# GUIDE TO THE PHARMACEUTICAL PACKAGE

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# TABLE OF CONTENTS

# Introduction

The European Commission will soon adopt the highly anticipated Pharmaceutical Package, which contains revisions of the **general pharmaceutical legislation**, as well as the legislation on medicines for children (‘**Paediatric’ Regulation**) and rare diseases (‘**Orphan’ Regulation'**). Originally slated for adoption in the final quarter of 2022, the Commission have since postponed its publication on multiple occasions. The package will also feature a Council Recommendation on **combating antimicrobial resistance** in a one health approach, emphasising the importance of this issue.

This Explainer will primarily focus on the changes that will be brought in the general pharmaceutical legislation and the paediatric and orphan regulations. These files are flagship initiatives of the Pharmaceutical Strategy and have been eagerly awaited by the European Parliament, Member States, citizens, and a wide range of stakeholders.

Although the responsibility of providing healthcare services in the EU falls primarily on the Member States, the EU has put in place a health policy that operates in conjunction with national frameworks to guarantee the highest standard of care for all citizens. Regarding pharmaceuticals, EU legislation dates back to 1965 when the European Community decided that authorisation was needed for the sale of medicines. This measure was conceived to harmonise the internal market and protect public health. Throughout the years, multiple legislative acts have been adopted in order to further contribute to achieving these goals. At present, the current general pharmaceutical legislation and the rules covering medicines for rare diseases & children represent the central EU-wide framework in which pharmaceutical products are being placed on the market.

As part of the Work Programme for 2021, the Commission presented the Communication on the Pharmaceutical Strategy for Europe (‘the Strategy’) which outlined multiple existing policy challenges in the pharmaceutical sector, including the prevalence of unmet medical needs, lack of innovation, unequal access to medicines, affordability problems, unfair competition, lack of regulatory flexibility or environmental concerns.

The General Pharmaceutical Legislation incorporates two legal acts, namely Directive 2001/83/EC and Regulation 726/2004/EC. These procedures establish the framework for the authorisation, production, distribution, and surveillance of medicines throughout the European Union. They also outline rules related to the operation of the European Medicines Agency (EMA), the national medicines authorities, and their subsequent interaction. This framework is complemented by more specific legislation on rare diseases - Regulation (EC) No 141/2000 - and on medicines for children - Regulation (EC) No 1901/2006. These files address the particular needs of patients with rare diseases and children, who often face difficulties accessing appropriate treatments. They provide a targeted framework of rewards and incentives to stimulate research and development of medicines in these areas.

# Prevalent issues in the current frameworks

1 **A lack of therapeutical innovation in areas of unmet medical needs**, especially related to the development of novel antimicrobials or preventing excessive use of antimicrobials across the EU. The issue of antimicrobial resistance (AMR) is burdening healthcare systems across the globe. Addressing unmet needs is a pivotal component of the revision of the paediatric regulation and rare disease regulation.

**95%**
**of rare diseases have no treatment option**

2 **Uneven access to medicines for EU citizens and discrepancies in pricing and reimbursement policies**, especially in relation to orphan and paediatric drugs. Existing legislation does not mandate pharmaceutical companies to introduce new medication in all Member States (MS). The only requirement is that they launch a product within 3 years of obtaining marketing authorisation - otherwise, authorisation expires due to the '*sunset clause*.' Other factors like market size, pricing policies, and regulatory framework differences in MS contribute to the issue.

3 **A need to modernise the framework to adapt to scientific development,** including new technologies such as Artificial Intelligence (AI) or genomic-related technologies. The uptake of digital tools is a focus, in addition to increasing synergies with other frameworks such as medical devices or substances of human origin. The Commission acknowledges the need to simplify procedures, shorten timelines and reduce administrative burdens in order to enhance the attractiveness and competitiveness of the EU. Definitions also require work, for example, the definition of rare diseases may not be flexible enough to account for the variety of rare diseases diagnosed in the EU.

