



AESGP Position Paper

**on the European Commission's proposal for a
revision of EU general pharmaceutical
legislation**

14 July 2023

Executive Summary

AESGP welcomes the Commission Proposal for a Revision of the EU general pharmaceutical legislation, and more particularly:

- **Directive** on the *Union code relating to medicinal products for human use*, and repealing Directive 2001/83/EC and Directive 2009/35/EC [COM(2023)192].
- **Regulation** laying down *Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency*, amending Regulation 1394/2007 and Regulation 536/2014, and repealing Regulation 726/2004, Regulation 141/2000 and Regulation 1901/2006 [COM(2023)193].

This has been a long-awaited revision that will streamline dispersed legislation and consolidate successive updates that happened over the past 20 years, to keep track of healthcare product and regulatory evolution.

Although the legislation aims to address affordability while fostering innovation, and ensure security of supply while raising regulatory agility, **AESGP has some concerns relating to unintended impacts on non-prescription medicines, that could have adverse consequences on medicines availability, patient access and health system sustainability.**

PRESCRIPTION STATUS

DIR. — Art.17, Art.51(e), Art.51(f), Art.69

AESGP supports the European Action Plan against Antimicrobial Resistance and the objectives of the Chemical Strategy for Sustainability. However, we are **concerned about proposed changes that include two new prescription criteria for “antimicrobial” products and for medicines containing an active substance which could be deemed concerning for the environment.**

The broader definition of antimicrobials, as proposed, goes beyond antibiotics and drags into scope a broad category of common non-prescription products, including, but not limited to:

- antivirals (e.g., oral herpes and wart treatments),
- antifungals (e.g., dandruff, athletes’ foot, fungal nail infections, oral and vaginal thrush),

Controversial resistance to topically applied preparations against viral and fungal infections from the non-prescription area **has not been sufficiently investigated to draw final conclusions** or even restrict the use of these products. Self-care antivirals and antifungals help people to take timely action and avoid aggravation of the condition which could result in a require-

ment for higher dosages and longer-term usage due to the delay in treatment. This **time-sensitive availability reduces the burden on national healthcare systems**, freeing doctors for more complex pathologies, and prevents escalation of the infection or its transmission which is wise from a public health point of view.

AESGP believes that the new criteria for a blanket prescription legal status should be restricted to antibiotics for which an AMR risk has been proven.

Parameters such as **PBT or PMT are hazard-based classifications, which, alone, do not determine environmental risk.** Should an environmental risk be identified in the assessment that would require any risk mitigation, **the medical prescription would not be the appropriate tool to reduce the environmental exposure.**

A pre-requisite before authorizing a medicinal product is to provide scientific data showing predicted impacts on environment and public health. AESGP believes that **the new criteria to attribute prescription legal status for medicines containing an active substance which is PMT, vPvM, PBT or vPvB, should be removed.**

ENVIRONMENT

DIR. — Art. 4, Art. 22, Art. 23, Art. 24,
Art. 47, Art. 87, Art. 195, Art.196

Non-prescription medicines are often the first choice to address common illnesses. However, as an inevitable consequence of taking medicines, traces of pharmaceuticals can find their way into the environment.

Since 2006, producers must include an environmental risk assessment (ERA) when approving human medicines.

The Commission proposed changes to ERA, however, **will not address known issues such as repetition of studies, inconsistent and conflicting ERA conclusions and non-equitable testing burdens** on individual companies which are unforeseen at the point of application.

In light of EP resolution on Pharmaceutical Strategy, it is **concerning and inappropriate that marketing authorisation could be refused due to environmental concerns** without health benefit-risk considerations, as proposed in the COM text.

When an ERA based on worst-case assumptions indicates a potential risk, appropriate binding and time constrained **post-authorisation measures should ins-**

tead be used to give applicants the opportunity to address the potential concerns without delaying patient access to medicines.

The Pharmaceutical Industry proposes an “**extended ERA**” (eERA) to address environmental risks associated with human medicinal products. This should be the main regulatory tool for assessing environmental risks of APIs, as **it is crucial to not only consider environmental risks at the point of a market application but also post-authorisation and across products containing the same active pharmaceutical ingredient (API).**

We ask for more clarity in the updated data requirements, and we believe that the **ERA monograph system must be based upon high-quality scientific data (Klimisch and CRED quality approach), with clear criteria for the inclusion or exclusion of studies.**

The EMA should keep overall control of the ERA for human medicines and closer collaboration with industry. **We recommend full alignment across agencies and legislative dossiers as long as risk-based approaches are considered, and all legislative dossiers are subject to the same standards.**

SHORTAGES

REG. — Art. 116, Art. 117, Art. 121,
Art. 130, Art. 132

The pharmaceutical industry, including the non-prescription medicines sector, are committed to avoid medicine shortages and, whenever unavoidable, mitigate the effects on end-users.

