EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

**For EUCOPE Members Only

An Initial Breakdown of the ENVI report on the EU Pharmaceutical Package

On 19 March 2024, the European Parliament's Committee on the Environment, Public Health and Food Safety (ENVI) adopted the two proposals that form the Pharmaceutical Package. The Pharmaceutical Package, initially presented by the European Commission in April 2023, consists of two legislative proposals:

- A "master" Regulation on *Authorisation and supervision of medicinal products for human use and governing rules for the European Medicines Agency*, merging Commission Regulation No 726/2004, Orphan Medicinal Products (OMP) Regulation No 141/2000 and Paediatric Regulation No 1901/2006;
- A Directive on *Medicinal products for human use*, repealing Directive 2001/83/EC and Directive 2009/35/EC.

Although ENVI has adopted the proposals, they must still be voted on in the Plenary on 11 April before an official Parliament position is established. Note, it is possible that Member of the European Parliament (MEPs) make amendments to the text during the vote on 11 April.

In parallel, the European Council is also working on their position on the Pharmaceutical Package, which they are expected to conclude in 2026. Once their position is established, we will move to trialogue negotiations, involving the European Council, European Parliament and the European Commission. The legislation is not expected to go into force until 2028 at the earliest.

Below is a brief overview of the key provisions on EUCOPE's priority topics. **On many topics**, including Regulatory Data Protection, Orphan Market Exclusivity, and the Launch Conditionality, the **ENVI proposal is an improvement on the initial Commission's proposal**. However, there are still a number of concerns, including the Environmental Risk Assessment (ERA) provisions.

Following the adoption of the two Reports in the Plenary, EUCOPE will organise another "townhall" meeting to discuss the Parliament's position.

Key Provisions

(HIGH) UNMET MEDICAL NEED – (H)UMN

The ENVI committee has retained both the concept of UMN and HUMN. These two serve as a central piece of the Pharmaceutical Package, aiming to drive companies to invest in specific disease areas. The concepts will be used to modulate incentives and govern regulatory support. Beyond the legislation, EUCOPE is concerned they will be used to inform pricing and reimbursement (P&R) negotiations.
Both concepts have been slightly clarified and amended by ENVI. However, significant uncertainty will remain until the support guidance documents are adopted. An important success is that **industry is now explicitly listed as one of the partners that will be consulted** when the EMA and Commission draft the (H)UMN guidance under Article 162 (Regulation).

UMN

- The **criteria UMN remain consistent, in comparison to the Commission's proposal**. However, **the reward for addressing UMN is increased to 12-month RDP** (6-month in the Commission's proposal).
- According to the definition, a product is considered addressing UMN:
  - if it relates to a "**life threatening or severely debilitating disease**" and there is **no medicinal product authorised** in the Union for such disease, or, where despite medicinal products, the disease is associated with a "**remaining high morbidity or mortality**", and:
  - the use of the medicinal product results in a "meaningful reduction in disease morbidity or mortality" for the relevant patient population.

- ENVI proposes some **positive clarifications in the recitals on UMN**, stressing that **UMN should not influence P&R decisions**, and that the concept of "morbidity" should include various factors, such as quality of life, burden of disease and treatment, and take into account Patient Experience Data (PED).
- The EMA will set scientific guidelines for the application of UMN criteria, and ENVI amendments clarify they should **involve all key stakeholders, including industry**.
- **All orphan drugs will be considered as addressing UMN**.

HUMN

- The **criteria for HUMN remain broadly consistent with the proposal presented by the European Commission**.
- HUMN will be used to inform the incentive modulation. It will no longer be used to determine PRIME eligibility for orphans as **all OMPs will now automatically be eligible for the PRIME** scheme.
- To receive HUMN classification, a therapy **must meet one of the two criteria**:
  - there is **no medicinal product authorised** in the Union for such condition; OR
  - **where a medicinal product is authorised** for such condition, addition to having a **significant benefit**, it will **bring exceptional therapeutic advancement and** the use of the Orphan Medicinal Product results in a **meaningful reduction in disease morbidity or mortality** for the **relevant** patient population.
- This represents a **slight broadening of the concept**, as under the Commission proposal, even first-in-disease therapies would need to meaningfully reduce morbidity or mortality.
- A key element in the definition of HUMN will be the definition of **exceptional therapeutic advancement.** Often described as representing the 'game changing' therapies, the guidance is still to be written.