4 **Vulnerabilities in the supply chain of pharmaceuticals** can result in shortages of all kinds of medicines, and **environmental pollution** can result from the development and disposal of the products.

# Revision of the General Pharma Legislation

To tackle these issues, the Commission will consider various policy options. According to a draft document, one key aspect of the proposal will be the **promotion of innovation**, especially in regard to unmet medical needs. Stimulating innovation in the pharmaceutical sector is strongly correlated with **intellectual property rights** and the system of **regulatory protection and incentives** offered to medicinal products.

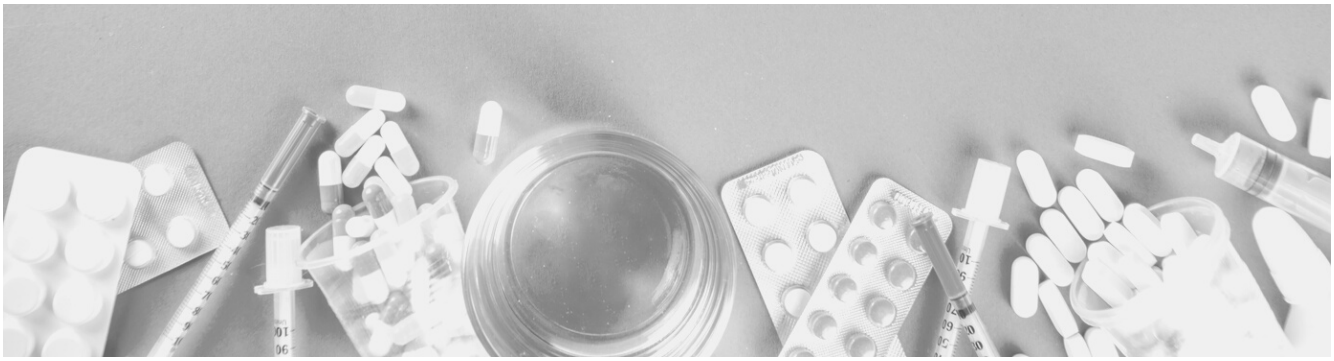
## EU's system of incentives

Besides patents, the EU possesses a regulatory system of incentives for pharmaceutical companies to promote and reward innovation in the industry, offering data and market protection for innovative medicinal products. Article 14(11) of Regulation 726/2004 governs this system of incentives. Per this legislation, following marketing authorisation, a new medicinal product may benefit from regulatory protection through the 8+2 (+1) rule.

### What is the 8+2 (+1) rule?

The marketing authorisation holder (MAH) is granted **8** years of data exclusivity, during which no other applicants can use the medicine's preclinical and clinical trial data to support their own applications for marketing authorisation of generic or biosimilar products. Once the data exclusivity period ends, there is a **2**-year market protection period where a generic medicine or biosimilar medicine cannot be placed on the market. An additional **1** year of market protection may be granted if a new formulation or route of administration of the medicine brings significant clinical benefit compared to existing treatments. The total period of regulatory protection in the EU cannot exceed 11 years.

These incentives are designed to encourage innovation in the pharmaceutical sector, as R&D is often costly, lengthy, and risky. Thus **the aim is to secure the long-term viability of such investments and ensure that competitors' products coming onto the market would not be required to repeat unnecessary and expensive clinical tests**. The upcoming legislation targets this framework, which would impact other issues, such as overall access to medicines as well as pricing & reimbursement policies. There is a **possibility that the 8-year data exclusivity period will be shortened**. However, this reduction could be counterbalanced with more focused incentives that extend the period of market protection under specific circumstances.



## Fostering Access

Patients' access to medicines is dependent on several elements: i.e. pricing and reimbursement policies, market size, or the Member State's regulatory framework. There is significant variation across the Union in the amount of time it takes for a medicine to be approved and then made available to patients.


