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SCIENCE MEDICINES HEALTH

Personalised Medicine Regulatory Issues

INFRAFRONTIER / IMPC Stakeholder Meeting

Presented by Marisa Papaluca on 14 November 2017
Senior Scientific Advisor, Scientific Committees Regulatory Science Strategy

An agency of the European Union

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Declaration of Interests

I am full staff member of the European Medicines Agency and I do not have interests that might pose a conflict with my duties.

Outline

Background notes on medicines and personalised medicine in EU.

Framework of collaboration with Academia

Did you know?

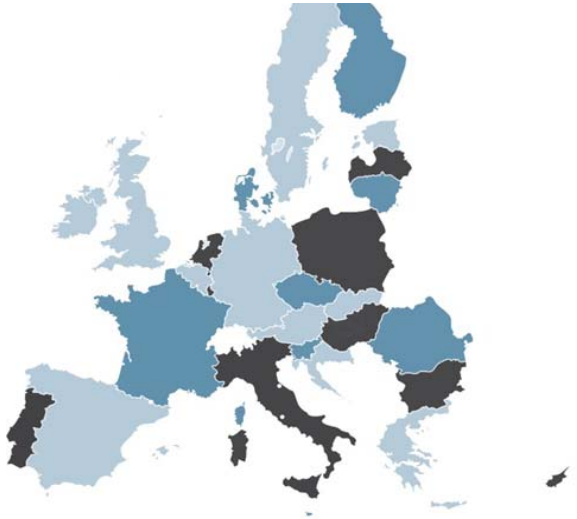
Conclusions

The European medicines regulatory network

Closely-coordinated regulatory network of national competent authorities (~50) in the Member States of the European Economic Area (EEA) working together with the European Medicines Agency (EMA) and the European Commission

How are medicines approved?

Centralised procedure (via EMA)



National procedures (via NCAs)

Which medicines are approved through the centralised procedure?

The centralised procedure is **compulsory** for human medicines containing a new active substance to treat:

- human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS)
- cancer
- diabetes
- neurodegenerative diseases
- auto-immune and other immune dysfunctions
- viral diseases
- medicines derived from biotechnology processes, such as genetic engineering
- advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines
- orphan medicines (medicines for rare diseases)
- veterinary medicines for use as growth or yield enhancers

It is **optional** for other medicines:

- containing new active substances for indications other than those stated above
- that are a significant therapeutic, scientific or technical innovation
- whose authorisation would be in the interest of public or animal health at EU level

Personalised medicine and regulatory science: Background

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No commonly agreed definition of the term "personalised medicine".

Widely understood that personalised medicine refers to a:

- medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention.

- Personalised medicines relates to the broader concept of patient-centered care, which takes into account that, in general, healthcare systems need to better respond to patients needs.

Council conclusions (7 December 2015)

Council of the European Union

Personalised medicine: direction of travel

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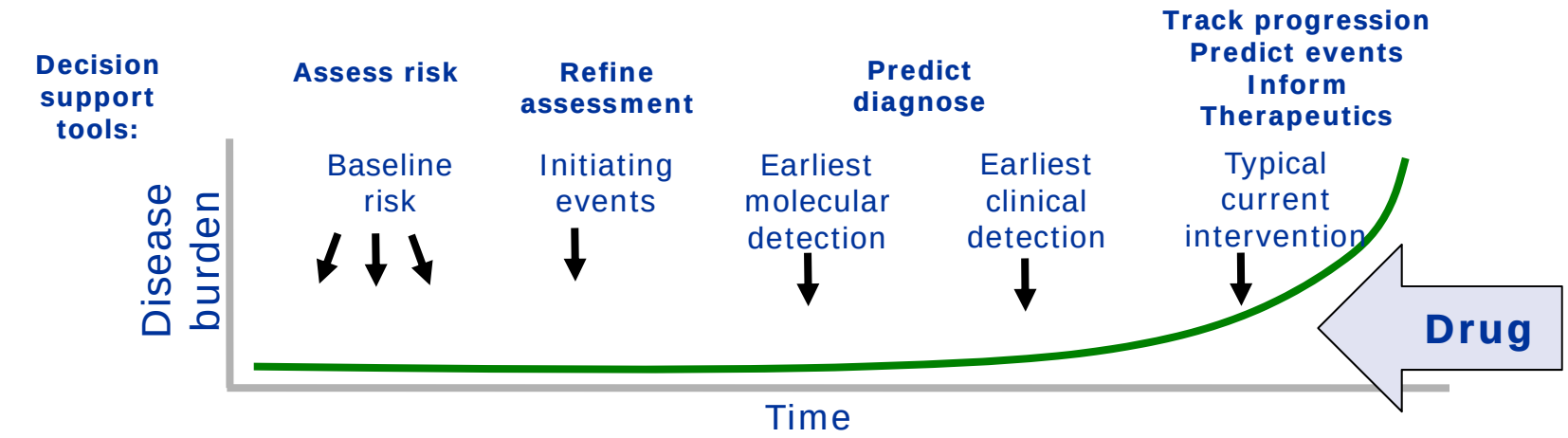