ORPHAN FRAMEWORK

Orphan Market Exclusivity (OME)

- ENVI retains a three-tiered modulated incentive framework:
  - **11 years** of OME for products **addressing a HUMN** – this represents an **increase from the Commission proposal** (10 years)**;**
  - **4 years** for products authorised based on **bibliographic data & well-established use**. This refers to active substances where there is no reference product, but the applicant can demonstrate that the active substances have been in well-established medical use for at least 10 years – this has been **decreased from the Commission proposal** (5 years);
  - **9 years** for **all other Orphan Medicinal Products** – has **not changed** compared Commission proposal**;**
- The period of marketing exclusivity can be **extended by a total of 2 years**. If the therapy receives a MA for a new orphan indication, the period of protection is extended by +1-year, which can happen twice. For more details, see the GOMA section below.
- The **maximum possible OME period in the new system is 13 years for products addressing a HUMN and 11 years for other orphan products**. The maximum threshold for HUMN has remained unchanged, but decreased by 1 year for all other orphans as the launch conditionality has been delinked from the incentive framework. Products authorised based on bibliographic data & well-established use cannot have their OME extended beyond the 4 years.

Global Orphan Marketing Authorisation (GOMA)

- The GOMA principle has **remained unchanged** in the ENVI report.
- A **single period of exclusivity will be provided for therapies with the same active substance**, this is in line with the approach of the Global Marketing Authorisation.
- This can be extended by +1 year if the developer moves into a new orphan indication. **This extension can be offered twice – representing a total possible increase of 2 years of OME**.
  - While the Regulation continues to state that developers who benefit from GOMA will not be able to receive the RDP extension for moving into a new indication, the RDP

incentive has also been changed in the Directive, which could require further corrections in the Regulation.
  - However, developers can continue to benefit from the +1 year of Market Protection offered under Article 80 of the Directive, submitted under Annex I.

Significant Benefit and Orphan Designation

- The **definition of Significant Benefit** has been updated by the ENVI committee to address a concern raised by EUCOPE. The definition of significant benefit is now:
  - 'Significant benefit' means a clinically relevant advantage or a major contribution to patient care of an Orphan Medicinal Product if such an advantage or contribution benefits a ~~**significant**~~ **relevant** part of the target population.
  - EUCOPE had been concerned by the interpretation of 'substantial' in the Commission's proposal. While this assessment is *de facto* already used by the EMA when assessing a therapy, the inclusion of the text in the Regulation itself does reduce flexibility and might raise the barrier to entry. The use of the term 'relevant' entails a more reasonable threshold.
- **Criteria for Orphan Designation**
  - The **prevalence of 5/10,000 is maintained**, and where a product is already on the market, the developer must demonstrate it represents a significant benefit.
  - The inclusion of an article that would allow the **Commission to use implementing acts to update the Orphan Designation criteria** for cases where there is a condition which should be considered as addressing an orphan indication, but it is not eligible due to the prevalence criteria has **been removed**.
  - A **recital has been updated** in the Regulation that states that medicinal products prepared for an individual patient in a pharmacy according to a medical prescription, **SHOULD ALSO** be considered as satisfactory treatment.
  - ENVI has **retained the principle that Orphan Designations will remain valid for 7 years** – but can be extended and expires when a product receives an Orphan Marketing Authorisation.

REGULATORY DATA PROTECTION (RDP)