*(Research conducted by EFPIA)*

Through its system of incentives, the EC is able to influence access: generic and biosimilar medications can only be made available to the public after the regulatory protection for the original medication terminates. By **decreasing the length of this protection**, the Commission considers it possible to introduce generic and biosimilar medications into the market earlier, enhancing the availability of these medicines. The revision may also feature **incentives that oblige or reward the launch of medicines across all Member States within a specific timeframe**, as well as penalties for companies that fail to do so. **Simplifying the application process** for drugs could also be on the table, and this could benefit SMEs.

## Improving Affordability

The affordability of medicines is another paramount issue strongly linked to access. After receiving authorisation, pharmaceutical companies must apply for pricing and reimbursement (P&R) for their products in the Member States. Although the EU has limited powers in this area, the general pharmaceutical legislation could indirectly affect medicine affordability.

The upcoming revision may modify the incentives and regulatory protection system, which could result in the Commission **reducing the period for regulatory protection**. This move is intended to **encourage competition** and facilitate the entry of generic and biosimilar medicines, which could lead to **lower prices** and increased competition. It remains to be seen whether a reduction in the regulatory period would be counterbalanced by introducing other types of incentives.

The topic of access and affordability of medicines was discussed in a Health Council configuration meeting in December 2022, during which several Member States, including Slovenia, Germany, Malta, and Poland, stressed the need to ensure affordable access to medicines for all EU citizens and incorporate this in the upcoming revision. Italy highlighted the need to collaborate with the pharmaceutical industry to enhance access. In the same vein, the EC could impose obligations on companies to disclose their R&D costs, as demanded in a joint statement by associations representing healthcare providers, patients, healthcare professionals and payers. According to them, such a measure "*would help national authorities negotiate fairer prices*."

## Stimulating Innovation

In the area of unmet medical needs (UMN), the Commission strives to better define the concept. **Commission Regulation 507/2006 defines UMN as a condition without a satisfactory method of diagnosis, prevention or treatment, or where the concerned medicinal product offers a major therapeutic advantage.** However, stakeholders and public authorities have highlighted the definition's vagueness.

During a debate in EP ENVI in November 2022, Deirdre Clune (EPP, Ireland) demanded a clearer definition "*that would leave no patient behind*". In response, Anna Eva Ampelas (DG SANTE), stated that **a new definition would consider disease severity, morbidity, and whether the new potential treatment provides a significant improvement over existing alternatives**. Stricter criteria would be established in the upcoming revision for cases of high UNM, particularly for diseases without any existing treatment. She underlined that medicines meeting this classification would enjoy the longest market exclusivity period. The Inception Impact Assessment also emphasises the need to accelerate the approval of drugs for unmet needs, potentially by integrating the European Medicines Agency's (EMA) priority medicines scheme (PRIME) into the process and promoting academic research and the participation of SMEs.

## AMR and transferable exclusivity vouchers

The topic of UMN is a key element that is also contained in the orphan and paediatric legislation. However, in the general pharmaceutical revision, the EC regards antimicrobial resistance (AMR) as a pivotal area of unmet needs and seeks to promote the development of new antimicrobials. The EC is contemplating introducing a novel incentivising mechanism - transferable exclusivity vouchers (TEVs). This represents a form of regulatory incentive that would allow the manufacturer of an antimicrobial to extend the exclusivity rights for another product in their portfolio, or to sell the voucher to another pharmaceutical company.


*Source: BEUC*

The proposed implementation of this approach has garnered significant attention. 14 Member States have expressed their opposition to the introduction of TEVs, citing high costs and transparency concerns. Nonetheless, these states do acknowledge the urgent need to reform the current system, particularly through the provision of more direct financial incentives. In the December 2022 Health Council, Slovakia supported novel incentives to tackle AMR. However, they articulated its worries about the potential hindrance of competition that could arise from transferring vouchers to high-priced, blockbuster medicines whose exclusivity rights were expiring. Similarly, Slovenia voiced concerns about the substantial costs of such a measure. In response, Commissioner Kyriakides reassured that a potential implementation of these vouchers would be carried out under "*very strict conditions*" to minimise the costs on health systems and promote a just return on investment for developers.

