PHARM 840

PHARMACEUTICAL COMMITTEE
21 October 2022

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Furthermore, the topics explored in this document are based on feedback from consultations. They represent elements tested in the impact assessment. Feedback from the discussion in the pharmaceutical committee will feed into the on-going impact assessment. The document is only for the purposes of the discussion at the pharmaceutical committee and should not be distributed further.

Revision of the general pharmaceutical legislation

1. Novel incentives for the development of antimicrobials addressing AMR and prudent use measures

The effect of drug-resistant infections due to the emergence and spread of pathogens that have acquired new resistance mechanisms to antimicrobials (AMR) is well known to regulators. The dry pipeline for novel antimicrobials that are able to tackle AMR can derive from objective limitations (e.g. lack of science) however, it also relates to a market failure in the antimicrobial sector.

Incentives for the development of novel antimicrobials

Two novel incentives for the development of novel antimicrobials were examined in the impact assessment of the pharmaceutical revisions: *first a model* that requires all companies that do not hold a antimicrobial in their portfolio to pay into a fund for the development of novel antimicrobials addressing AMR (*pay or play model*). The impact assessment indicates that this model would not directly increase the number of novel antimicrobials and may risk increasing prices and social costs; it would negatively impact companies (particularly SMEs) with no expertise in AMR product development. A *second model* foresees the creation of a transferable regulatory data protection voucher (or transferable exclusivity voucher) which allows the developer of a novel antimicrobial product that fights AMR to benefit from an additional year of data protection on another product in their portfolio or sell the voucher to another company to use. The voucher comes with a high cost for health systems. Vouchers can work only if their number is very restricted (i.e. max 1 per year). To achieve this, only those medicines that are 'game changing' antimicrobials can receive 'novel antimicrobial' status (under strict criteria) and can be considered for a voucher. Even if found eligible additional supply requirements, transparency preconditions on funding received and on the sale or transfer of the voucher and other criteria and conditions would apply. This model has

the potential to raise a significant amount of funds that can cover the EU's 'fair share' of the cost of development of a novel antimicrobial.

Other pull incentives are being considered outside the pharmaceutical legislation: e.g. a multi-country pull incentive of procurement mechanisms where Member States would buy a guaranteed access to existing antimicrobials (service contract) for a given volume and period. Such a scheme can target either newly approved antimicrobials, and/or old antimicrobials which are not available in all EU Member States. A combination of both tools could be part of the EU's response to this long lasting problem.

Prudent use of antimicrobials
AMR is accelerated by the misuse and overuse of antimicrobials. The prudent use of antimicrobials is a cornerstone in addressing antimicrobial resistance. Measures such as introducing a prescription status for all antimicrobials for systemic use, introducing an obligation for to conduct an AMR lifecycle management plan and an enhancement of the environmental risk assessment along with the imposition of relevant risk minimisation measures on the manufacture, use and disposal of antimicrobials will also contribute to reducing AMR though the environment.

Questions:
- What can be the conditions linked to the vouchers to make them deliver on AMR and at the same time have a cost that is still 'acceptable' for health systems?
- Can we afford not to propose a novel incentive for the development of novel antimicrobials? What other alternatives do we have to take action for the development of novel antimicrobials to reduce AMR?
- What other measures related to prudent use could this legislation include?

2. Measures to improve access to medicines and market launch in all Member States

Increasing access to medicines for patients across the EU is a key objective in the pharmaceutical strategy and the pharmaceutical revision.

Even though the central authorisation procedure (CAP) theoretically allows a medicine to be marketed in all EU Member States, the number of EU countries in which CAPs are launched has been steadily decreasing. Substantial differences have been reported in terms of time to entry on the market. A company receiving a MA today is free to choose when and where it will place its product on the market, which can create uncertainty for Member States. The reasons for these delays are not only linked to company's business decisions, they also relate to national pricing and reimbursement decisions or policies and whether the added therapeutic value of the product is proven or not. Delays can also link to administrative delays and differences among Member States health systems.

While national pricing and reimbursement decisions are in the national remit and this legislation cannot influence them as such, it can act as an enabler to increase the rewards of a successful placing on the market.

