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Health systems, medical products and innovation
Medicines: policy, authorisation and monitoring

STAMP 4/21

STAMP Commission Expert Group
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Subject: Regulatory framework applicable in the field of personalised medicine

Agenda item 7

In 2013, the Commission adopted a **Staff Working Document**[1] (EC SWD) that takes stock of the progress made in personalised medicine, and the opportunities and challenges it presents for healthcare systems. The report concluded that personalised medicine has the potential to offer new treatment opportunities for the benefit of patients, including better targeted treatment, avoiding medical errors and reducing adverse reactions to medicines.

More recently, the Luxembourgian Presidency made personalised medicine one of its health priorities and adopted on 7 December 2015 **Council conclusions**[2] in this field. In the Council conclusions, 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.* In this context, the Council invited the Member States and the Commission through the STAMP to analyse issues related to the implementation of European Union pharmaceutical legislation with the aim of identifying ways to maximise effective use of existing European Union regulatory tools and further improve safe and timely access to medicines for patients, including innovative medicinal products; and to continue, to monitor progress on the adaptive pathway pilot project undertaken by the European Medicines Agency and its potential to allow early authorisation of a medicine for use in a well-defined patient population with a high level of medical need.

Equally important, the Directorate General for Research and Innovation funded a project to generate a strategic research and innovation agenda with general recommendations and research activities which could foster the further implementation of personalised medicine. This study "**Shaping Europe's Vision for Personalised Medicine - Strategic**

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[1] Use of '-omics' technologies in the development of personalised medicine (EC SWD (2013) 436 final) (http://ec.europa.eu/health/files/latest_news/2013-10_personalised_medicine_en.pdf)

[2] Council conclusions on personalised medicine for patients (2015/C 421/03) (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2015_421_R_0003&from=EN)

Research and Innovation Agenda (SRIA)"[3] (PerMed) will be the basis for the work of the future International Consortium on personalised medicine to be launched mid-2016. Amongst several recommendations, the PerMed Study called for a *simplified, harmonised and predictable regulatory procedure across all regulators.*

Based on the Council conclusions and the Commission and PerMed Reports, a number of challenges have been identified along the lifecycle of a 'personalised' medicinal product and the STAMP is invited to reflect upon these.

1. Clinical development phase

Personalised medicine starts by integrating all health data (e.g. - omics data, medical imaging, lifestyle data) to generate and implement meaningful interventions. Such processes should in certain cases be supported by re-classifying diseases at the molecular level and by developing pre-clinical models to validate hypotheses resulting from molecular analysis.

To date, an increasing number of biomarkers are being discovered. A biomarker should be able to predict susceptibility to a certain diseases (susceptibility biomarker), to diagnose the diseases (diagnostic biomarker), to assess the stage and the evolution of a disease (prognostic biomarker) and to predict the response to treatment (predictive biomarker). Also, a combination of several biomarkers may be needed to identify the most effective therapy (biomarker signature). Biomarkers research will be accelerated by access to biobanks. But the biomarkers cannot be used in clinics or in medicine development if they do not meet validation criteria. It was noted in the PerMed report that a Europe-wide process to validate and qualify biomarkers, together with studies to further characterise diseases and their progression would support ongoing efforts towards this integration and re-classification. The European Medicines Agency can provide assistance through its innovation task force or in the form of scientific advice on the qualification procedure for biomarkers.

As far as the clinical trials are concerned, the current clinical trial designs are not always applicable for small populations. Smaller patient population in pivotal clinical trials are also challenging, due to higher uncertainties, the confirmation of positive benefit/risk ratio and the identification of adverse events (AEs) are more complex. Concerns include the regulatory acceptance of studies with small magnitude of effect in small populations and how to extrapolate data result when clinical studies are not feasible for a particular patients population.

Innovative designs will have to cope with smaller populations for these trials. A range of new, more flexible alternative clinical trial designs and data generation approaches, statistical methods and analysis tools need to be considered (EC SWD). Some companies are now considering collaboration to test different medicines in a single type of cancer to faciliate development. Nevertheless, such an approach could require consideration to allow cross referencing to separate marketing authorisation and aspects of data and market protection.

[3] Shaping Europe's Vision for Personalised Medicine - Strategic Research and Innovation Agenda (SRIA) (http://www.permed2020.eu/_media/PerMed_SRIA.pdf)

The Council invited the Member States and the Commission to encourage early dialogue and provision of parallel scientific advice between innovators, regulators and health technology assessment (HTA) bodies, taking into account, as appropriate, input from patients, healthcare professionals and payers, to support evidence generation and regulatory authorisation, while fully respecting the competences of Member States.

A number of regulatory incentives exist in the current pharmaceutical regulatory framework such as the Orphan designation and protocol assistance and the reduction of fees for scientific advice for SMEs[4] and some new scientific approaches and schemes have been developed by EMA, notably the adaptive pathway pilot programme to support identification of disease areas/models, the PRIME (Priority Medicines) scheme.

