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An Initial Breakdown of the Reports by the European Parliament Rapporteurs on the Pharmaceutical Package

On 4 and 5 October, the **draft Reports**, by the European Parliament's Rapporteurs, related to the Union Codes to Medicinal Products (**Directive**) and the Union procedures for the authorization and supervision of medical products (**Regulation**) were made public. These form part of the Pharmaceutical Package, which is reviewing the 'Human Medicinal Products Directive' 2001/83/EC and the 'EMA Regulation' No. 726/2004, the 'OMP Regulation' No. 141/2000 and the 'Paediatric Regulation' No. 1901/2006. The Reports are the first official reflections from the Rapporteurs, **MEP Pernille Weiss** (EPP, Denmark) and **MEP Timo Wölken** (S&D, Germany) on the Directive and Regulation, respectively, which start the extensive review process in the European Parliament.

This document outlines the initial changes and amendments proposed by the two Rapporteurs. A **number of EUCOPE suggestions are reflected in the Reports** (especially in the Directive). This document should be seen as a companion document to the overview shared by EUCOPE in April, following the European Commission's proposal. Note that these are suggested modifications, the information outlined below is subject to change. It is not expected that all the information below will be taken up in the final Report from the European Parliament, which is not expected before April 2024, and likely only after the European Parliament elections.

OVERVIEW

These Reports indicate **two distinct visions for the future of the pharmaceutical industry in the EU**. The Directive updates the Commission's proposal to further strengthen the incentive framework and update regulatory provisions to support and bolster innovation. The Regulation, by contrast, significantly increases the obligations on developers, regulators and other stakeholders. In addition, the Regulation's Report recommends the removal of the Regulatory Sandbox system and introduces a so-called European Medicines Facility as an independent agency that shall conduct public research and, *inter alia*, develop novel antimicrobials as well as support public research and development in other areas of unmet medical need. Cost containment and the creation of downward pressure on drug prices are among the objectives of the draft Regulation.

Thus, the two reports show a strong **political divide on important topics** between the two main political Groups in the European Parliament. However, these positions and proposals are not set in stone, as MEPs (including the Rapporteurs themselves) will have the opportunity to submit amendments until 13 and 14 November. However, they show what are the overall stances of the centre-right EPP and the centre-left S&D; as for many other dossiers, the **centrist Renew will play a key role** as a "tiebreaker". Moreover, the (far-)right Groups (especially the ECR) might play an important role, but MEPs within those Groups might have different internal positions based on their country of origin.

These initial positions of the Rapporteurs, therefore, will be a **bargaining token** where all negotiations between the Groups will begin. However, these positions are probably far apart from the final stances that will be voted in ENVI and, consequently, in Plenary. Important discussions, not only between the EPP and S&D but also with other Groups, will take place in the coming weeks and months, and the final text will likely go towards a **compromise between the proposed drafts**. Thus, there is **room for improvement** and for a better outcome for small and mid-sized pharmaceutical companies.

Key Provisions

Directive

The proposed changes to the Directive strengthen incentives for the pharmaceutical industry (with a baseline period of 9-year RDP), introduce a broader definition of unmet medical needs and adopt a more balanced approach on 'launch'. In particular, 'launch' has been re-written to 'submission of P&R',

with several caveats for small and mid-sized companies and specific products (such as OMPs and ATMPs); it is also de-linked from incentives. Other provisions make it more difficult to remove marketing authorisation due to environmental risk assessment. Moreover, hospital exemption is clarified and proposals to future-proof the system (such as 'platform technology') are introduced. Generally, the Rapporteur calls for a strong incentive and IP framework, to foster pharmaceutical innovation, and recognises the role of small and mid-sized companies. Another key theme that emerges is a restriction of the use of joint procurement, only to case where it is foreseen by the existing legislation. Below you will find the key changes proposed by the Report as they pertain to EUCOPE's priorities.

UNMET MEDICAL NEEDS (UMN)

MEP Weiss proposed a broader definition of unmet medical needs (UMN), including quality of life, delay on the onset or side effects. However, the use of qualifiers such as 'severely', 'high', 'meaningful' or 'significant' remains.