The consultation has shown a broad support from Member States to amend the current 'one size fits all' incentives system towards a modulated model. A modulation of the system of regulatory incentives (data and market protection) would link a part of the data protection to the successful launch of the medicine in all the Member States where the Market authorisation

is valid thus increasing the reward of a successful market launch. Such a provision would need to be applied in a pragmatic way in order to ensure legal certainty and predictability for companies (both innovative and off-patent) as well as public authorities.

Questions:

- How can the market launch provisions be applied as pragmatically as possible? For example could each Member State issue a certificate that a product was launched on their market in the quantities and presentations needed for their patients?
- Should there be other conditions linked to the incentive?

3. Revised hospital exemption for ATMPs

An important number of novel ATMP's have been initially developed in university hospitals. Some of them are still prepared by hospitals, others at a later stage were brought into the central marketing authorisation pathway by industry.

The hospital exemption (HE) clause has been interpreted in different ways in different Member States, ranging from facilitating the use of ATMPs to patients who are not eligible for clinical trials (similar to compassionate use) to providing access where no centrally authorised ATMP is available. Furthermore, hospitals use the HE in parallel to other regulatory frameworks, like clinical trials or compassionate use, without clear delineation.

The HE has proven to be an effective instrument for local manufacture of ATMPs within hospitals and patient access to safe therapies that cannot be achieved otherwise. However, the evidence generated during the implementation of HE can often not be used to support neither a clinical trial authorisation application or a central marketing authorisation application. Nevertheless, the university hospitals mostly seem to lack the financial and human resources as well the regulatory expertise to pursue the central marketing authorisation pathway.

The revision of the pharmaceutical framework brings an opportunity to move towards a more harmonized approach of these hospital-prepared ATMP's. The Commission is, therefore, exploring the introduction of more standardised requirements under the HE, like on the application and authorisation process, on preparation and use of these products, on exchange of knowledge between hospitals within the same MS or across different and on vigilance and traceability. As discussions on HE are often complicated by a lack of transparency, the Commission is also exploring possible requirements on data collection on safety and efficacy and central notifications of HE authorisations to the Agency. The Commission is not considering changes to the scope of the HE in the legal text or the national HE rules in different Member States.
The Commission will follow the developments closely, with an overall aim to understand how HE can be further improved to ensure EU-wide patient access to safe and effective advanced therapy medicinal products.

Questions:

- For an implementing act, what should we foresee this to cover in terms of implementation of the conditions for authorisation of HE, data collection on use, safety and efficacy (regarding HE applicant-NCA and NCA-EMA relationship)?

- Which regulatory changes could enable the translation of research done under the HE framework into an authorised medicine, while ensuring the standards of safety,

quality, efficacy and continuous access of patients to safe ATMPs prepared in hospitals?

4. Strengthening the Environmental Risk Assessment of medicines

The Commission proposes the strengthening of the environmental risk assessment (ERA) of medicines along their lifecycle i.e. at the time of marketing authorisation and post-authorisation, with obligations to sufficiently address identified risks (risk mitigation measures). The ERA covers the evaluation of risk for the environment and/or public health from the use, storage and disposal of medicines. "Medicine" means all components i.e. the active substances and the excipients. Companies would also have to update the ERA post-authorisation based on new evidence. To facilitate the reuse of ERA studies from generic companies, these would be published by the Agency.

We also propose a separate ground for refusal of a marketing authorisation in case companies do not provide adequate evidence for the evaluation of the environmental risks or if the proposed risk mitigation measures are not sufficient. Finally, for medicinal products authorised before December 2006 that have not been subject to an ERA, a programme of ERA of these substances would be set on a risk based approach.

Questions:

- Should the manufacturing of the medicines also be covered by ERA?
- If yes, should the manufacturing of all medicines or only of antimicrobials (due to AMR) be covered?

5. Active substance master file

A scheme for certification of active substance master files will be established to optimise the use of resources for both applicants of marketing authorisation and the competent authorities assessing such applications. The use of the certificate should be mandatory for subsequent marketing authorisation applications using the same active substance master file to avoid duplication of assessment.

The use of an active substance master file certificate should not change the responsibility of the marketing authorisation holder for their medicinal product.

The examination of the application for an active substance master file should be coordinated by the Agency that will also grant the certificate. The Commission should be empowered to adopt by delegated act the details of the scheme.

Currently, for active substances, the applicant for a marketing authorisation can use of an active substance master file and a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) to provide information in the dossier about the active substance. In practice, a European Pharmacopoeia monograph may be developed after the first active substance master file has been submitted for application for a marketing authorisation.

