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European Confederation of Pharmaceutical Entrepreneurs AISBL

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An Initial Breakdown of the Publication of the EU Pharmaceutical Package

On 26 April, the European Commission finally published the Pharmaceutical Package. Consisting of two legislative proposals, it includes a proposal for a "master" Regulation, merging Commission Regulation No 726/2004, Orphan Medicinal Products (OMP) Regulation No 141/2000 and Paediatric Regulation No 1901/2006, and a proposal for a Directive, repealing Directive 2001/83/EC and Directive 2009/35/EC.

On 31 January, EUCOPE reported on insights from an early draft of the Commission's proposal. Today's **official publication is broadly in line with what was previously shared, with a key and troubling changes to the Regulatory Data Protection (RDP) system**. Below is a brief overview of the key provisions, including any notable changes from what was previously shared. EUCOPE will be providing a more in-depth assessment in the coming weeks, and **discuss the proposal at our Town Hall on 4 May** (connection details are attached).

In the coming days, EUCOPE will share an update on the positions being taken by key Member States.

Key Provisions

(HIGH) UNMET MEDICAL NEED – (H)UMN

The Commission has proposed including the concepts of (H)UMN into the legislation as a means to drive and direct research and innovation. Both concepts will be used to modulate incentive frameworks, and provide additional regulatory support.

UMN

- The definition of UMN remains mostly unchanged, in comparison to the leaked version. The main difference is that, in case of existing products, the reference to diagnosis and prevention methods is removed. However, **the reward for addressing UMN is 6-month RDP**.
- 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.
- The EMA will set scientific guidelines for the application of UMN definition.
- **All orphan drugs will be considered as addressing UMN**.

HUMN

- The Commission has retained the definition of HUMN in the proposal, which will be used to modulate orphan incentives (see the next section).
- The **definition for HUMN remains broadly** the same, notably:
    - There are **no authorised treatments** – the reference to other methods, including diagnostics has been removed;
    - If there **is an authorised treatment**, the new therapy must demonstrate it has a **significant benefit and bring an exceptional therapeutic advancement** – the concept of exceptional therapeutic advancement remains undefined;

- The EMA will adopt scientific guidelines to clarify the discussion on HUMN, and industry may be consulted in that process – the explicit reference to industry is a change from earlier versions and something EUCOPE has been calling for.

ORPHAN FRAMEWORK

Orphan Market Exclusivity (OME)

- The Commission retains a three-tiered modulated incentive framework:
  - 10 years of OME for products **addressing a HUMN;**
  - 5 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;
  - 9 years for **all other orphan medicinal products;**
- The period of marketing authorisation can be **extended by a total of +3-year for the first and third categories** by launching in all Member States in a fixed time period (see the section on launch below) and moving into 2 new orphan indications.
- The **maximum possible OME period in the new system is 13 years for products addressing a HUMN and 12 years for other orphan products**. Products authorised based on bibliographic data & well-established use cannot have their OME extended beyond the 5 years.

Global Orphan Marketing Authorisation (GOMA)

- Only 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**.
  - A developer will not receive the corresponding RDP extension for moving into a new therapeutic indication.

Significant Benefit and Orphan Designation

- The **definition of Significant Benefit** has been updated to include “a substantial part of the target population”. While this 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.
- **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
  - In 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, the Commission can use delegated acts to supplement the criteria for certain conditions.
  - The paragraph in an earlier leak, which would require the EMA to consider all therapies that overlap with the indication has been removed in the final proposal – this is an important development, as this presented a risk that therapies could have been disqualified from receiving their orphan designation, for example, if a product fell under Hospital Exemption.
  - **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)

- Regulatory Data Protection is reduced and modulated, partly in line with the earlier leak. The **baseline period is 6 years RDP, followed by 2 years market protection** (8 years total).
- RDP (excluding market protection) can be extended upon conditions, to **a maximum of 10 years:**
  - +2 years for launch in all EU Member States (see next paragraph);

  - +6 months for addressing UMN;
  - +6 months for conducting comparative clinical trials;
  - +1 year for new indication with significant clinical benefit.
- The **total protection (RDP and market protection) can be 12 years** (without a cap).
- An RDP period of 4 years is granted to **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.

