European Alliance for Personalised Medicine

Public consultation on the preliminary opinion on "Access to health services in the European Union" by the Expert Panel on effective ways of investing in health.

The following is the response from the European Alliance for Personalised Medicine (EAPM) to the European Commission and its Expert Panel.

The Alliance has comments on several key elements of the preliminary opinion and these begin with the sentence **"medicines have become financial products, and companies face tremendous pressure to obtain high profits in the short term".**

EAPM and its multi-stakeholder membership contends that those responsible for the provision of modern-day healthcare, in a Europe of 500 million potential patients across 28 Member States, should not consider financial concerns only as the basis for all discussion and progression.

Healthcare in the 21st century must be about **putting patients at the centre of their own healthcare decisions** as well **as allowing and facilitating innovation**, through investment in research and workable reimbursement policies at the pan-European level. In this sense, **incentivising access to health technologies that bring value to patients and health systems across Europe, whether they be medicines, therapeutic interventions or medical technologies such as diagnostics, should be the guiding principle for the selection and provision of health services and their implementation at the pan-European level**. **Investing in health as a human capital**, as recognised by the European Commission, will bring **the value of improved health outcomes for individual patients and society, contribute to the sustainability of health systems** and drive economic growth.

As indicated by the expert panel, the introduction of austerity measures in many European countries can be associated with an increased trend in unmet needs for citizens. The focus on costs only in relation to personalised healthcare initiatives could lead to longer-term losses in health outcomes, resulting in underperforming health services, with increasing inequalities in access to valuable innovation.

Personalised medicine technologies may be very effective in supporting the optimisation of limited healthcare budgets and achieving equitable access to drugs, diagnostic technologies. and health services.

Investing in diagnostic technologies and personalised medicines,considering their broader and longer-term benefits for patients and health systems alongside a thorough analysis of the economic advantages; will lead to a healthier Europe where resources delivered are matched with the needs of the European citizens.

In the 10 years since the completion of the Human Genome Project, advances in genomic technologies have led to an exponential decrease (> 16,000-fold) in the cost of characterising the genes of a patient through DNA sequencing. Patients have benefited from major biological insights and medical advances, including the development of drugs whose application is underpinned by the appropriate employment of pharmacogenomic analysis. Yet the challenges of equitable access remain in Europe.

EAPM believes that in order to achieve a "Healthy Europe", effective but affordable health care that is

clearly matched to patients' needs must be delivered. Adopting personalised medicine is a priority at European level, to ensure improved health outcomes and help promote the economic sustainability of European health systems.

COMMENTS ON THE PRELIMINARY OPINION

Page 25 'Financial resources are linked to health need - To ensure an adequate level of spending on health:

On recommendation 'It is important for public funding to be used effectively, rather than simply driving up the prices of resources whose supply is constrained, such as technology or highly specialised staff'. We would like to emphasise the role of medical technologies such as diagnostics in promoting economic sustainability rather than as a cost driver. Investments in diagnostic technologies will promote cost containment, as their use in selecting patients according to their response to therapy maximises the effectiveness of the therapeutic intervention, while minimises inefficient use of resources (avoiding non-effective interventions and their health and economic consequences).

Spending on medical technologies is an investment in human capital. These invested resources enable people to regain health more rapidly, thus underpinning their return to society, where they can contribute at both social and economic levels. Stimulation of the economy by technology manufacturers also results in increased jobs and investment. Thus improved health outcomes and economic gains offset the initial input invested. It should be noted that medical devices are one part of the overall medical technologies spectrum which includes diagnostics. Diagnostics account for less than 2 % of the overall healthcare expenditure.

Page 51: Services are relevant, appropriate and cost-effective

On the recommendation to address this issue: 'Put in place systematic priority-setting processes to enable HTA-informed, cost- effective coverage decisions for both new and existing technologies.' Priority setting and HTA of medical technologies such as diagnostics, both at national and European level, should be guided by national decision makers and patients' demands and needs.

