Personalised Medicine 2020 – Regulatory Aspects and Early Dialogue

EHFG-Forum 4 “Personalised Medicine 2020” - October 2nd 2014, Bad Hofgastein, Austria

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Disclosures and Disclaimer

Nothing to disclose

Some views presented are my own and should not be perceived as made for or on behalf of the European Medicines Agency or its Scientific Committees or Working Parties
Agenda

• Experience with stratified medicines – where are we?

• Early dialogue - Tools for “more” personalised medicine:

• Personalised medicine – challenges and outlook
EC Def.: Personalised medicine approaches refer to a medical model using molecular profiling for tailoring the right therapeutic strategy for the right person at the right time, and or determine the predisposition to disease and/or to deliver timely and stratifies prevention.

→ Need to distinguish grade of individualisation:

- Binary stratification (e.g. HER2)
  (30 authorised Products with patient selection by 14 different genomic biomarkers)

- Multi-stratified medicine (e.g. CFTR-directed therapy, ca. 1800 ‘strata’)
  Cystic fibrosis transmembrane conductance regulator (CFTR) is a protein[1] that in humans is encoded by the CFTR gene

- Personalised medicine (e.g. autologous cellular therapy)
Targeted Therapies on the increase:

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.

The number of pharmacogenomic biomarker in EU product label have been steady between 1999 and 2010 and since then gradually increasing in recent years. Initially, they have been intended for information only, progressing into becoming one of the important determinant for selection of patients likely to benefit from treatment and “more” individualised dose selection. Biomarker information may also be included in the labelling in case of negative selection (i.e., if the biomarker is used to select a population unlikely to respond) or in case of uncertainty about the value of the biomarker but where a negative selection is suspected, e.g. vandetanib.
Why more personalised medicine?

→ Genetic variants and drug response:

- **30–50% of all clinically used drugs** are metabolised by functionally polymorphic enzymes → plasma levels of some drugs at the same dosage can vary **5-20-fold** among individuals

- **most cases in which pharmacogenomic information** has been included in drug labelling have been based on research conducted **after the regulatory approval** of the drug (phase IV)

→ **EMA – MHLW – FDA guidance on pharmacogenetics in drug development (phase I-III)**
Entry Doors at the European Medicines Agency

EMA support and contact:

- **EMA SME office** smeoffice@ema.europa.eu
  

- **CHMP/ Innovation Task Force (ITF)** itfsecretariat@ema.europa.eu

  Briefing meetings with EMA Committees /FDA/PMDA
  

- **CHMP Scientific Advice and Novel methods qualification** scientificadvice@ema.europa.eu

Gatekeepers and Enablers: How Drug Regulators Respond to a Challenging and Changing Environment by Moving Toward a Proactive Attitude

Changing landscape of pharmaceutical R&D
- Decline in R&D
- Generic pressure
- Increasing development costs
- Increasing regulatory demands
- Changing markets
- Multistakeholder involvement

Creation of supportive regulatory frameworks
- Innovation task force
- Procedure for qualification of novel methodologies
- Support for orphan drugs and SMEs

Creation of multistakeholder interaction
- Global regulatory forums and joint scientific advice
- Dialogue with HTA bodies

Proactive regulatory approach: regulators as "enablers"

Address unmet regulatory needs
- Explore and evolve adaptive licensing
- Quantification of benefit–risk
- Enable innovative clinical trial designs and data analyses
- Enable personalized medicine
Challenges and Outlook → PerMed 2020:

Tools for more PM: Biomarker development / Companion diagnostic CDx

Scientific evidence to market PerMed health care

Different Stakeholder perspective: Patient/HCP/Payer/Industry

Novel manufacturing technologies:
- Continuous manufacturing / QbD
- Nanotechnology
- Biomaterials

Novel treatment technologies:
- Epigenetic
- External activated products (magnetic / photo)
- Borderline products / combined treatment approaches
- Microbiomics
- M-health and EHR
- Disease modelling
- Treatment algorithms (CT → software?)
### Need for “novel” trial designs?

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Christophe Le Tourneau, Institut Curie
From adaptive licensing to adaptive reimbursement

Managed entry schemes

Financial schemes
- Objective: Total cost for all patients
- Monitoring: Discounts, Price/volume
- Instruments: Initial discount on all doses or free initial doses
- Impact: Cap on number of doses, total cost reimbursed per patient, after which the manufacturer assumes the cost

Performance-based agreements
- Objective: Total cost per patient
- Monitoring: Patient/dose dependent discount, Utilisation/price capping
- Instruments: Discount, reimbursement of free doses after the agreed spending/volume threshold is reached
- Impact: Reimbursement if drug is not effective, Treatment interruption if drug is not effective according to pre-established targets

Utilisation in the real life
- Objective: Evidence regarding decision uncertainty
- Monitoring: Outcome guarantees, Patient eligibility + patient registry
- Instruments: Country specific instruments
- Impact: Reassessment which may lead to price changes, conclusion of new agreements, or new reimbursement decision

Combination of financial and performance elements

Pers. Medicine outlook → e.g. liquid BM / MRD

Sources of New Biomarkers:
- Baseline Risk
  - Stable Genomics:
    - Single Nucleotide Polymorphisms
    - Haplotype Mapping
    - Gene Sequencing
- Preclinical Progression
  - Dynamic Genomics:
    - Gene Expression
    - Proteomics
    - Metabolomics
    - Molecular Imaging
- Disease Initiation and Progression
- Therapeutic Decision Support

Decision Support Tools:
- Assess Risk
- Refine Assessment
- Predict Diagnose
- Track Progression
- Predict Events
- Inform Therapeutics

Baseline Risk → Initiating Events → Earliest Molecular Detection → Earliest Clinical Detection → Typical Current Intervention

Drug

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
Recent Initiatives enabling PM:


- **Policies to aid the adoption of personalized medicine** Nature Reviews Drug Discovery Volume: 13, Pages: 159–160 Year published: (2014) DOI: doi:10.1038/nrd4257


Legislation:

• Clinical Trials Directive → facilitate “adaptive” multi-national CT

• IVD/MD regulation → more stringent requirements for cl utility, co-labelling?

• Pharmacovigilance legislation → Prd-class appr., patients report ADR, PSUR B/R

• ATMP potential recast → Gene-, Cell- and Tissue engineered Medicinal Products

• Data Protection / Transparency → EU wide harmonisation of requirements
Conclusion

• Innovative “more personalised” medicines addressing unmet medical needs making their way to patients in Europe

• Collaborative research platforms facilitate and accelerate PM development (liquid BM, MRD)

• Innovative regulatory approach (Regulatory Science) enables product development making them available in a timely manner (Adaptive Licensing pilot, New legislation, EU-ITF network initiative)

• Multi-stakeholder / multi-disciplinary approach necessary for a real improvement in treatment and health care for the patients

• Only a www (win-win-win) situation for all stakeholders will enable real change to the benefit to the patients
Be part of it

Shape it

EU Innovation in times of transforming science

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Thanks for your attention

Acknowledgement:
HG Eichler
Marisa Papaluca