Sources of new biomarkers:

Baseline risk	Preclinical progression	Disease initiation and progression
Stable genomics: Single nucleotide Polymorphisms Haplotype mapping Genome sequencing Genome editing	Dynamic genomics: Epigenetic Gene expression Proteomics Metabolomics / omics Molecular pathways Molecular imaging Genome editing	Therapeutic decision support

Modified from Source: "Personalized Medicine: Current and Future Perspectives," Patricia Deverka, MD, Duke University, Institute for Genome Sciences and Policy; and Rick J. Carlson, JD, University of Washington

Framework for Personalised Medicine

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R&D the basics	R&D stratifying tools	R&D test in human	Towards the market	Uptake in healthcare	In patients
"Omics"	Biomarkers Identification	Clinical trials methodologies	Diagnostics & therapies	Pricing & Reimbursement	Availability & usability in the clinic
Technologies	Qualification Validation	Patient - recruitment	Approval processes	Health economy	Patient perspective
Data	Data modelling tools		Regulatory aspects	HTA	Equal treatment
Samples	Technical aspects & challenges			Novel models of healthcare organisation	Social and legal issues
Statistics					Education and training

Source: Irene Norstead EMA Workshop on Per Med March 2017

Prediction - Prevention – Treatment - Cure

Mice research **integrated** in a modern «pre-clinical» science space

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Omics sciences and Genome editing for personalised medicines:
New targets discovery, new pathways, new biomarkers, comparative omics
Preservation of molecular pathways, in and off treatment, receptors distribution and prediction of effects
Genome editing on target and off target effects, environmental factors (including medicines) epigenetic impact and downstream consequences

Transgenic mice and the "avatar" mouse trials
Patient-derived iPSC/cell lines: integrate methods relying on individual patient material both for early efficacy testing (e.g. to test drug combinations or support Proof of concept for histology-agnostic trials in oncology or treatment sequence for emergence of resistance ;

Use of in silico software for risk assessment – the most advanced field is genotoxicity testing; there has also been progress in the development of in-silico models of cardiotoxicity

Non-clinical: Computer-based models for PK/ADME prediction and translation in to PBPK modelling

Use of organs-on-chip methodology to complement current test systems and increase the value of weight-of-evidence approaches to address uncertainties in risk assessment.

Systems biology and –omics approaches probably should integrate and complement current testing methods to increase the level of information (both qualitatively and quantitatively) that can be obtained by the classical non-clinical tests.

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Regulatory acceptance of 3R (replacement, reduction, refinement) testing approaches

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This guideline applies to human and veterinary medicines.

Current effective version	**Adopted guideline**
Reference number	EMA/CHMP/CVMP/JEG-3Rs/450091/2012
Published	22/12/2016
Effective from	01/07/2017
Keywords	3Rs, regulatory acceptance, testing approaches, non-clinical, quality, human medicinal products, veterinary medicinal products, qualification, validation, replacement, reduction, refinement
Description	This document describes the process for submission and evaluation of a proposal for regulatory acceptance of 3R testing approaches for use in the development and quality control during production of human and veterinary medicinal products. It also presents the scientific and technical criteria for validation of 3R testing approaches and explains the pathways for regulatory acceptance of 3R testing approaches.