Page 76 of the above refers to controversy about impaired access to innovative medicines and medical devices including diagnostics (page 81 on).

EAPM notes that patient access to innovative personalised medicineremains sub-optimal and varies dramatically between EU Member States. The fact that a new medicine or innovative product usually takes more than a decade to get from bench-to-bedside is not only clearly undesirable but is arguably unacceptable in the 21st century. And aside from the years of translation, patient access in the absence of flexible pricing and reimbursement systems is frequently restricted to patient subgroups and often further delayed or not affordable at all in less affluent parts of Europe.

The public is one of the most important stakeholders in decisions related to personalised medicine, yet there is a paucity of studies regarding citizens' values, concerns and expectations it. Further efforts to engage with the public are warranted, in order to inform the effective, efficient and equitable translation of personalised medicine into clinical practice.

On diagnostics:

The approaches to reimbursement for companion diagnostics vary widely across and within Member States; decisions are decentralised, not taking into account the value of diagnostic information, only considering prices.

Unlike for drugs, HTA plays a role only for a few diagnostics, and when assessments are performed they don't lead to changes in funding, reimbursement or adoption. There is a need to make diagnostic assessment linked to funding decisions in order to allow implementation into clinical practice and the need to follow-up on this implementation.

When HTA is performed on diagnostics, there is a lack of clarity and country differences on the criteria used to assess and make recommendations, leading to the need for methodological guidelines acknowledged throughout Europe. Diagnostics cannot be assessed in the same way as drugs.

There is a need for a timely assessment as the cycle of development of diagnostics is shorter than drugs. HTA timing should be short enough and applied at the right moment in the life cycle, to be relevant to clinical practice, so companion diagnostics reach patients at the right moment to allow personalised medicines to be effective.

On companion diagnostics:

Companion diagnostics provide intrinsic value of diagnostic information, increasing effectiveness of treatment by stratifying responder patients. They decrease patient and providers uncertainty through their ability to 'rule out' response to treatment, which allows fast initiation of a better suited option and diminishing the sense of 'ambiguity', increasing patient empowerment, improving adherence to therapy, and fostering a sense of well-being.
Diagnostic information decreases also payers uncertainty, by reducing costs and loss of quality of life associated with adverse events of non- responders, also avoiding time delays in selecting appropriate interventions.
Diagnostic information from companion diagnostics, combined with the targeted therapy, can delay the progression of the disease and increase patient survival. Companion diagnostics can also predict safe use by ruling out those at risk of serious adverse events.

On HTA, the Alliance recommends:

- Generating evidence on citizens' expectations and the wider societal benefits and costs off-sets of personalised medicine technology and services. This is a pre-requisite for their successful introduction into routine patient care.
- Actively backing the adoption of support methodology for HTA, appraisal and patient access decision making that helps to ensure that multiple and conflicting decision criteria are fully recognised and dealt with in a transparent and balanced manner, while specificities of the different health technologies are accounted for.
- Placing patients at the centre of the healthcare process and ensuring their more actively participation in HTA and appraisal
- Further advancing existing recommendations and methodology to incorporate patients' perspectives in HTAs.
- Supporting Member States with limited experience of involving the patient and citizen perspectives in HTA through best-practice sharing.
- Developing mechanisms to establish internationally shared standards for relative effectiveness assessments in general and for personalised medicine technology and services in particular.
- Ensuring that technology assessments jointly conducted by national HTA agencies can be accepted as input in patient access decision processes in the respective countries.

Regarding companion diagnostics:

- Creating clear, transparent and timely market access processes suitable for the specificities
- of companion diagnostics throughout European Member States.
- Accounting for the value of diagnostic information in funding, reimbursement and adoption decisions on companion diagnostics and personalised medicines
- Generating HTA processes that are fit-for-purpose for diagnostics i.e. linked to coverage, reimbursement, funding, and/or use decisions
- Fostering HTA methods that take into account the multidimensional value of the diagnostic information and the therapy as complementary items, considering the improved efficiencies to healthcare systems offered by companion diagnostics through the avoidance of unnecessary therapy costs achieved through the targeted diagnosis.
- Generating incentives that will further drive innovation and continuously improve patient care;
- Shift from cost to value considerations and take a broader societal perspective.