- ENVI maintains a modulation of Regulatory Data Protection. However, the **baseline period is increased to 7 years and 6 months RDP**, in comparison to the Commission's proposal (6 years baseline RDP)
- RDP can be extended, upon conditions, to **a maximum of 8 years and 6 months**. There are more conditions that a MAH could benefit from. The possible extensions of RDP are:
  - **+12 months for addressing UMN** (in comparison to 6 months from the Commission);
  - **+6 months for conducting comparative clinical trials** (in line with the Commission's proposal);
  - **+6 months if significant R&D (including preclinical development) is carried out within the EU in cooperation with a public entity of the EU**. This is a brand new condition introduced by ENVI.
- The total RDP is followed by **2 years market protection** (unchanged from the Commission's proposal).
  - **Market protection can be extended by 1 year if a new indication with significant clinical benefit is developed** (differently from the Commission's proposal, that instead provided 1 year RDP for fulfilling this condition).
- The **total maximum protection (RDP and market protection) can be 11 years and 6 months**.
- There are no significant changes to **4 years RDP period for repurposed medicinal product**, if such product has not previously benefitted from data protection, or 25 years have passed since the granting of the initial marketing authorisation of the medicinal product concerned.
- ENVI includes a new article, clarifying that intellectual property rights (IPR) are not a valid ground to suspend regulatory or administrative procedures related to Bolar exemption. The **Bolar exemption is also expanded** to cover all regulatory and administrative activities.

LAUNCH CONDITIONALITY/ACCESS PROPOSAL

- The launch conditionality or access proposal **has been substantially reformed** by ENVI.
  - Rather than completing a P&R procedure, **developers must only file for P&R**.
  - The access proposal has been **delinked from the incentive framework**. Failure to meet the requirements **could potentially result in financial penalties**. However, there are questions about the language and application of these proposals.
- The new **access proposal** is as follows:
  - **Member States must request that a marketing authorisation holder (MAH) files** for P&R in their country **within 1 year** of receiving marketing authorisation (or, at least, inform the MAH that they will request later in time to file for P&R).
    - The report recognises that industry does not have full control over access discussions.
  - In case of a **positive P&R**, **MAH must ensure appropriate and continued supply** to cover the needs of patients in that Member State.
  - A MAH must **file for P&R within 12 months of a request coming from the Member State**. This is **extended to 24 months** for the groups listed below. The groups provided a longer time-period are consistent with the Commission's original proposal:
    - not-for-profit entities,
    - SMEs (as in Commission Recommendation 2003/361/EC), or
    - **undertakings that have received not more than five centralised marketing authorisations.**
  - MAH can request a **prolongation of 6 months** to the aforementioned timelines and, generally, MAH and Member States **can negotiate separate timelines**.
  - **OMPs and ATMPs companies may choose to only fulfil the P&R filing** requirement where **relevant patient population is identified.**
  - The European Commission will **develop a list of products that will be exempt** from the launch requirement. The list will include products that should be exempt due to the nature of the product or its market.
  - The article foresees the **creation of a conciliation mechanism** to resolve disputes between MAH and Member States.
  - The commission shall set up a new **EU Access to Medicines Notification System** for the notifications of the new access proposal.

SHORTAGES OF MEDICINES AND SECURITY OF SUPPLY

- The provisions on medicine shortages and notification requirement in case of supply disruptions remain broadly unchanged in comparison to Commission's proposal. However, some **additional requirements are introduced by ENVI**:
  - MAH shall **'explain the reasons'** of any supply disruptions or suspensions.
  - Temporary suspension or disruption of supply shall be notified as soon as possible (and no later than six months before the start of the disruption) *if foreseeable* by the MAH **or the national competence authority**, or as soon as the MAH become aware in case of *unforeseeable* disruption.
- ENVI proposes to **reinforce responsibilities and role of the EMA, the MSSG and Member States on monitoring and addressing shortages**. Among others, the EMA can assess Member States' actions to address shortages, while Member States shall collect and assess information on shortages and publish regular updates.
  - A national website on medicine shortage shall be created.
  - The Executive Steering Group on Shortages and Safety of Medicinal Products **(MSSG) may recommend monitoring forecast of supply and of available stocks**.
  - Member States and the MSSG may activate the "**Voluntary Solidarity Mechanism for medicines**", which should be coordinated by the MSSG and would allow to transfer

medicines suffering from shortages between Member States; however, any exchange should take into account the impact on the total stock of medicines.
    - The MSSG should also assess the shortage prevention plans of critical medicines.
- The **role of patient organisations and healthcare professionals is reinforced** in ENVI reports, especially involving them in defining the list of critical medicines.

