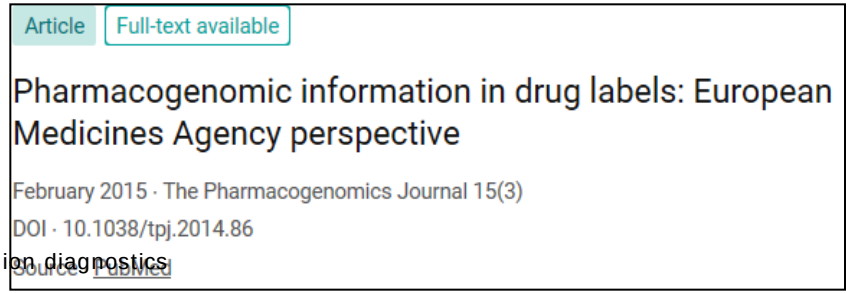
→ **Please submit your CDx related questions to Scientific Advice**

Back-up slides

Objectives of the workshop 18 June:

To discuss feed-back and clarify issues raised during consultation of the Concept Paper including:

- Data requirements for CDx (detail, overlap): clinical and analytical
  - (Cross-) Labelling considerations for CDx and medicinal product
- Future interactions between EMA/NCA and NBs (as in IVDR)
- Post-authorisation and pharmacovigilance requirements for CDx
- Data requirements and review process / regulatory oversight for “follow-on” assays (CDx)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Stakeholder diversity providing comments on the Concept Paper

...including Notified Bodies, HTAs, Government Departments, Insurance platform, Industry (associations) [pharma and device], Research Institutions, NCAs, Academia,

1	ACRO (Association of Clinical Research Organizations)
2	Astellas Pharma Europe B.V.
3	AstraZeneca
4	Royal College of Physicians (RCP)
5	HAS (Haute Autorité de Santé)
6	Illumina, Inc.
7	IQWiG – Institute of Quality and Efficiency in Health Care – GERMANY
8	HTA agencies collaborating in the EMA/EUnetHTA joint work programme Personalised Medicine work stream (HAS, IQWiG and NICE)
9	Department of Pharmaceutical Policy, National Institute for Health and Disability Insurance (NIHDI, Brussels, Belgium)
10	MPA
11	Leica Biosystems
12	EuropaBio – the European Association for Bio-Industries
13	European Biopharmaceutical Enterprises – EBE European Federation of Pharmaceutical Industries and Associations – EFPIA
14	Alexion Biomarkers and Diagnostics
15	MedTech Europe
16	Personalised Medicine Coalition (PMC)
17	European Social Insurance Platform (ESIP)

EMA guidance and concept papers on biomarkers

1. Guideline on the evaluation of anticancer medicinal products in man (2016; draft, revision 5)
2. Reflection paper on co-development of pharmacogenomic biomarkers and assays in the context of drug development (2010; draft)
3. Reflection paper on methodological issues associated with pharmacogenomic biomarkers in relation to clinical development and patient selection (2011; draft)
4. Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle

Practicalities:

- Proposed programme

  Programme- Expert meeting on CDx-MP co-development guideline

  EMA/136048/2018

  https://docs.eudra.org/webtop/drl/objectId/090142b283e9ac08

- List of participants **Closed expert meeting by invitation only**
  - EU industry stakeholder experts nominated by trade association (Pharma and MedTech)
  - Stakeholders who provided relevant comments during CP consultation
  - Notified Bodies representatives nominated by “overarching organisation”
  - Guideline DG and other involved PGWP and CHMP members including NCA device expertise

- Intended distribution / broadcast / FU
  - Relevant interested EMA colleagues to follow in person (max 15)
  - External link to broadcast upon specific request and invitation only (case by case)
  - Notes/minutes not for publication → to guide guidance development

Background:

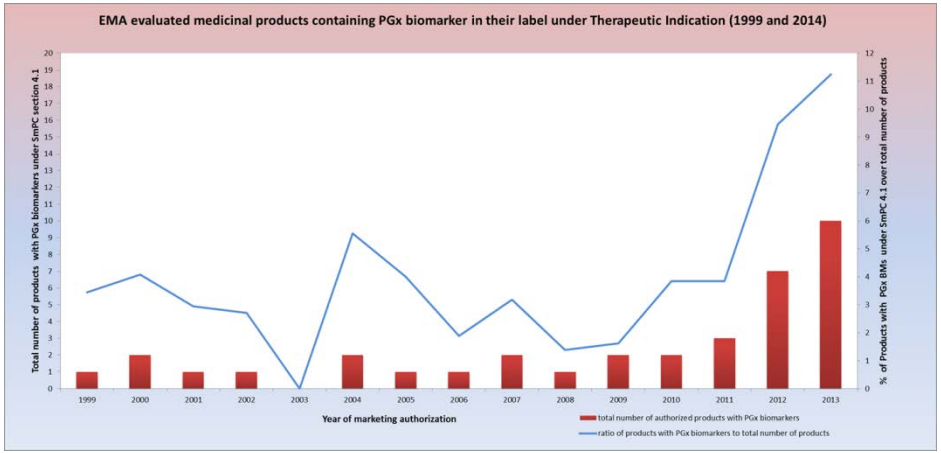
Companion Diagnostics: The Expanding Reach Of Personalized Medicine

14 Mar 2017 **ANALYSIS**

Executive Summary

Personalized medicine is becoming the hallmark of care in oncology, but its use is also increasing in other therapeutic areas including inflammation, respiratory, infectious diseases and central nervous system disorders, as scientific understanding of these diseases advances. The expansion of companion diagnostics beyond oncology has impacts on dealmaking, clinical practice and the R&D pipeline.

SCRIP



An analyses of the patient population studied (BM+ and/or –) in the pivotal trial submitted for initial MAA leading to marketing authorisation and biomarker inclusion in the therapeutic indication section of the product label showed that… …**only 10 out of 30 products (1/3) have been including biomarker positive and negative patients in their pivotal clinical trial**.

The Pharmacogenomics Journal (2015), 1 – 10