Elsewhere, the opinion refers to **pricing**, noting that high prices are becoming an increasingly important barrier to access. Producing medicines has not become any cheaper. If anything, the opposite is true with development costs rising almost exponentially in recent decades. The latest figures suggest the average medicines still take more than $1bn and around 12 years to bring to market.

At the same time, the size of the market on which private sector companies are able to recoup their costs has become much smaller – a natural result of increasing the personalisation of treatment. So, does the fact that it's more expensive to produce medicines for fewer people necessarily mean that medicines are (or will be) unaffordable for healthcare systems? Our answer to this is, no – at least not necessarily.

The key challenge for healthcare systems managing medicines spending – whilst also delivering on innovation - will be ensuring 'rational use'. Where it is possible to treat a patient utilising an existing, cheaper medicine, this principle should be followed. But if a patient needs a newer more targeted approach, access should be provided at reasonable prices that reflect both the added value and the volume across the market.

New medicines

Increasingly, managed-entry agreements (MEAs) - are used in a number of Member States. An MEA is an arrangement between a manufacturer and payer/provider that enables reimbursement of a medicine subject to specified conditions. Although combinations are possible, there are two main groups of MEAs, one group links reimbursement to health outcomes and the second facilitates access to new medicines through financial instruments.

The current legislative framework, which requires the generation and communication of these data, would benefit from increased coordination. Currently, post-marketing data on effectiveness of medicines is required by regulators in the framework of post-approval surveillance studies, and by payers and their associated HTA agencies at the national level.

EAPM believes that the expert panel document should discuss managed-entry agreements as a solution to control cost; while monitoring the cost-effectiveness of new medical technologies.

Paying for performance: rewarding innovation

Personalised medicines have the potential to improve healthcare and patient experiences. However, healthcare systems need to be able to appropriately assess them and reimburse them. There is substantial inequality in access to medicines in Europe. This growing inequity is not compatible with European social values and policies for cohesion.

Payers need to recognise the key role they play in incentivising and providing access to innovation by developing a new model for Price and Reimbursement (P&R) which rewards innovation and value and is transparent.

Rewarding innovation for medicines means that:

- P&R conditions should reflect value assessments, building on aligned and complementary regulatory assessments and HTAs, followed by price discussions at a national level; differential pricing should be made possible by agreeing on an appropriate framework for use of international reference pricing amongst Member States.

- P&R conditions should be regularly updated, in order to learn from new data produced post-authorisation; managed entry agreements can be a first step in a longer-term evolution of progressive patient access, i.e. progressive authorisation and progressive reimbursement mechanisms.

Furthermore, to overcome some of the financial barriers which lead to unequal access to medicines, prices in a given country should be commensurate to the affordability of that country to pay, and could differ between EU countries. This will ensure that all patients can have access to personalised medicines in a timely and equal manner.

Benefit/risk and real-world evidence

Specific considerations for new regulatory pathways for personalised medicine and other defined categories of products require further deliberation, in conjunction with adequate incentives on the demand side (pricing and reimbursement approaches) as approval, reimbursement and incentives are integrally related.

Achieving this objective will require collaboration between the Commission, EMA and reimbursement bodies to ensure transparency of the intent and application of the regulatory process and promote use and reimbursement of medicines approved via a progressive regulatory process.

There has been substantial work, via the EMA and various think-tanks, to define a better, more structured and more patient-responsive approach to defining benefit-to-risk. There have been several instances in which patient pressure and/or the urgency of the situation has resulted in regulatory agencies reconsidering their approach to the benefit/risk balance.