ANTIMICROBIAL RESISTANCE (AMR) AND TRANSFERABLE EXCLUSIVITY VOUCHERS (TEV)

- The ENVI committee's reports proposed **several changes to the chapter on AMR and TEV**:
    - A category of "**priority antimicrobial**" is introduced. Such priority antimicrobial can be awarded with **milestone payments** and other support (this was not included in the Commission proposal).
    - The Commission and any Member States may engage in **joint procurement procedures of antimicrobials**, taking the form of multi-year subscription (this was not included in the Commission proposal).
    - Priority antimicrobials can be granted a TEV. Such **voucher could have a duration of 12, 9 or 6 months of RDP**, for 'critical', 'high' or 'medium' antimicrobials respectively (criteria to be defined by delegated acts). However, the voucher cannot be used for products that have already benefitted from the maximum RDP period. The **TEV is made stricter in comparison to the Commission proposal** (TEV duration was 1 year and without RDP cap).
    - In ENVI's proposal, there is **much unclarity** on how the duration of TEV would be assigned, on how the milestone payments would work and whether the milestone payments would exclude obtaining a TEV.

HOSPITAL EXEMPTION (HE)

- The Hospital Exemption discussion has **become highly politicised in the European Parliament**, with vastly different proposals having been debated.
- The final ENVI position **broadly follows the Commission's initial proposals, with a few important changes**.
- HE products must continue to be delivered on a **non-routine basis** in a hospital under the exclusive professional responsibility of a medical practitioner.
    - The non-routine basis of HE is re-emphasised; however, **rather than having additional principles included in the legislation**, ENVI supported the Commission's proposal that **guidelines governing the harmonised implementation of the preparation and use of HE on a non-routine basis is established through implementing acts**.
    - The **scope of who can manufacture HE products has been expanded** to include hospital pharmacist.
- HE applicants must now include evidence on quality, efficacy, and safety. This **must be carefully reviewed from both a feasibility perspective**, considering the data sets that are available, and to ensure that this **does not create the basis of a *de facto* parallel approval pathway**.
- ENVI has **reinforced the Commission's data reporting requirements for HE products**, including a more explicit call for long-term follow up data. All data should also be reported in a structured and standardised manner. Member States must collect data on the use, efficacy, and safety of HE products. Many of these requirements and standards will be specified through implementing acts.
- ENVI has also **strengthened the cross-border exchange of HE**, more easily allowing for Member States to authorise their exchange.
- The recitals **include references to the EMA pilot to support academic developers** undergo the centralised procedure, and articles to support non-profits and academics to fulfil the reporting requirements.

REGULATORY PROVISIONS

- Provisions on **Environmental Risk Assessment (ERA)** are retained in ENVI's report, with both **positive and negative changes**, in comparison to the Commission's proposal:
  - The ERA should **cover the entire life-cycle of a medicine, including manufacturing**. ERA assessment should be made publicly available (deleting all sensitive information).
  - The ERA of products approved before the new legislation shall be updated and mitigation measures should be implemented. For products approved before October 2005, there are only minor changes to the Commission's proposal.
  - On the other hand, **refusing or revoking a MA will be made more difficult**, in comparison to the Commission's proposal. A MA can be refused or revoked if there is **no justification for an incomplete ERA**, and **only if risk cannot be mitigated** (following a decision of suspension), and any such decision should **take into account the benefit of the product, the need of patients and alternative treatments available**. For products approved before October 2005, the MA can be revoked if the ERA is incomplete, and the product is identified as a potential harm to the environment.
- The ENVI report updates the changes to the **EMA structure** proposed by the Commission to streamline decision-making. EMA would have the following committees, Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC). ENVI retains the concepts of scientific working parties, however rather than leaving it ambiguous which groups will be established, **ENVI explicitly calls for the creation of ad-hoc working groups on the topics listed below**, while allowing for further groups to be created:
  - Ad-hoc working group on advanced therapy medicinal products.
  - Ad-hoc working group on Orphan Medicinal Products.
  - Ad-hoc working group on Paediatric Medicinal Products.
  - Ad-hoc working group on Environmental Risk Assessment.
- The timeline for drug approvals as remained consistent with the Commission proposal, ensuring **faster authorisations of new medicines**. For its assessment, EMA will have 180 instead of 210 days. For the authorisation, the Commission will have 46 instead of 67 days.
  - Similarly, the EMA retains the ability to provide sponsors with Orphan Drug Designation.
- ENVI has **expanded PRIME eligibility**. In order to be eligible for PRIME, developers must now only meet **ONE** of the criteria listed below. In this context, it is important to note that all OMPs are considered as addressing an UMN.
  - Are likely to address and UMN;
  - Are an Orphan Medicinal Products and likely to address a HUMN;
  - Are expected to be of major interest from the point of view of public health, in particular as regards therapeutic innovation, **or provided for in the 'WHO priority pathogens list for R&D of new antibiotics', specifically those listed as priority 1 (critical) or priority 2 (high), or taking into account as a priority any equivalent list of priority pathogens adopted at Union level**.
- ENVI has retained the **phased review** concept, and slightly **expanded the eligibility criteria**. In addition to therapies that are likely to offer an exceptional therapy advancement in the diagnosis, prevention or treatment of a life-threatening, seriously debilitation or serious and chronic condition, therapies that are **expected to be of major interest form the point of view of public health or for conditions with no authorised alternatives** will also be eligible.
  - A major concern with the phased review is that it can be stopped at any point by the EMA should there be insufficient data and the provision that applicants must provide complete data sets.
- ENVI also recognises the **importance of RWE**, outlining it as an element that should be considered as part of regulatory decision-making, building on the general support from the Commission proposal.
- The ENVI report also provides an explicit **reference to Platform Technologies**, with the establishment of a **definition for the technology, and a dedicated Platform Technology Master File**.