- At disease level, **'progressive diseases'** are included.
- At product level, in addition to a high morbidity or mortality, the product can be associated with a **'significant negative impact on quality of life'**.
- On the efficacy of the product, alternatively to meaningful reduction of morbidity or mortality, additional criteria are included:
    - Meaningful reduction of **'severity or long-term side effects'** of a disease are included alongside a meaningful reduction of morbidity and mortality;
    - a meaningful positive **'impact on quality of life'**;
    - a meaningful **'delay of the onset of the disease or its complications'**.
- Industry is included among stakeholders that ***shall*** be consulted by the EMA in the guidelines on UMN.

REGULATORY DATA PROTECTION (RDP)

Regulatory Data Protection (RDP) is still modulated, but the baseline has been increased.

- The **baseline period is increased to 9 years RDP**, followed by 2 years of market protection (11 years total).
- RDP (excluding market protection) can be extended upon conditions:
    - **+12 months** for addressing UMN;
    - +6 months for conducting comparative clinical trials (whose scope is broadened);
    - +1 year for a new indication with significant clinical benefit.
- **'Launch' conditionality** is redefined and de-linked from incentives (see next paragraph).
- The **total protection (RDP and market protection) can be 13 years and 6 months**.
- The provisions on **compulsory licensing** and RDP are clarified and made stricter.
- The **Bolar exemption** is restricted, excluding, for instance, marketing authorisation applications or pricing and reimbursement (P&R).

LAUNCH CONDITIONALITY ('released and continuously supplied into the supply chain')

The 'launch' conditionality has been delinked from RDP/OME, and a more balanced system which acknowledges the responsibilities of Member States and unique nature of orphan therapies and ATMPs has been introduced.

- The launch conditionality has been **de-linked from incentives** (RDP and OME) and a new system has been introduced.
- Should a marketing authorisation holders (MAH) fail to meet the new filing requirements (see the bullet below), the **MAH will be subject to effective, proportionate and dissuasive financial penalties**. These will be **governed by national legislation**.
- **On the request of the Member State**, MAH must **file for P&R within 2 years**. However, some exemptions are foreseen:

  - **SMEs and undertakings with no more than 7 centrally approved products will have 4 years**.
    - The 'undertakings' category has been expanded to **7 centrally approved products,** from 5 in the Commission's proposal.
    - The Report calls for a **new definition of SME for application of this Directive**.
  - MAH and Member States can jointly agree on a separate timeline.
  - **OMPs and ATMPs are exempt from this filing requirement**, and may instead choose between:
    - **Making the product directly available** to patients and the prescribing doctors who requested it. This can include various pathways, such as cross-border, named-patient supply, or through centres of excellence.
    - Submitting an application for P&R only in the Member States where the relevant patient population has been identified.
  - Recognising that some therapies cannot be launched in all Member States, the Commission should create **a list of products that, based on their characteristics, are exempt from the filing requirement**.
- After a developer has filed, the **Member State must hold to the Transparency Directive timelines.** Should a Member State fail to abide by the timelines, for the purposes of the financial penalties, it will be deemed that the MAH has fulfilled its filing requirements.
- An **electronic notification system** ('EU Access to Medicines Notification System') shall be created through which MAH notify their compliance with this requirement.
- The Commission will establish a **conciliation mechanism** to facilitate discussions and resolve disputes related to the submission of P&R applications.

HOSPITAL EXEMPTION (HE)

The HE framework remains broadly the same as outlined by the Commission, however, important clarifications have been proposed.

- A reference has been added outlining that HE should only be used when **there is no authorized therapy, clinical trial, or compassionate use programme for which the patient is eligible in the Union.**
- A **definition of non-routine has been introduced** into the text and will no longer be based solely on a yet to be written implementing act. In addition to the bullet above, an activity is considered routine if it uses a standardized or repetitive process, or advanced planning beyond what is needed to address immediate clinical needs of the individual patient.
- HE licences have been made valid for renewable 12-month periods, and the HE manufacture must demonstrate they meet the requirements for non-routine use.
- Recital 18 of the Commission's proposal has been updated, leaving the reference to an EMA report assessing the use of HE in the Union, but removing the explicit call for the EMA to explore an adaptive framework for less complex ATMPs developed under HE.