LAUNCH CONDITIONALITY

- The definition of launch is retained as in the leaked document. Launch is defined as "**released and continuously supplied** into the supply chain in a sufficient quantity and in the presentations necessary to cover the needs of the patients in the Member States".
- To obtain the reward, launch should be fulfilled within two years from marketing authorisation, or three years in case of:
  - not-for-profit entities,
  - SMEs (as in Commission Recommendation 2003/361/EC), or
  - **undertakings that have received not more than five centralised marketing authorisations** (this is an addition, compared to the leaked version).
- The **launch incentive is differentiated for RDP and OME**, with:
  - +24-months RDP;
  - +12-month OME.
- Within 60 days from the request of the marketing authorisation holder (to prolong RDP or OME), the Member State shall issue a confirmation of compliance or, a reasoned statement of non-compliance or alternatively provide a statement of non-objection.

SHORTAGES REQUIREMENTS AND NOTIFICATIONS

- The provisions on shortages and notification requirement remain broadly unchanged in comparison to the leaked version:
  - **All companies will be requested to develop shortage prevention plans** (SPP), to be updated. The EMA, or the national competent authority, may request the marketing authorisation holder to submit a shortage mitigation plan.
  - A **list of critical medicines** (i.e., medicines considered to be most critical for health systems at all times) will be established. Recommendations on measures to be taken will be made to companies and other relevant stakeholders to strengthen the supply chains of those medicines.
  - Companies, that will decide to **permanently cease or withdraw** the marketing authorisation of a product, will have to notify 12 months in advance. Company that will **temporarily suspend** the marketing of a product, will have to notify at least 6 months in advance. A **temporary disruption** should be notified no less than 6 months before the start of such temporary disruption of supply or, if this is not possible and where duly justified, as soon as the marketing authorisation holders become aware of such temporary disruption.

AMR: TRANSFERABLE EXCLUSIVITY VOUCHERS

- The Commission includes a unique incentive to encourage the develop 'priority antimicrobials' – notably a transferable exclusivity voucher, which can be sold to other developers, and is used to extend the RDP of a product by 12 months.
- The voucher system would cease to be valid 15 years after the directive goes into effect, or 10 such vouchers have been issued, whichever comes first. It will encourage early movers, and limit the total number of vouchers that will exist in the system. The voucher programme has received significant criticism from many Member States and civil society groups.

HOSPITAL EXEMPTION (HE)

- There has been a **substantial update to the HE provisions** in the final proposal – the reference to creating an adaptive framework for routine use of less complex ATMPs has been removed.
- HE products must continue to be delivered on a non-routine basis, in a single Member State in a hospital under the exclusive professional responsibility of a medical practitioner.
- Member States must ensure that HE products meet GMP standards, ATMP traceability and pharmacovigilance requirements.
- Member States must collect data on the use, efficacy, and safety of HE products.
- The Commission shall adopt implementing acts related to:
    - Details of the application for the approval of hospital exemption;
    - The format for collection and reporting of data on the safety, efficacy and use of HE;
    - modalities for the exchange of knowledge between hospital exemption approval holders within the same Member State or different Member States;
    - modalities for preparation and use of advanced therapy medicinal products under hospital exemption on a non-routine basis.
- The implementing act related to an exchange of knowledge between hospital exemption holders could introduce a degree of deregulation and should be carefully monitored.