- The **definition of Additional Quality Master Files has been expanded** to explicitly include a reference to information on the quality of a substance, preparation or other material present or **used in the manufacturing of cell and gene therapies**. It is **accompanied by a recital** that spells out, that **raw materials, vectors and other starting materials** and starting raw materials for the **manufacturing of cell and gene therapies be included**.
- ENVI has also updated the **definition of a 'gene therapy medicinal product'**. The committee proposes two definitions for gene therapies, type 1 and type 2 gene therapies:
    - "Type 1 gene therapy medicinal product" means a medicinal product, that contains or consists of a substance or a combination of substances that edit the host genome in a sequence-specific manner or that contain or consists of cells subjected to such modification.
    - "Type 2 gene therapy medicinal product" means a medicinal product, except vaccines against infectious diseases, that contains or consists of a recombinant or synthetic nucleic acid used in or administered to human beings with a view to regulating, replacing or adding a genetic sequence that mediates its effect by transcription or translation of the transferred genetic materials or that contain or consists of cells subjected to these modifications.
- Despite intensive discussions in the ENVI committee, the **final report maintains the Regulatory Sandboxes**. The report largely leaves the Sandboxes unchanged, aside from a few clarifications reaffirming that the Sandbox is meant to be used in cases where no other pathway exists, and for the benefit of the patient. Ultimately, a lot of the context around the sandbox will be determined by implementing acts. The ENVI committee did stress that the creation of a Sandbox should be done on a case-by-case basis, with the EMA also publishing an annual report.

PAEDIATRICS

- The 6-month SPC incentive, aimed at encouraging research into medicinal products for children, remains unchanged from the Commission's proposal.
- For marketing authorisation applications lacking a Paediatric Investigation Plan (PIP) or a comparative study, applicants must provide justification and, if applicable, evidence from post-marketing long-term studies.
- The outcomes of PIP assessments, specifically compliance with the paediatric investigation plan, will be made public.
- The EMA is tasked with creating application guidelines for waivers.
- The 5-year cap on deferrals for PIPs is retained, requiring justification based on scientific and technical, or public health considerations.
- EMA may grant waivers for products intended solely for adult populations, unless scientific data demonstrate that the product's molecular target OR mechanism of action is linked to a different disease or condition in children within the same therapeutic area as the adult indication.
- MAH have a 20-day period to contest the EMA's scientific conclusions regarding PIPs waivers or deferrals.
- Requests for changes or deferrals to PIPs due to implementation challenges are permitted, including when updating elements of initial PIP.

R&D Transparency requirements

- ENVI **broadens requirements on R&D Transparency**, compared to the Commission's proposal:
    - The MAH shall declare any **public and no-profit funding**, irrespective of the location of the entity, and any **indirect financial** support received from any public authority in the EU or Member States, related to any R&D activity.