2. Marketing Authorisation phase

2.1 Regulatory pathway

While medicinal products and the screening of genomic characteristics with diagnostic tests are closely inter-linked in personalised medicine, the current EU regulatory frameworks for the marketing of medicinal products and the corresponding diagnostic medical devices are different. Medicinal products administered to the patient fall under the regulatory framework for medicinal products while diagnostics as such are covered by the legislation governing *in vitro* diagnostic medical devices. According to the PerMed report, the joint development of medicinal products and medical devices seems complicated in the European Union due to the different regulatory systems.

The Commission proposal on the legislation on *in vitro* diagnostic (IVD) aims to ensure that IVD used in the context of personalised medicine offer the appropriate and consistent level of safety and performance. For companion diagnostics intended to assess patient eligibility for treatment with a specific medicinal product, the Commission proposal on the *in vitro* diagnostic legislation provides for a consultation procedure with the EMA or one of the competent authorities designated by the Member States in accordance with Directive 2001/83/EC in the context of the conformity assessment procedure for the companion diagnostic. The consultation will concern the suitability of the companion diagnostic in relation to the safe and effective use of the medicinal product in question.

It is worth noting that these medicinal products are potentially eligible for a number of regulatory pathways/incentives namely the use of the conditional marketing authorisation, the authorisation under exceptional circumstance in situations where standard development is not feasible, the accelerated assessment or the 10 years market exclusivity through the orphan designation.

International harmonisation of regulatory requirements could also facilitate the acceptance of products across the borders and may be promoted.

[4] Academia are not covered by these fee reductions.

2.2 Labelling and packaging information and use of the product

The Council pointed out the crucial importance of the training and awareness of healthcare professionals in the field of personalised medicine. In this context, the summary of product characteristics (SmPC) is the basis of information for healthcare professionals on how to use the medicinal product safely and effectively. In certain cases, the presence of certain mutation in the gene should be determined by genetic testing before using the treatment. The use of biomarkers can allow identifying the population which is more responsive to treatment. Equally important, personalised medicine is broader than genomic based medicines. For example, the molecular characterisation of pathogens can be important before prescribing the right antibiotic to the patients and avoid subsequently multi-drug resistance.

According to the information from PerMed, the current labelling practices and SmPC should be revised to include harmonised information on selected population, clear description of biomarkers used to select the population and degree of importance of the biomarker (e.g. compulsory vs. optional). PerMed notes that the selection of indication in terms of exact targeted population may be a big challenge (e.g. who really benefits and who does not? Is there an unmet need for the broader indication?). The availability of the diagnostic as an IVD or a test in hospital is also of crucial importance for the use of the medicinal product. Incorporation of information may require alternative approaches (websites, expanded QR code).

Correct information for the healthcare professionals is crucial to ensure the right treatment to the right patients. It will therefore be critical to adapt the indication to this information, indicate which mutations had been studied or not, which population suffering from which mutations were responsive to the treatment and, if necessary, which test has to be used to take an informed decision.

2.3 Post-approval changes to products and monitoring

After granting a marketing authorisation, manufacturing changes, either to components (e.g. a medicinal product or *in vitro* diagnsotic) included in the product or to the product as a whole, could have an impact on the marketing authorisation application.

Appropriate synergies between the two sectors should be ensured to have a continued understanding of the benefit/risk profile of these products during their life cycle.

Moreover, adverse reactions to medicinal products will be closely monitored. The post marketing surveillance through the pharmacovigilance system would potentially allow detecting rare adverse reactions which were not detected in the clinical trial launched on a smaller subgroup.

2.4 Points for discussion at STAMP:

The aim of the questions listed below is to stimulate discussion between STAMP members regarding the implementation of personalised medicine within the EU pharmaceutical regulatory framework.

1. Is the current model of clinical development appropriate for personalised medicines? What are the specificities and the possible hurdles in the clinical development phase of such medicinal products?

2. Are there challenges for the marketing authorisation of personalised medicines? Would the move to smaller subset of diseases lead to more conditions associated with 'orphan' designation?

3. Could existing regulatory routes be used better and in what way (e.g. conditional marketing authorisation) to take into account personalised medicine?

4. Is there a need for new regulatory tools and/ or pathways (non-legislative) to support the development, authorisation and access to personalised medicine (e.g. adaptive pathway, research on the qualification/validation of biomarkers, scientific guidelines)?

5. What is the interplay between the legislations on medicinal products and *in vitro* diagnostics (IVD) and what are the elements to be taken into account to allow for an optimal authorisation and use of personalised medicine? Is the availability of the IVD a matter of concern for the suitable use of the medicinal product?

6. What synergies could be created between innovators, regulators and HTA bodies, taking into account, as appropriate, input from patients, healthcare professionals and payers, to support evidence generation and regulatory authorisation and patient access to personalised medicine?

7. Are the current guidelines for defining the product information (SmPC, product leaflet) properly addressing the specificities of personalised medicine and the needs of health care professionals and patients?

8. What are the possible challenges after marketing authorisation? How could these be addressed?