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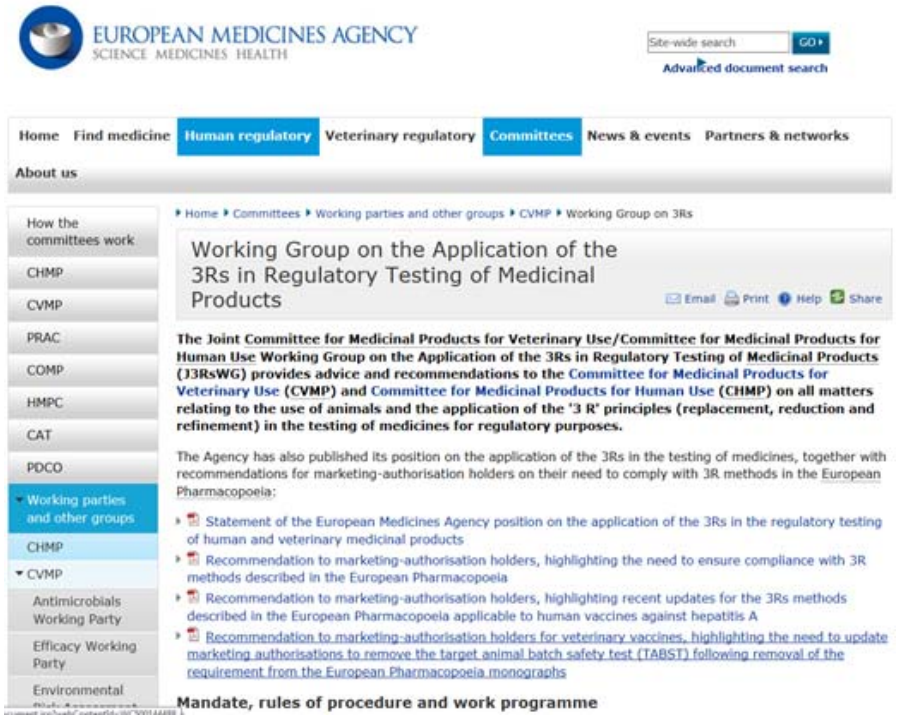

- Criteria for regulatory acceptance
  1. demonstration of method validation
  2. demonstration that the new or substitute method or testing strategy provides either new data that fill a recognised gap or data that are at least as useful as, and preferably better than those obtained using existing methods.
  3. demonstration of adequate testing of medicinal products under real-life conditions (human and veterinary) which can be generated through the safe harbour process

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1. Demonstration of method validation
   - defined test methodology/standard protocol with clear defined/scientifically sound endpoints
   - reliability
   - relevance

The information needed and the criteria applied will depend on:

- regulatory and scientific rationale for the use of the method,
- type of method being evaluated (e.g. existing test, new method),
- proposed uses of the method (e.g. mechanistic, total or partial replacement, as part of a testing strategy),
- mechanistic basis for the test and its relationship to the effect(s) of interest,
- history of use of the test method, if any, within the scientific and regulatory communities

Guido Rasi, EMA Executive Director

"***EMA wants to move to a new level of collaboration with academia***. *Science is progressing fast and we see an unprecedented level of complexity in the development and evaluation of new medicine.* ***Academia play an important role in helping the EU medicines regulatory network*** *to keep abreast of the opportunities and challenges brought by science and to have access to the right expertise to evaluate these innovative medicines. Interaction with EU regulators and a* ***better understanding of the regulatory environment*** *can help* ***academia translate their discoveries*** *into patient-focused medicines. I believe that* ***working more closely together*** *will bring great* ***benefits to public health***".

Framework of collaboration with academia

Objectives

Framework of collaboration with academia

Methodology

INFORM

e.g. dedicated web pages, relevant news items, Q&As, information days, information materials

CONSULT

e.g. e.g. public consultation on policies or guidance, surveys

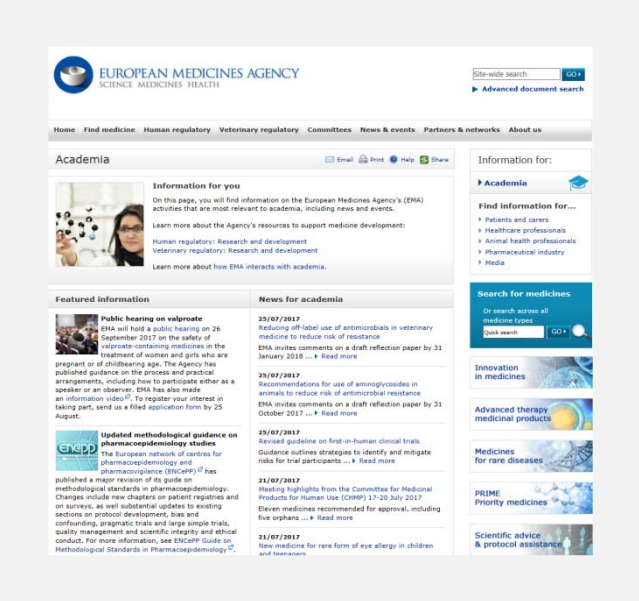
CONSULT & INVOLVE

e.g. multi-stakeholder meetings, workshops, conferences, development of regulatory guidelines