REGULATORY PROVISIONS

- Provisions on **Environmental Risk Assessment (ERA)** are introduced. An ERA will have to be submitted at the moment of marketing authorisation, including information such as hazard risks for humans and the environment, and proposed risk minimisation strategies. **The marketing authorisation can be refused if ERA is incomplete or insufficiently substantiated** by the applicant or if the risks identified in the ERA have not been sufficiently addressed by the applicant. Moreover, after the marketing authorisation, the competent authority of the Member State may impose the marketing authorisation holder to conduct a **post-authorisation environmental risk assessment**; in such case, this will be mandatory to maintain the marketing authorisation. The ERA is extended in case of risk of antimicrobial resistance (AMR).
    - Pharmaceutical products will be exempted from the GMO regulation and instead, the ERA will include provisions for developers that use GMOs in their products.
- The **EMA's committee structure will be revised** in an effort to streamline decision-making. While the Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC) will continue to exist, groups such as the COMP and CAT will not continue. Instead, the EMA will aim to maintain this expertise through different forum, such as scientific working parties and advisory groups.
    - The regulatory framework is simplified with **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.
- The proposal codifies the **PRIME scheme**, introducing a more restrictive interpretation of which therapies will be eligible for consideration, namely therapies that address an UMN (or HUMN in the case of orphans) or will be of major interest from a public health point of view;
- The proposal introduces the concept of a **phased review** for therapies that that are likely to offer an exceptional therapeutic benefit, however, this process can be stopped at any point by the EMA should there be insufficient data or it no longer meets the exceptional therapeutic benefit condition.
- The proposal recognises the **importance of RWE**, outlining it as an element that should be considered as part of regulatory decision-making.

PAEDIATRICS

- The European Commission has maintained the 6-month Supplementary Protection Certificate (SPC) as a primary incentive to reward research in medicinal products for children.
- The Commission has proposed the creation of a new incentive for the development of paediatric medicines which are not covered by a patent or SPC, this would be called the 'paediatric use

marketing authorisation'. Products authorised under this system would receive their own Regulatory Data Protection Period.

- A 5- year referral cap for PIP has been introduced by the Commission, with the possibility, in duly justified cases, to be prolonged.

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. The proposals also outline a number of different provisions outlining how various elements of the legislation will be implemented over time.

INITIAL ASSESSMENT

Overall, the Commission's proposal continues to be very concerning. Despite the delay**, a number of open questions remain,** for instance about how certain provisions or concepts will be interpreted, especially regarding (H)UMN and concepts such as exceptional therapeutic advancement or 'meaningful' reductions in morbidity and mortality. These provisions could have significant negative implications for industry and the pricing and reimbursement ecosystem. During the press conference announcing the package, **Vice-President Schinas clearly stated that they want to see prices fall**.

While the orphan incentive framework has remained consistent with the previous insights shared by EUCOPE, the **changes to the RDP system**, especially by increasing the impact of launch conditionality, **are troubling and create a less predictable system**. However, the Commission has opened the door to increased leeway for launching, as developers with fewer than 5 centrally authorised products have an additional year to launch. EUCOPE will explore how this can be factored into future advocacy.

While **some of the concerns raised by industry and EUCOPE have been addressed through recitals**, these are not reflected in the proposals themselves. Changes to the Hospital Exemption framework still need to be carefully assessed, but demonstrate that the Commission have given the change additional thought.

There are a number of **welcome changes being introduced by the Package**. Firstly, the Commission has maintained a separate Directive and Regulation. In addition, a number of the **Regulatory provisions will help to streamline and accelerate regulatory approvals** such as the reduction of the timelines for EMA approvals to 180 days. Changes including the renewed EMA structure (which will also include a stronger patient voice), wider scope for products that can be included in the centralised procedure, the regulatory sandbox, and an openness to RWE could all play an important role in future-proofing the regulation.

NEXT STEPS

The proposal now **moves to the next phase of the legislative process and will be discussed and debated by the European Parliament and Council of the EU**. This will be a long process and we do not expect a final vote to take place during the current Parliamentary term.

As part of the legislative process, **stakeholders will also be able to provide feedback** to the proposal, note that the comments will not be taken onboard by the Commission to change the proposal, but will be shared with the European Parliament and Council who might choose to consider the comments. **EUCOPE will draft a response that will be circulated to Members for approval in the coming weeks**.