ENVIRONMENTAL RISK ASSESSMENT (ERA)

Provisions on environmental risk assessment (ERA) remain in place, but the overall requirements appear to follow a more balanced and data-oriented approach in line with EUCOPE's suggestions.

- It is clarified that **risk-mitigation measures** shall only be included in the ERA where the ERA identifies a risk to the environment.
- The MAH shall only be obligated to update the ERA if new information becomes available that actually *leads* to a change of conclusions of the ERA (instead of the likelihood leading to a change of conclusions of the ERA).
- It is clarified that the outcome of the ERA, including the data submitted by the MAH, shall be made publicly available.
- **Refusal of MA** because of ERA is restricted only to cases when post-MA studies would not be sufficient to ensure environmental protection.

- **MA may only be revoked** in case environmental risks **clearly outweigh the loss of positive therapeutic effects** of the medicinal product for the concerned patient population **and** the **environmental risks cannot be mitigated** following a decision of suspension or modification.
- Less onerous regime for medicinal products authorised before 30 October 2005 which shall only be subject to an ERA if the Agency identified a potentially *unacceptable risk* (instead of "*harmful*") to the environment and such legacy programme to be capped at 10 years.

PAEDIATRICS

The Commission's proposed provision remains mostly unchanged.

- The 6-month Supplementary Protection Certificate (SPC) remains as the primary incentive to reward research in medicinal products for children. However, **the SPC reward is extended to 12 months for PIP conducted in different diseases than the adult indication**.

OTHER PROVISIONS

- The amendments introduce an expanded and future-proofed regulatory framework of **Advanced Therapy Medicinal Products (ATMPs) and other innovative technologies** by expanding the scope of the **Active Substance Master File** to cover starting materials for ATMPs, such as vectors. In addition, the Report introduces dedicated approaches to **Platform Technologies**, facilitating their authorization in the Union.
- **Transparency of public funding**: it is clarified that only funding provided by public authorities or publicly funded bodies of the EU is in scope.
- **Electronic Product Information (ePI)**: in case there is no Member State-specific rule, both electronic and paper package leaflets are to be provided. In case a Member State adopts electronic leaflets only, the patient could ask for a printed version. Where the medicinal product is not intended to be delivered directly to and administered by the patient, the leaflet can be made mandatorily electronic.

Regulation

The proposed changes to the Regulation introduce a host of new financial penalties on developers for failing to meet the requirements outlined in the Regulation. In the recitals, the Rapporteur reiterates messages from the BeNeLuxAI reflection paper, 2021 Dutch Government Study, and Massimo Florio's STOA report, including the assertion that there is a mismatch between the pharmaceutical industries R&D priorities and public health. In addition, the activities of the EMA have been expanded, while their budget and resources are not covered through this legislative act. Throughout the Report, the role of the patient and consumer community in providing feedback on the development of EMA guidelines has been substantially expanded. Substantial changes are also introduced to the OMP framework. In parallel, explicit references have been made to cost-containment, with concrete measures to introduce downward pricing pressures. Below you will find the key changes proposed by the Report as they pertain to EUCOPE's priorities.

HUMN

The concept and criteria for HUMN have not been substantially updated in the Report by MEP Wölken. The changes that have been made are:

- In developing the guidelines around HUMN, a clear reference is made that the stakeholders in Article 162 (including patient groups, academics, and industry) shall be consulted.
- The second HUMN eligibility requirement has been updated to state that the OMP must result in a **substantial** as opposed to a **meaningful** reduction in disease morbidity or mortality in the relevant patient population.
    - The true impact of this change is not clear, as it will depend on how the concepts are clarified the yet to be developed guidelines.
- While not a change to HUMN, a change to the OMP eligibility criteria means that therapies for **non-rare indications could theoretically be classified as HUMN**. The OMP eligibility criteria

has been expanded to its existing definition under Regulation No 141/2000, covering therapies that would not generate sufficient return on investment to justify investment (see ODD section below).