COOPERATE

e.g. participation to research projects, cooperation in activities of education and training, cooperation with established EMA stakeholders and networks

Academia web pages



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Support and advice to medicines development at **National level**

- National Competent Authorities (NCAs) are responsible for specific areas
  - *Good Lab Practices, Clinical trial authorisation, hospital exemption, compassionate use, etc.*
- NCAs provide scientific advice (H/V) (fees might apply)
- Depending on the NCA there can be specific schemes/services (fees might apply)
- EU-Innovation Network (EU-IN) (H) *
  - Network of 23 Innovation Offices and EMA (co-chair)
  - Specifically set up to support **medicine innovation** and early development of new medicines (specific support to academics)
    - Identify challenging issues from emerging innovation to be further discussed in scientific advice
    - Orientation towards the right competencies inside the NCA and at EU level
    - Meetings for most innovative projects

Did you know? Support at EMA level

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Research and development: early development advice services **at EU level (EMA)**

- Innovation task force safe harbour (H&V) *
- Scientific advice (H&V)
- Paediatric investigation plan (PIP) (H) *
- Qualification of novel methodologies (H)
- Orphan medicine designation * (follows protocol assistance, fee reductions, market exclusivity)(H)

- Advanced therapy medicinal product classification (H) *
- Regulatory and administrative assistance for small-and medium-sized enterprises – SMEs (H&V) *
- PRIME scheme (PRIority Medicines) (H)
- EU-Innovation Network (EU-IN) (H) *

What to keep in mind: **time** and potential fees (Note on fees payable to EMA and exemptions)

*** No fee applied**

Did you know? **Qualification of Novel Methodologies**

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- Advice or opinions on the regulatory validity and acceptability of a specific use of a proposed method in R&D context (in non-clinical and clinical studies)
- Voluntary, scientific pathway for innovative methods or drug development tools (e.g. biomarkers) not yet integrated in the drug development and clinical management paradigm
- Joint qualification EMA/FDA can be requested
- One procedure with clear outcomes:
  - Letter of support, OR
  - Qualification Advice, OR
  - Qualification Opinion

10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

Long-term benefits from EMA perspective: Speed-up the time to regulatory acceptance of novel approaches and time to new marketing authorisations, improve public health

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0#section3

Did you know? **Qualification of Novel Methodologies**

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Letters of support

Based on qualification advice, the Agency may propose a letter of support as an option, when the novel methodology under evaluation cannot yet be qualified but is shown to be promising based on preliminary data.

Letters of support aim to encourage data-sharing and to facilitate studies aimed at eventual qualification for the novel methodology under evaluation.

These letters include a high-level summary of the novel methodology, context of use, available data, and on-going and future investigations. The Agency publishes letters of support on this page, if the sponsors agree.