Questions:

- In the future scheme, should it be the choice of the applicant of a marketing authorisation to rely on an active substance master file (certificate) or a CEP?
- If no, should an active substance master file certificate have priority over a CEP or vice versa?

6. Formal recognition of HMA network in legislation

The HMA network is an established cooperation between the national regulatory authorities to support the implementation and application of the EU pharmaceutical legislation. Among other things HMA is active in addressing key strategic issues for the network, such as the exchange of information, IT developments and sharing of best practices, focussing on the development, co-ordination and consistency of the European medicines regulatory system and ensuring the most effective and efficient use of resources across the network. This includes developing and overseeing arrangements for work-sharing co-ordinates the mutual recognition (MRP) and decentralised procedures (DCP). The HMA network is one of the success factors of the EU system, however unlike for other sectorial legislation it is currently not formally recognised in the EU legislation.

Questions:

- We seek the feedback on whether it would be useful to include a high level provision to that respect in the future legislation.
- If yes, we would be interested whether particular tasks of HMA should be highlighted in the legislation and whether there is a need to recognise a role of HMA as a network when discussing resource allocation from national competent authorities in the context of the scientific assessment of centrally authorised medicinal products.

7. Creation of a 'sandbox' provision

Regulatory sandboxes can provide the opportunity for advancing regulation through proactive regulatory learning, enabling regulators to gain better regulatory knowledge and to find the best means to regulate innovations based on real-world evidence, especially at a very early stage of development, which can be particularly important in the face of high uncertainty and disruptive challenges, as well as when preparing new policies.

Such sandboxes have been already tested in other regulatory sectors. Council conclusions in 2020 identified them as tools for an innovation-friendly, future proof and resilient regulatory framework and they are now also considered as a tool in the future pharmaceutical legislation.

Questions:

- Do you have any experience with sandbox clauses at national level?
- Which types of safeguards are necessary if such testing environment is introduced for medicinal products?

8. Establishment of a mechanism to clarify the regulatory status of products

The creation of a central classification mechanism for advice on whether products are medicines or not was an element tested in the impact assessment. The current EMA Committee for Advanced Therapies (CAT) mechanism for ATMPs has a similar mechanism.

Conclusion of the IA

The IA recognises that medicines are increasingly being used in combination with a medical device, usually to enable the delivery of the medicine. However, such products have brought regulatory difficulties for NCAs and regulatory uncertainty. A classification mechanism would improve consistency of the classification of borderline products and the resulting choice of the most appropriate pathway through the EMA committee structure. It should also

harmonise coordination between concerned authorities in particular in the framework of medical devices and substances of human origin, and thereby deliver some small efficiency gains. It may also improve the overall timeliness of assessments. The creation of a central screening mechanism for centrally authorised medicines may be timely as more classification questions arise.

Public consultation

The public consultation (Question) 6 also reflected a general need for more clarity on classification issues and indicated a general approval for the creation of a central mechanism that provides non-binding scientific advice on borderline questions (see below).

How would you assess the following measures to create an adapted, agile and predictable regulatory framework for novel products? : 2. Create a central mechanism in close coordination with other concerned authorities (e.g. those responsible for medical devices, substances of human origins) to provide non-binding scientific advice on whether a treatment/product should be classified as a medicine or not.

		Answers	Ratio
Very important		151	31.59 %
Important		122	25.52 %
Fairly important		81	16.95 %
Slightly important		19	3.97 %
Not important		15	3.14 %
Don't know		40	8.37 %
No Answer		50	10.46 %

Overview of a possible scientific advice mechanism

Companies or Member States should be able to raise the classification question early on (even years before formal MA). The scope of the mechanism would be open to all (potential medicinal) products that would potentially be eligible as CAPs (therefore excluding nationally authorised products). The mechanism would give the EMA committee the responsibility to provide a non-binding scientific assessment on whether the product in question is a medicine and (if relevant) an ATMP. The mechanism would include the obligation to consult other concerned authorities where relevant, in particular in the frameworks of medical devices and substances of human origin.

Questions:

- What would be the role of EMA and NCAs in the creation of a central scientific classification advice?
- Would we need a recourse mechanism at EU level if a Member State disagrees with the scientific recommendation?