ORPHAN FRAMEWORK

Orphan Market Exclusivity (OME)

The OME system has been made more restrictive in the Report, however, by comparison, the incentive for HUMN becomes more relevant.

- The Report creates a four-tiered incentive system:
  - 10 years of OME for products **addressing a HUMN** – this is unchanged from the Commission's proposal**;**
  - 5 years for repurposed therapies;
  - **3 years (it was 5 years in the Commission's proposal)** 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;
  - **8 years (down from 9 years in the Commission's proposal)** for **all other orphan medicinal products;**
- In the case of both bibliographic authorisation and repurposed therapies, the Report explicitly states that the OME will not block the generic and biosimilar use of the therapies for other indications. This creates a significant risk of economic off-label use.
- With the change to the launch conditionality, no additional OME is awarded for launching in all Member States.
- No changes are made to the GOMA framework (see below).
- The **maximum possible OME period in the new system for therapies that manage to secure all possible extensions is 12 years for products addressing a HUMN and 10 years for other (non-repurposed / bibliographic authorisation) orphan products**.

Global Orphan Marketing Authorisation (GOMA)

The GOMA framework is not changed in the report. It functions as follows:

- 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 Report introduces some significant changes to the ODD framework when compared to the Commission proposal, the most notable changes are:

- The proposed **definition of Significant Benefit** has been changed to remove the addition made by the Commission ("if such an advantage or contribution benefits a substantial part of the target population") which is **warmly welcomed by EUCOPE**. While this expanded definition 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.
  - The Report **reintroduces the second eligibility criteria for ODD (Return of Investment (RoI)) which is found in Regulation No 141/2000** – namely, "that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment".

- The Report also **reintroduces the 5-year reauthorisation of the MA**, along with the RoI assessment to determine if the therapy is still eligible for OMP incentives. Unlike under the current framework, the re-authorisation of MA would be for 10 years, not unlimited as is currently the case.

AVAILABILITY AND SECURITY OF SUPPLY REQUIREMENTS

While there are no major changes to the chapter concerning the availability and security of supply of medicinal products including the notification timelines on supply disruptions or withdrawal, a fer proposal strengthen the efficacy of the proposed rules. Moreover, the involvement of patients, healthcare professionals and consumer organisations is strengthened through consultation mechanisms and public disclosure requirements (amongst other things).

- When a product is withdrawn from the market, the MAH should provide detailed reasons and specify whether it is because of commercial considerations.
- It is proposed that **patients, healthcare professionals (HCPs), consumers and other relevant stakeholders** (but industry is not mentioned) **are consulted** in several decisions around shortages, such as:
  - Development of guidance for shortage Prevention Plans (SPP), which should be made available to patient organisations and HCPs;
  - Establishment of the (Union) critical list of medicinal products.
- To make provisions **more compelling**, it is proposed that the MAH "*shall comply with*" (instead of '*take into account'*) EMA or MSGG recommendations in case of shortages.
- The MSGG role is expanded to explore **cost-containment policies for critical medicines**.
- **Member States may impose more robust provisions** than those set out in the Regulation.
- **Financial penalties are also extended, to cover cases when a MAH:**
  - does not provide notification of supply disruptions;
  - does not have in place a detailed SPP;
  - does not comply with recommendations in case of critical shortages.

ANTI-MICROBIAL RESISTANCE (AMR) and TRANSFERABLE EXCLUSIVITY VOUCHERS (TEV)

The chapter has been entirely re-written, with the **removal of TEV** and the introduction of some extremely concerning provisions, such as the **'play or pay' model**. The new chapter is titled "Addressing pharmaceutical market failures in the Union and further incentives for the research and development of priority antimicrobials".