Clinicians, health systems, regulators and HTA agencies are increasingly demanding real-world data on the performance of medicines. With the advent of mobile health and other tools, the collection of such personal data has become much easier and less expensive. There should be models for use of registries or the mining of electronic health records or claims databases.

Real-world evidence is crucial to the implementation of adaptive clinical trials. Medical Adaptive Pathways to Patients (MAPPs) are currently being tested in an EMA pilot project, which calls MAPPs “a prospectively planned process, starting with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the marketing authorisation to expand access to the medicine to broader patient populations.”

It is the ‘iterative phases of evidence gathering’ that will ideally utilise real-world evidence to more accurately detect patient responses to new therapies in real time.

Current barriers to the implementation of real-world evidence

- The required data infrastructures do not exist everywhere in Europe

- Data collection systems are not harmonised and many of the most successful are customised locally

- The technology evolves quicker than regulation can adapt
- Regulatory authorities at Member State level are not currently equipped to base decisions on real-world evidence
- The current "Right to Be Forgotten" data protection legislation may compromise the ability to use real-world evidence in clinical development
- Next-generation healthcare harnessing real-world evidence will be increasingly multisectoral and multidisciplinary, challenging the current status-quo of regulatory oversight.

On Page 63 of the opinion, it is stated that: "The advent of **high-speed Internet** holds out the possibility of innovative models of care delivery, although so far claims about benefits have far outweighed actual evidence of cost-effectiveness."

EAPM notes that the availability of biomedical data, very much driven by digitisation and the decreasing costs of human full-genome sequencing have outpaced Moore's Law, heralding a new era for healthcare comparable to that of computers transforming society over the past decades. The development and disseminations of tools and processes able to analyse and interpret the data is vital. This will create new knowledge that can benefit patients accurately and directly, rather than at the endpoint of a lengthy process riddled by trial-and-error treatments and policy bottlenecks.

Research and development (R&D)

The draft opinion states that the current system of funding R&D through medicine prices encourages pharmaceutical companies to focus on areas likely to be most profitable for them rather than areas in which there is unmet need.

EAPM's view is that, certainly, science has led to major advances in the understanding of the role of genomics in diseases, in the discovery of biomarkers, in the development of new statistical methods and in the invention of dynamic tools for collecting real-world effectiveness and safety data. Conversely, the basic R&D and regulatory process is largely unchanged and, within an unchanged framework, it has simply become steadily more burdensome to develop innovative medicines and diagnostics.

Stimulating further diagnostic development and overcoming high business risks are two critical factors that can only be achieved through the implementation of a multifaceted, multi-stakeholder and targeted approach that will cover the whole spectrum of development– from funding to regulatory aspects to reimbursement – all of which must be in place in order to achieve successful approaches to personalised medicine.

There is a need for simplification of complex and inflexible regulatory procedures within the current development and regulatory framework, a requirement for review of the supportive incentive system in order to improve innovation, and the need for predictability of the regulatory processes to reduce R&D costs and allow earlier access for patients to innovative medicines and diagnostics.

Incentivising innovation through development funding for diagnostics

In acknowledging that the resources required to develop companion diagnostics are high, incentives should be in place to foster innovation that is targeted specifically towards areas of unmet needs. Examples of innovation schemes can be found in the Strategic Industrial Innovation (ISI) programme in France that promotes collaboration between industry and academia to help bring products and technological breakthroughs to the market through support from public funding. This national initiatives should be supplemented by appropriate incentives at EU level for the development of companion diagnostics on a broader scale.

Authorisation

The draft opinion states that two key issues warrant attention. First - insufficient controls and unnecessary controls and barriers. Second - the conflicts of interest that arise when regulatory agencies are financed (at least in part) by pharmaceutical companies. EAPM notes that all stakeholders are funded by some agency. The clear issue is to have rules in place and to ensure transparency.