Industry representatives like the European Federation of Pharmaceutical Industries and Associations (EFPIA) consider that TEVs would encourage companies to develop new antimicrobials, resulting in a sustainable pipeline and significant cost savings for Member States related to AMR. On the other hand, the European Public Health Alliance and ReAct Europe stated that TEVs are "*a very inefficient and unequal choice for the EU and the world*" mainly due to the additional costs that could be generated. This stance was also reflected in a statement by Medicines for Europe. All in all, while there is disagreement on the best approach, there is a shared recognition of the need to incentivise the development of AMR medicines, which would be included in the upcoming revision. Besides TEVs, the Commission could incorporate provisions designed to promote more prudent use of AMR medicines throughout the EU.

## Shortages of Medicines

The EC is anticipated to propose additional measures to address shortages that have resurfaced in late 2022 and early 2023. These measures could include increased obligations on companies to provide earlier notifications of shortages and withdrawals, improve the transparency of stocks as well as enhance prevention and monitoring activities throughout the supply chain. Nevertheless, the EU's reliance on China and India for active ingredients and medications, along with other issues in the global supply chain, may limit the effectiveness of these measures. Several MS also recognised the need to upgrade the current legislative framework as "*it failed to secure sufficient supplies of a number of medicines*". The forthcoming revision will feature provisions targeting the digitalisation of the sector and reinforce the environmental requirements assessment (ERA) for pharmaceutical companies in developing medicines.

# Revision of the Legislation on Medicines for Rare Diseases & Children

The orphan and paediatric regulations are extensions of the general pharmaceutical legislation, designed to achieve comparable objectives but with a more focused system of rewards and obligations. Thus, the policy options that the Commission will consider go hand in hand with the ones contained in the revision of the pharma legislation.

## Defining the Term

Defining the concept of rare diseases plays a pivotal role in promoting innovation in the field and improving care for individuals afflicted with these conditions.


This concept has ramifications for the paediatric regulation as there are many rare diseases that mainly affect children. Thus, the development process of a medicine designed to target rare diseases - orphan medicinal products (OMP) - is strongly linked to this definition. The 2020 joint evaluation of the orphan and paediatric legislation questioned whether the threshold criteria was the right tool to identify rare diseases.

MEPs also touched upon the threshold. Nicolás González Casares (S&D, Spain) claimed it was a problematic concept considering that "*each rare disease had its own threshold*". Deirdre Clune (EPP, Ireland) stated that a narrower definition could further reduce the development of orphan drugs. In that same debate, a DG SANTE representative argued that a potential change should be flexible enough to enable R&D and to allow the inclusion of other diseases in the future. On a previous occasion Vlastimil Válek, Minister of Health, Czech Presidency also wondered "*if the time had come to reconsider the definition of rare diseases*." Hence, a potential recalibration of the concept would impact other areas, as described below.

## Orphan designation and the system of incentives

Currently, both regulations provide specific incentives for pharma companies to develop therapies for rare diseases and for children. The process might not otherwise be financially feasible due to the limited patient populations and the need for specialised formulations or dosages. All orphan medicines need to receive authorisation through the centralised scheme, via the EMA. Prior to marketing authorisation, pharma manufacturers can undergo the orphan medicine designation review - a regulatory process carried out by the EMA designed to assess whether the future medicine qualifies for treating a rare disease. An authorised orphan medicine receives a 10-year market exclusivity from the competition with similar drugs. The protection is extended by 2 years if the medicine has also developed a paediatric investigation plan (PIP) during the orphan medicine designation review. Other incentives include regulatory fee reduction, scientific protocol assistance from EMA, and priority assessments. Overall, these files managed to boost the development of medicinal products for rare conditions and children, but there was still a high prevalence of such conditions across the EU.