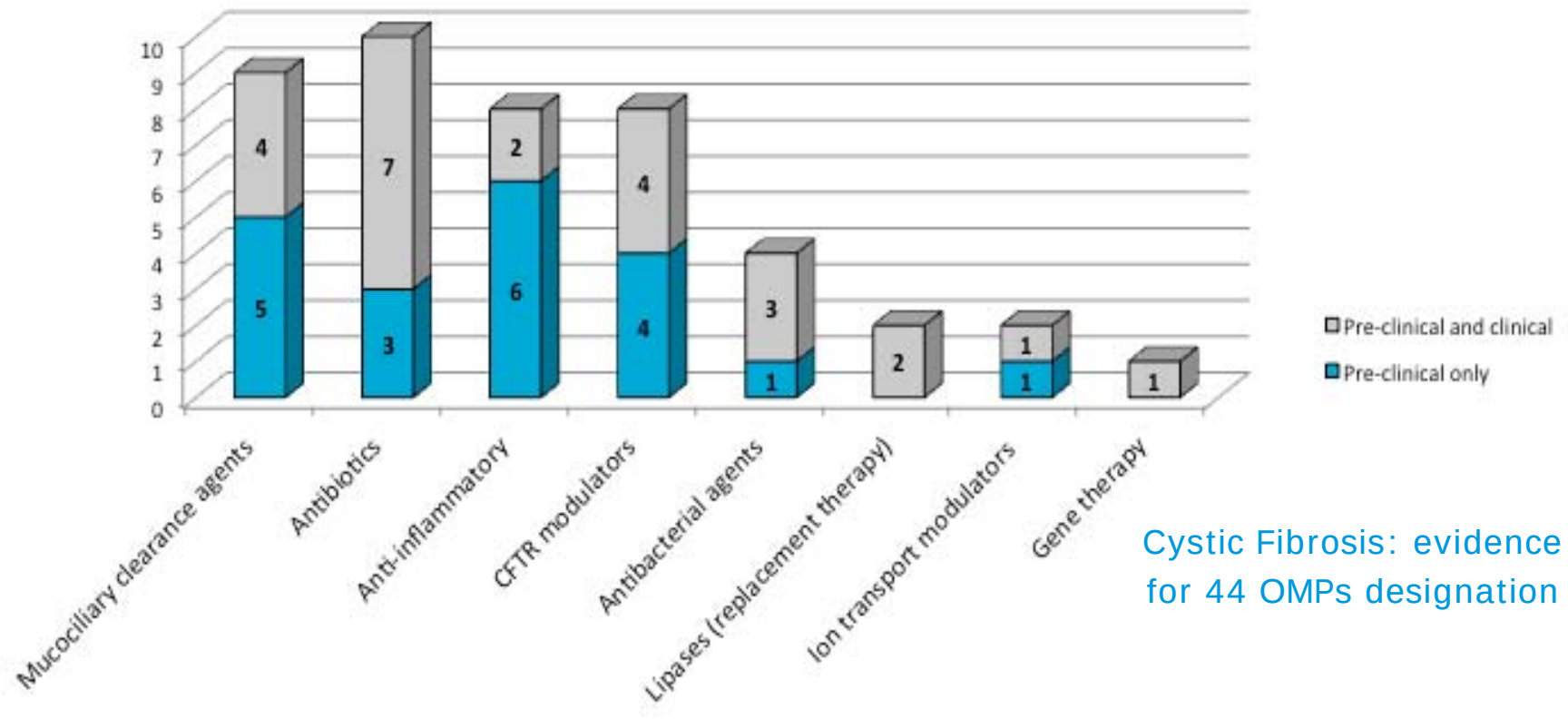
Letters of support

Document(s)	Language	Status	First published
Letter of support for drug-induced renal tubular injury biomarker(s)	(English only)		12/01/2017
Letter of support for molecular imaging of the dopamine transporter biomarker as an enrichment biomarker for clinical trials for early Parkinson's disease	(English only)		07/10/2016
Letter of support for drug-induced liver injury (DILI) biomarker	(English only)		30/09/2016

***14 Letters of Support** have been issued, 4 related to safety markers;*

***13 Qualification Opinions** have been published http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&mid=WC0b01ac0580022bb0*