- The TEV has been completely removed.
- An **EU push and pull incentive scheme** is proposed to promote and accelerate the development of novel antimicrobials. This includes:
  - research grants under Union funds with conditionalities linked to the affordability and supply of new and existing antimicrobials;
  - milestone prizes for novel antimicrobial developers with conditionalities linked to the affordability and supply of new and existing antimicrobials;
  - **voluntary joint procurement** with subscription payment mechanisms or market entry rewards that delink or partially delink revenues and sales;
  - **'play or pay' fee systems** in which pharmaceutical companies are subject to a levy on the sale of their existing medicinal products, unless they prove an equivalent investment in antibiotic research and development.
    - This proposal is extremely concerning and worrisome, especially for smaller and mid-sized companies, with a limited portfolio and focussing on development in different therapeutic areas.
- It is proposed to establish a **new European Medicines Facility**, namely an independent public agency to address market failures and develop therapies in underserved areas (such as (H)UMN) or with high price.

  - This proposal comes as part of a broader push towards **price reduction and cost-containment**.

REGULATORY PROVISIONS

- The Report **removes the Regulatory Sandbox** concept from the Commission's proposal in its entirety without further argumentation.
- The **EMA's committee structure will be revised** to streamline decision-making. While the Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC) will continue to exist, committees such as the COMP and CAT will not continue.
  - The Report explicitly calls for the creation of an Orphan, ATMP and Paediatric *ad-hoc* working group to maintain the expertise in the EMA. In addition, it recommends expanding the CHMP to include not only patient representatives but 4 co-opted members from the ad-hoc working groups based on the needed experience.
- 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.
  - As part of the Report, **ATMPs would automatically be eligible for inclusion** in the PRIME scheme.

OTHER PROVISIONS

- **Repurposing from no-profit entities**: repurposing from no-profit entities will apply to all products (not only to UMN, as in the Commission's proposal). The EMA *might* submit the variation (instead of the MAH, which in the Commission's proposal *ought to* submit the variation), after consulting the MAH.

NEXT STEPS and TIMELINES

It is expected that there is still a substantial period of time before the European Parliament adopts its final position on both the Directive and Regulation. Importantly, there is also a Parliamentary election planned for June 2024, and EUCOPE does not expect that a final position will be adopted before then. **Even after the Parliament adopts its position, there are a number of steps** which must be completed, with the **deliberations in the Council of the European Union expected to be the main factor leading to a delay** in the final adoption of the new legislation. EUCOPE does not expect the **new framework to go into effect until 2028 at the earliest**.

The next steps in the European Parliament, according to their planned timeline, are as follows:

- On 7 November, the Rapporteurs will present their Reports in ENVI.
- MEPs, including the two Rapporteurs, will have time to **present amendments until the 13 and 14 November** on the Regulation and Directive, respectively.
- Following the submission of amendments, the Rapporteurs, along with the Shadow Rapporteurs, will prepare **compromise amendments**, negotiating and aiming to propose consolidated amendments that reflect the positions of several different MEPs or Groups based on the amendments that were officially submitted. This process could take several months.
- In parallel, **ITRE** will adopt its opinion (on both the Directive and Regulation).
  - ITRE MEPs will be able to submit amendments until 30 November.
  - The opinion vote in ITRE is scheduled in February 2023.
- An **ENVI vote** on the amendments and both Reports is **scheduled for 7 March**.
  - EUCOPE sees this as very ambitious, seeing the significant differences in opinion between the different Groups. If this deadline is missed, the Plenary vote cannot happen.
- The final **vote in the Plenary** is scheduled for **10 April** (during the last Plenary Session before the end of the current European Parliament's mandate).

Independently from the adoption of the European Parliament, the actual entry into force will still require a few years. The Member States, in the **Council**, will start discussing selected topics of the

Pharmaceutical Package under the Belgian Presidency in the first half of 2024, while thorough work may only begin in the **second half of 2024** under the Hungarian Presidency.

Only after the Council has reached an agreement, negotiations with the European Parliament and the Commission will begin, the so-called "**trialogues**". We can predict that the whole process will take until at least (late) 2026, when both institutions could adopt the final text. Hence, the revision of the general pharmaceutical legislation would not **go into effect before 2028**, namely 18 months after the entry into force.