Distribution, coverage, prescribing and use of medicines

Patients want information about medicines, firstly to help decision-making, and then for ongoing decisions about the management of those medicines. In this respect, community pharmacists may provide expert information about medicines and other pharmacy products – for example relating to prevention and management of side-effects, pharmacological interactions and instructions on how to take the medicines to avoid error and improve adherence.

However, the process of involving patients in their care decision does not only imply health literate patients, but also a "health literate friendly system" which provides transparent and credible information about the chance of benefit and the risk from various medical interventions, and which decrease the information and power asymmetry between doctors and patients (i.e. the doctor knows everything, the patient nothing). Patients need to be recognised as active participants rather than passive recipients

This means increasing patients' medical information through a language that is matched to their educational level, and allowing patients to effectively state their own preferences and concerns.

Alliance recommendations

Health professionals should:

- Assess each patient's health literacy;
- patient adapted literature, involve patients in the generation of literature for patientts and to its effect on each patient;
- Monitor and facilitate each patient's understanding of diagnosis and of therapeutic strategies;
- Assess each patient's information needs;
- According to each individual's information preferences, provide details about different treatment options, the possible benefits and risks, the rationale for diagnostics and pre-emptive testing;
- Assess each patient's decision-making capacities and needs including decisional conflicts, values, willingness to participate/not participate in the decision process, family/social support and resources
- Monitor and facilitate each patient's ability to communicate about their preferences, values, lifestyle,
- Health professionals may be helped by information technology tools in performing these tasks via screening tools and profiling tools may provide information about the cognitive characteristics of each patient.

Regulatory needs

Regulators should facilitate health information technology implementations driven by best practices with the understanding that all processes will need to adapt rapidly to evolving technologies, and:

- EU regulators should support projects that investigate the use of real-world data for approval and reimbursement of new therapies at the Member State level

- The opinions of patients with conditions for which there are currently limited treatment options must be incorporated when considering alternative evidence bases such as real-world data

- The current data protection legislation should be reconsidered with regards to healthcare, as it may place Europe at an international disadvantage for the use of real-world data
- The EU should allow for a wide scope of eHealth and mHealth applications without over-regulating the sector, similar to the 'light touch' approach of the FDA with regards to mHealth
- Programmes such as Innovative Medicine Initiative that support a multidisciplinary approach/dialogue are vital to implement real-world evidence based development in Europe.

For companion diagnostics:

- Develop regulatory pathways that do not jeopardize access by duplicating already existing regulatory processes for companion diagnostics such as individual conformity assessments.
- Establish clear technical requirements for clinical evidence that companion diagnostics are required to meet, whilst ensuring a high level of safety and performance.
- Companion diagnostics should only be permitted to benefit from the in-house exemption (accordingly, there is no need to fulfil the requirements of the proposed Regulation) in instances when no equivalent test is available and no longer eligible once the equivalent test is CE-marked.
- The unique case of companion diagnostics must be acknowledged with an adapted and appropriate review process that accounts for their specificities in terms of the clinical evidence required, how to collect the data and conduct performance studies that provide safe and streamlined processes,
- This approach should not be repeated for all in vitro diagnostics, as it would not be appropriate and, in some cases, may be not just impractical, but also impossible, as IVDs never interact directly with patients. Any risk to patients – as emphasised by the new risk-based classification system – would stem from the information that IVDs provide.

Meanwhile, the need to address the disconnection between regulators and HTA bodies has been recognised in the EMA Road map plan to 2015, which envisages initiatives to increase collaboration and reduce duplications in data requirements by the EMA and national drug reimbursement agencies.

Coordination is also needed between HTA processes and decision making at national level for companion diagnostics, so if HTA is performed it should inform a decision on funding, reimbursement and/or adoption. Also, Member States should strengthen their infrastructure and use of electronic patient records and mobile health solutions to collect and analyse both clinical and patient-reported outcomes.

Collection of evidence post-marketing also requires a thorough discussion about the involvement of health professionals and patient, since the collection of qualitative data depends on their dedication and commitment, and the right legislative framework of access to data.

ENDS

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