Personalised medicine towards the market and patients: the approval process

European Medicines Agency’s perspective

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Introduction

- The European Medicines Agency (EMA) is a decentralised body of the EU since 1995 – HQs London -UK

- Foster **scientific** excellence in the evaluation and supervision of **medicines**
  ..to protect **public health**

against the consequences of untreated disease

against unsafe or ineffective drugs

responsible for the **centralised procedure** and co-ordination of **EU network** + plays a role in **stimulating innovation and research** in the pharmaceutical sector, for the benefit of **public and animal health** serving over 500 million users
One Benefit/Risks evaluation, one Marketing Authorisation with the same Product Information and name.
Which patient is right for this drug?

innovative tools
Prognostic/predictive markers
( genomics, imaging,
genomes and cells manipulation,
“nano”, ICT)

Which drug is right for this patient?

The right medicine at the right dose to the right patient at the right time

Benefit/risks evaluation
Variability in drug response
Innovative tools
Which drug is right for this patient?

The right medicine at the right dose to the right patient at the right time

584 products authorized by the EC to date
~20% contain also "genomics" information to "personalise" use of medicines (CYP 450 polymorphisms and dose, DDI etc)

13 targeted/personalised medicines (cancer, HIV, injury) mandatory testing prior to treatment (safety, efficacy, quality) + information on assays or methods

~400 Scientific Advice/year: small but steadily increasing number of advices for personalised/targeted - medicines development

>300 Pediatric Investigation Plans/year

26 designated orphan drugs meet our understanding of "personalised medicines" (16 autologous cells)

Marisa Papaluca Amati – Personalized medicine May 2011
Personalised medicines development building blocks

Science, technology, methods

Development

Approval

Post-approval use and development
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<th>Integrated high-density information (-e.g. omics, imaging + standard parameters)</th>
<th>Biomarkers</th>
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<td>New “types” of products (ATMPs, complex biologicals, nano)</td>
<td>personal-ised products</td>
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<td>“Discovery” platforms, assays and methods</td>
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<td>Correlation of biomarkers with phenotype and frequency in the population</td>
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<th>EMA Innovation Task Force “safe heaven”</th>
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<td>Participation/leadership in to PPP projects</td>
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From biological plausibility to clinical validity
Early dialogue essential

- Biomarkers / products characterisation methods and “validation”

- Assays development fit-for-purpose (justified)

- Non-clinical models, in vitro methods, modeling

- Clinical development and foundations for clinical utility
  - Stratification
  - Enrichment
  - End points
  - Statistical methodology

EMA Innovation Task
Force platform with the Committees members (preparatory step)

- EMA qualification of innovative methods (since 2009 - formal - 14 dossiers to date)

- EMA Scientific Advice
  - -> harmonised protocols
  - -> interaction with HTA
  - -> Interaction with FDA and other global partners
Early identified regulatory issues

Main Issues identified

- New BM qualification/validation requirements
- Labelling
- Diagnostic co-development
- Use of retrospective analysis
- Data submission format
- Technology related issues
- GXP requirements
Clinical issues at the time of approval

Biomarkers associated issues
(scientific plausibility, functional purpose of the biomarker, reliability of the assay)

Choice of comparator

Design and statistical methodology
- Enrichment vs stratification
- Flexible design and interim analysis issues – e.g. un-blinding
- Missing data (including bio-specimen data)
- Retrospective data analysis
- Adjustment for multiplicity

Magnitude and clinical significance of effect

Clinical Utility
Positive

Benefit/Risk

Negative

Optimised population

Trial population

Label population

Inappropriate prescription

Added-value

Added-value

Lack of ext. validity

Lack of communication

Efficacy-Effectiveness Gap

(e.g. intolerants, non-responders, biomarker +ives, combinations)
Clinical Utility: the bridge to post-approval development

For the medicines Regulator: Risk/Benefit of therapy in the lifecycle (not all the story complete at MAA....)

- With a positive test/with a negative test/without a test
- Impact of false positives/false negatives
- Ethnicity and genotype variants

For the HTA Regulator

- How the test impacts on current practice
- Which would be the gain
- Is the test available and affordable
- IVD versus homebrew
Risk management

“Personalisation” implementation and further data generation for regulatory purposes after approval (full or conditional approval). CT well defined population and biomarkers standards + clinical practice

- Evaluate impact
- Treatment outcomes and decision making parameters (as appropriate)

Intelligence:
- Refine methods for quantitative B/R “validation”
- Identify novel markers for optimising benefit/risk of approved products

Communication
Opportunities

The European System flexible enough to embrace innovation such as personalised medicine: early and continued dialogue key success factor

- Clinical trials designs to address efficacy and added value

- Co-development/development / improvement of biomarkers assays and related information for drug and devices

- Monitor drug response and role of biomarker to confirm utility and explore further use

- Develop further quantitative B/R assessment in the lifecycle

- Clinical phenotype definitions, databases and Bio-banking as fundamental clinical research tools

- Pre-competitive research embedded in long-term PPP involving all stakeholders:
  - Establish/use specialised network for research
  - Contribute to generation of new tools (e.g. e-SPC, ITC Algorithms, artificial intelligence systems) to support clinicians and facilitate the patients’ access to personalised medicines
Personalised and stratified Medicines

Drugs candidates

Does the drug do more good than harm in a defined group of patients?

What are the health and cost consequences associated with this drug relative to other interventions in a defined group of patients?

How does the drug perform relative to other interventions in this patient?

Am I willing (and able) to take the drug as prescribed?

Am I willing and able to pay for this treatment out-of-pocket?

Regulatory Agency

Payer

Prescriber

Patient (as payer)

Patient access
Which patient is right for this drug?
Focus on predictive markers, pharmacogenomics, subpopulations

Which drug is right for this patient?
The right medicine at the right dose to the right patient at the right time

and
Thanks for your attention

Science: our basis
Medicines: our scope
Health: our purpose

Acknowledgments
H-G Eichler
S. Vamvakas