Did you know? **Non clinical data and orphan medicinal products (OMPs)**



Cystic Fibrosis: evidence for 44 OMPs designation

Did you know? **Genomics, development, authorisation of novel medicines**

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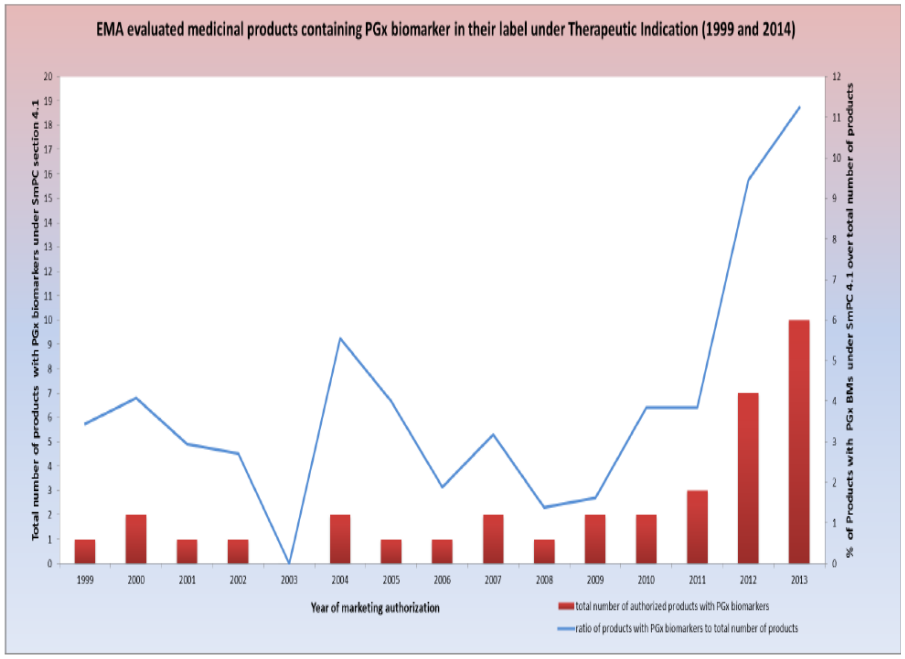
Table 4. Studied patient population (biomarker positive and/or negative) in pivotal clinical trial leading to initial marketing authorisation

PGx biomarker	*Active substance*	*Patient population studied in pivotal trial for initial MAA*
HLA-B*5701	Abacavir (Ziagen) Abacavir/lamivudine (Kivexa) Abacavir/lamivudine/zidovudine (Trizivir)	HLA-B*5701 positive and negative (not tested at time of MAA)
CD30	Brentuximab vedotin (Adcetris)	CD30 positive only
HER2	Everolimus (Afinitor) Trastuzumab (Herceptin) Lapatinib (Tyverb) Pertuzumab (Perjeta) Trastuzumab emtansine (Kadcyla)	HER negative only HER positive only
RAS	Panitumumab (Vectibix) Cetuximab (Erbitux)	Wild-type and mutant
EGFR	Cetuximab (Erbitux) Gefitinib (Iressa) Erlotinib (Tarceva) Afatinib (Giotrif)	EGFR positive only EGFR positive and negative EGFR positive only
ALK	Crizotinib (Xalkori)	ALK-positive and negative
BRAF V600	Vemurafenib (Zelboraf) Dabrafenib (Tafinlar)	BRAF V600 mutation positive only
BCR-ABL	Imatinib (Glivec) Dasatinib (Sprycel) Nilotinib (Tasigna) Bosutinib (Bosulif) Imatinib (actavis, accord, medac, teva) Ponatinib (Iclusig)	Philadelphia chromosome (bcr-abl) positive (Ph+) only Bioequivalence studies T315I+ mutation only
Kit CD117	Imatinib (Glivec)	Kit (CD 117) positive only
CFTR *G551D*	Ivacaftor (Kalydeco)	G551D positive mutation only
FIP1L1-PDGFR	Imatinib (Glivec)	FIP1L1-PDGFRα positive rearrangement only
T315I	Ponatinib (Iclusig)	T315I positive mutation only
RET mutation	Vandetanib (Caprelsa)	RET mutation positive and negative
PML/RAR-α	Arsenic trioxide (Trisenox)	t(15;17) translocation and/or PML/RAR-α positive and negative

2017: 60% Novel trials include BMs

(mostly enrichment/stratification)

Figure 2: Number of medicinal products and ratio of medicinal products containing a genomic biomarker (gene) in their product label under "Therapeutic Indication" per year.



In summary

- Research in the pre-clinical space is progressing rapidly along with technologies and new sciences: regulators expect that the scientific knowledge and the associated methods will support timely development of safe and effective new therapies
- Regulatory requirements can appear complex, but platforms for dialogue and guidance is readily available for innovators: new framework for Academia
- Regulatory support is available both at national and EU level
- Regulatory awareness and considerations can tangibly enhance the impact of your research programme
- Consider that time and capacity need to be counted in to fully incorporate regulatory input: open the dialogue early

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Thanks for your attention

Acknowledgments

Isabelle.Moulon@ema.europa.eu (Academia)
Monica.Ensini@ema.europa.eu (Academia)
Stefano.Ponzano@ema.europa.eu (Non-Clinical scientist)
Jean Marc.Vidal@ema.europa.eu (Non-clinical scientist)
Thorsten Vetter@ema.europa.eu (Scientific Advice Qualification)

Further info: Laetitia.Kprenou@ema.europa.eu