## Paediatric Investigation Plan (PIP)

Pharmaceutical manufacturers are obliged to assess the potential use of any new medicine in its abilities to treat paediatric populations by submitting a Paediatric Investigation Plan (PIP) to the European Medicines Agency (EMA). Paediatric clinical trials are generally conducted in parallel with adult trials. However, companies may be granted waivers or deferrals if such trials would delay the authorisation of the drug for adult use, or if the medicine is deemed too dangerous for children. Studies in children can also be initiated or completed after applying for adult authorisation. Once the PIP is conducted, the results are included in the marketing authorisation file. To compensate for the burden of such requirements, the main reward is a six-month extension of the supplementary protection certificate (SPC) - the patent covering the product - and another 2-year extension of the market exclusivity period if the drug is an orphan medicine. Additionally, companies may seek a Pediatric Use Marketing Authorisation (PUMA) - mechanism designed for any authorised and off-patent medicinal product developed for exclusive use in the paediatric population. PUMAs are granted by the EMA after the submission and approval of a PIP. Unlike other types of marketing authorisations, they provide market exclusivity for a maximum of 10 years market exclusivity, although the actual period of exclusivity may be shorter depending on the circumstances of the case.

## Potential Amendments

The forthcoming revision is expected to amend the system of obligations and rewards in order to direct and reward investments where they are most needed. For rare diseases, the Commission is likely to redefine the concept in order to better target such maladies. One possibility is the reduction of the 10-year market exclusivity for orphan medicines or providing a more variable duration of exclusivity based on clear criteria. This could be linked to clearly-defined criteria such as the type of orphan medicine, the level of innovation or the severity of the disease. These drugs may benefit from further or stronger exclusivities and regulatory support from the EMA. This view has also been reflected in the joint evaluation of these proposals as companies were mainly focusing on medicines with the highest expected return on investment. Consequently, a cluster of orphan medicine developments was generated in specific diseases while others were lacking any treatment. EFPIA proposed maintaining the current 10-year exclusivity but to be modulated up or down (between 7 and 12 years) based on a set of clear and predictable criteria. In the same manner, Eurordis oppose a potential reduction of the length of market exclusivity, "*at the very least should not be less than in the United States.*" This would further secure the EU's global competitiveness. TEVs could be introduced as a solution to foster innovation, especially in regard to HUMN in both orphan and paediatric legislation.

Similar to the general pharma revision, further rewards or obligations could be linked to launching a medicine within a specific period of time across all MS. In relation to paediatric medicines, a scenario taken into consideration by the EC is amending the rules on waivers and deferrals from the obligation to conduct clinical research in children. The goal is to ensure that disorders that are different in children to adults, such as paediatric cancers, would be effectively tested for them. To foster innovation in the area of unmet needs in children, the revision could grant the 6-month extension of the SPC only to drugs designed to tackle such diseases or provide more novel incentives. As mentioned above regarding the general pharmaceutical legislation, the implementation of these measures would have effect on the availability of medicines for rare diseases and children, pricing, competition, and the security of the supply chain.

# Expectations

The adoption of the pharmaceutical legislative package has been anticipated for a long time by the European Parliament, Member States, patients and a wide range of stakeholders. These initiatives were discussed at the end of last year in the Health Council configuration. During the debate, the Czech Presidency underlined the need to upgrade the general pharmaceutical legislation to take into account the latest scientific developments, and it was disappointed that the EC was continuously delaying its adoption. The Netherlands proposed shifting towards a demand-driven approach to address unmet medical needs and supported a more gradual system of incentives, lower than 10 years of exclusivity. On the other hand, Italy hoped that the forthcoming revisions would continue to secure IP rights for companies so that they would be encouraged to continue the research on medicines for children, rare diseases and antimicrobials. Overall, Member States have underlined the need to facilitate equal access for all EU citizens, and foster the affordability of medicines as well the security of supply.