Electronic Patient Information (ePI)

- ENVI reports maintain a **similar approach to the Commission's for what concerns electronic and printed leaflets**:
    - Member States will decide on the format of the leaflet. The electronic-only format shall be introduced after consultation with patients and other relevant stakeholder; moreover, in this case patients have right to a printed copy and MAH can voluntarily make printed

version available. If the Member States do not give any indications no indications, both formats are kept.
  - For leaflets of anti-microbial, some additional requirements (e.g., inclusion of an awareness card) are introduced.
  - ENVI also proposed that, **if the product is intended for dispensation by professionals, the leaflet can be made available only electronically**.

European Health Emergency Preparedness and Response Authority (HERA)

- ENVI introduces a new chapter in the Regulation on HERA, among others proposing:
  - Moving HERA to the ECDC.
  - Making HERA responsible of the EU long-term research and development agenda for biomedical countermeasures.
  - Expanding HERA's tasks in collaboration with third-party research, giving guidance to the Commission on EU grants, detecting biological and other health threats, assessing vulnerability of supply chains, ensuing availability of production sites for priority products, facilitating joint procurement.

TRANSITION PERIODS

- Both the Directive and the Regulation will go into effect at the same time, 18 months after the entry into force of the respective legislations.
- Both the initial Commission proposal and ENVI report also provide a number of different provisions outlining how various elements of the legislation will be implemented over time.
- EUCOPE will carry out a more detailed assessment on how and when different measures will enter into effect. The timelines for several of the regulatory provisions will be prolonged beyond 18 months.

INITIAL ASSESSMENT

After several months of extensive engagement by EUCOPE, and internal debates in the European Parliament, overall, the ENVI reports broadly reflects the Commission's initial proposal. **Several important changes have been made** that improve the report and represent a success in EUCOPE's advocacy efforts. Unfortunately, **other changes have reinforced the negative proposals made initially by the European Commission**, such as for the ERA and, partly, measures on shortages. A number of the concerns raised by EUCOPE have been addressed and taken up by the ENVI reports.
It is important to note that this **IS NOT** the final report from the European Parliament. It is also **NOT** the final text as the European Council is still working on their positions, and trialogues will need to take place when both EU Institutions have adopted their "first reading" positions.

The ENVI report has **increased the baseline of RDP** for all developers **compared to the Commission** proposal, and the **OME incentive for HUMN has also been raised**. The changes to the incentive framework have **introduced additional predictability** by ensuring that the level of incentive is less volatile with the duration of incentive less dependent on various criteria.

Similarly, **important changes to the regulatory system** have been either retained or further clarified, ensuring streamlining and future-proofing of the ecosystem, increased acceptance of RWE, recognition of Platform Technologies and changes to the Additional Quality Master File and GMO rules that support ATMP developers. The Hospital Exemption framework has remained broadly consistent with the Commission's initial text, avoiding the more dramatic and industry unfriendly changes that had been considered.

The **concepts of UMN and HUMN remain in the legislation**, with their initial terminology as well. The two concepts have been slightly broadened out, and industry will have a seat around the table in defining the concepts. However, **EUCOPE remains concerned** about the implication of these proposals to the wider pharmaceutical ecosystem, especially as they pertain to P&R discussions in Member States.

The **proposal on access** has been improved, de-linking a launch conditionality from incentives and ensuring a more nuanced approach to access in EU Member States, that replaces finalising P&R with filing for P&R, recognises the responsibility of other stakeholders besides industry and the specificities of some products, such as ATMPs and OMPs. The proposal still presents some criticism of its viability and legal aspects, but we expect that the Council will introduce major changes to it.

NEXT STEPS

The **Plenary vote in the European Parliament is scheduled for 11 April 2024**. In parallel, **discussions are ongoing in the Council**. When both the European Parliament and the Council have adopted their positions, trialogue negotiations can begin. It is not anticipated that the legislation will go **into effect until 2028 at the earliest**.

EUCOPE will arrange a Townhall meeting following the vote in Plenary to discuss the different changes in more detail and provide a more comprehensive assessment. Additional information on the Townhall will follow in the coming days.