The European Parliament has also discussed the package on multiple occasions. During an EP ENVI exchange of views with Commissioner Kyriakides, many MEPs raised similar issues: Kateřina Konečná (The Left, Czechia) claimed that access to medicine was strongly dependent on the Member States. Concerning the possibility to oblige pharmaceutical companies to launch a drug in all MS, Nicolás González Casares (S&D, Spain) was interested to know more about the practicalities of implementing such a measure and how national health systems ensure its application. In another meeting, Jutta Paulus (Greens/EFA, Germany) opposed the introduction of transferable exclusivity vouchers, due to a potential increase in costs, and in response, Jakob Forssmed, Swedish Minister for Social Affairs and Public Health stressed the importance of working with different types of models. Heléne Fritzon (S&D, Sweden) hoped that the MS would still be able to keep their national competence in health policy.

Previous discussions in Parliament regarding orphan and paediatric revision concentrated on market access, incentives, and affordability. In a debate in EP ENVI from November 2022, Anna Eva Ampelas of DG SANTE underlined that most orphan diseases lack treatment as pharmaceutical companies prioritise medicines with higher profitability, leading to limited development in specific diseases.

The Commission considers changing the market exclusivity duration based on product type, innovation level, and medical demand. Talking about boosting R&D in rare and paediatric medicines, Tiemo Wölken (S&D, Germany), questioned whether a possible requirement to launch a drug in all MS should be differentiated based on company size, as smaller entities may not have the manufacturing capacity to meet the obligations, potentially discouraging their investment in orphan drugs. He opposed the introduction of transferable exclusivity vouchers. On the other hand, Tilly Metz (Greens/EFA, Luxembourg) endorsed IP incentives like market exclusivity to drive R&D for unmet needs but under strict conditions, such as transparency in investment and universal accessibility and affordability of orphan drugs. Andrey Slabakov (ECR, Bulgaria) proposed fostering cross-border access to treatment for rare diseases - mainly because in some MS, these diseases only impacted a small number of people. Responding to the inquiries on incentives, the DG SANTE representative cited a study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe claiming that the EU had one of the most attractive incentive models. The study also showed that R&D investments were driven by other factors such as the quality of the labour force, taxation levels or R&D subsidies.

The range of stakeholder views on the forthcoming revisions suggests that the Commission will face challenges in delivering a perceived-to-be-balanced set of proposals. In a position paper, Medicines for Europe hope that the upcoming revision of the pharma legislation will foster the uptake of biosimilar drugs, "*to encourage huge investments in R&D and to contribute to lower healthcare budgets*". In the same vein, several organisations drafted a joint statement asking the EC to reduce, under certain circumstances the unconditional duration of data and market protection incentives, and to not introduce TEVs. These concerns are shared by European doctors (CPME) who demand a mandatory launch in all MS, and that "*intellectual property rights need to be reshaped in the public interest to be truly patient-centred*". Another joint statement by EURORDIS - the voice of patients suffering from rare diseases - and EFPIA stressed improving patients' access to orphan medicinal products, as it remained "*inequitable across countries and routinely delayed*".

EFPIA's campaign *Mind the gap* highlights a decline in investments in medicine R&D, fewer clinical trials and longer approval times for new drugs, which subsequently can compromise the EU's global competitiveness. They call on the EC to ensure that the EU's pharma legislation is equipped to face the challenges of the future, especially by maintaining the current IP rights, implementing transferable vouchers and harmonising processes that are now too fragmented between the EU and national levels. In its Regulatory roadmap to Innovation, EFPIA focused on ensuring a more efficient and simplified framework to shorten approval times as well as on fostering innovation in clinical trials. EUCOPE largely shares the same goals. Ultimately, these diverse perspectives indicate a complex landscape of stakeholder interests that the Commission will aim to best encapsulate in order to publish a well received proposal.

## Next Steps

The Commission is expected to adopt the package on 29 March, although the possibility of another delay cannot be ruled out. Once adopted, the work in the European Parliament will likely be led by the ENVI Committee. In the Council, the file is going to be examined by the Working Party on Pharmaceuticals and Medical Devices, and/or the Working Party on Public Health. Given the significance of the matters at stake, it will be interesting to observe whether the proposal will be concluded during this term. The initiatives have been already included on the provisional agenda of the Health Council configuration from June 2023.

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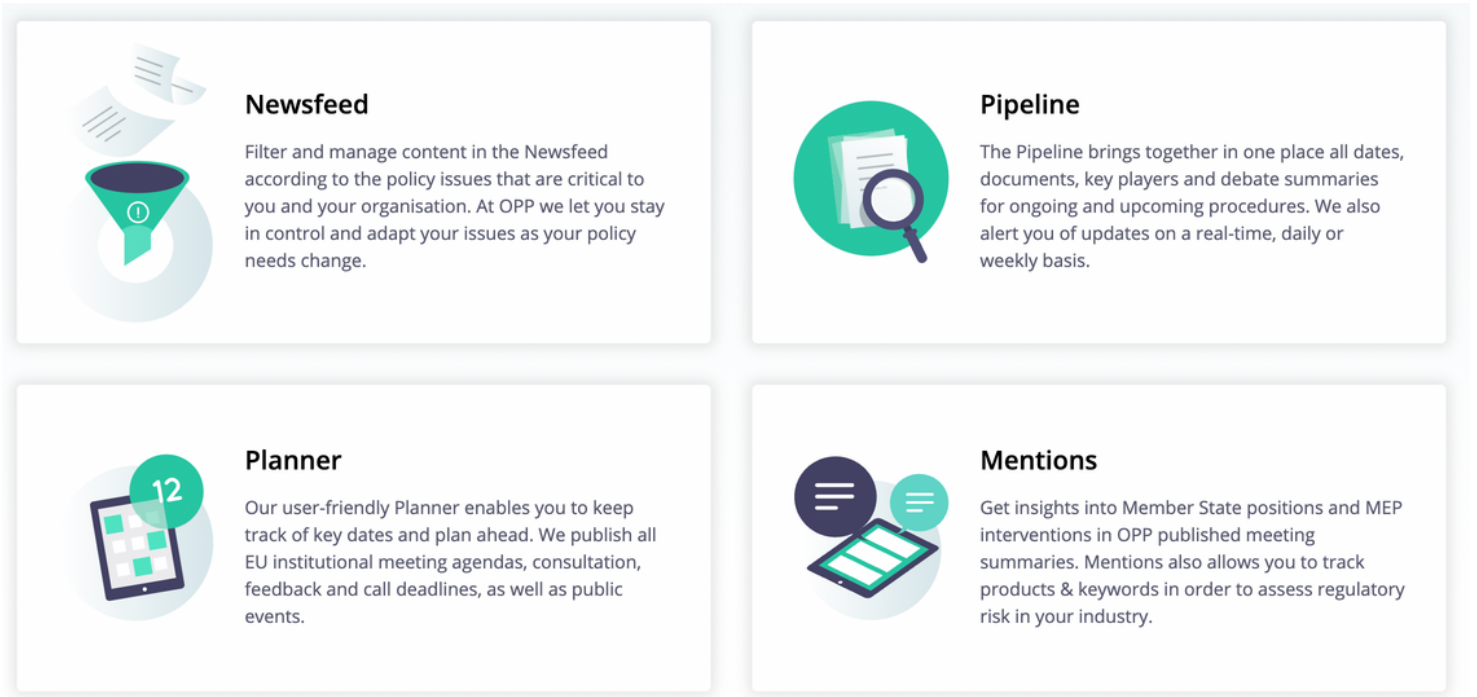


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