The European Commission’s structured dialogue on medicines supply has showed that shortage mitigation and management measures need to be adapted to the specifics of each situation. Shortages are of particular concern when they affect medicines for which no or limited alternatives are available, and where interruption of supply will result in a potential risk to public health.

Because of the very low frequency and low impact of shortages of non-prescription medicines, **AESGP believes that requirements for Shortages Prevention**

Plans (SPP) and shortage notifications should be restricted only to those non-prescription medicines that are listed in the critical medicinal products list. The shortage notifications should also be done no later than 2 months prior to occurrence to avoid overburdening regulatory authorities.

Furthermore, we believe that **Medicine Shortages Steering Group should NOT have a specific power to mandate inventory management and diversification of suppliers.** There is a wide variety of supply chain strategies that companies deploy when mitigating shortages and, instead, they should be further empowered to adopt the most appropriate strategy in each individual case.

INCENTIVES

The Commission proposals lacks adequate measures to incentivize innovation and investment within the EU for the change of legal status from prescription to non-prescription medicines.

Current one-year data exclusivity is insufficient, especially in a sector with long marketing authorization approval and launch delays. The EU faces disadvantages in focusing on innovation and investment in the self-care sector compared to other markets like

the US and Japan where a three-year data protection is granted.

Furthermore, the current provisions only cover "significant pre-clinical tests or clinical trials," ignoring the value of other types of evidence, such as behavioural studies or real-world evidence, valuable in assessing a switch's safety, effectiveness, and healthcare contribution.

PRODUCT INFORMATION

DIR. — Art. 62, Art. 63, Art. 64, Art. 65

AESGP believes that the future of product information is digital due to many of its benefits (e.g., facilitating quick updates, multiple language availability and

readability, accessibility to information, addition of multimedia and other tools to help increase medication and health literacy).

AESGP recommends that an orderly and harmonized approach to transition to digital product information is taken, and that the access to essential information for responsible use of a medicine is ensured at all times to aid self-selection of non-prescription medicines and self-treatment.

Transition should take place in a stepwise approach, by shortening and simplifying the current paper patient information leaflet and introducing a more detailed digital information support as a complement with an ultimate objective of maintaining only the digital leaflet.



REGULATORY AGILITY

DIR. — Art. 13, Art. 34, Art. 36, Art. 43

AESGP welcomes that there are no substantial changes to marketing authorisation procedures access and related requirements and the shortening of the procedure timings.

AESGP proposes to remove the requirement to notify all Member States at the start of a decentralised or mutual recognition procedure as well as the member state opt-in provision. As mentioned, there are other mechanisms available which would improve access and availability.

AESGP suggests that legal provisions include the requirement to consult Marketing Authorisation Holder (MAH) on any changes to the Summary of Products Characteristics (SmPC) as MAHs remain responsible for the content and update of the content of the marketing authorisation dossier.

AESGP proposes to maintain the "well-established use" application route as it is enshrined in the current legislation to allow for continued innovation in the self-care sector. This would furthermore avoid any further unnecessary clinical trials.



REAL-WORLD DATA AND REAL-WORLD EVIDENCE (RWD/RWE)

DIR. — Art. 4

Non-prescription medicines are indeed not prescribed nor reimbursed and, therefore, have no routinely collected data (outside of pharmacovigilance data). RWE has the potential to inform authorities' decisions on medicinal products, notably on the change of legal status' safety and effectiveness.

AESGP believes that the **new legislative package should introduce fit-for-purpose definitions of RWD and RWE, which recognise all data sources and are, therefore, also suitable for non-prescription medicines.**

PHARMACOVIGILANCE

DIR. — Art. 21

The removal of the obligation to submit Risk Management Plans for generics and biosimilars should be extended to medicinal products of “well-established use” where there are no existing or new significant safety concerns.

For other product categories, a risk-based approach should be applied to the Risk Management Plan (RMP) based on existing API safety information and indication. **The requirement for a Risk Management Plan should for these categories be delinked from the legal basis to minimise unnecessary work for both authorities and industry.**



MANUFACTURING AND QUALITY

DIR. — Art. 1, Art. 166

We consider that **supplier qualification is already sufficiently regulated in the Good Manufacturing Practice (GMP) Guide. AESGP proposes to adapt the articles mentioned accordingly and to delete “starting materials” from the scope of the application of the Directive.**

AESGP considers that the current rules, disregarding the financial flow, sufficiently safeguard the safety and

quality of medicinal products in the EU/EEA, concerning the requirement to have a Wholesale Distribution Authorisation (WDA) expanded to include obtaining medicinal products by financial transactions. **Requiring financial and physical flow to be aligned would create huge inefficiencies as well as concerns from a sustainability point of view.**

PRESCRIPTION CRITERIA

AESGP supports the European Action Plan against Antimicrobial Resistance and the objectives of the Chemical Strategy for Sustainability.

However, we are concerned by the proposed changes that include two new prescription criteria, namely for:

- “antimicrobial” products which would include antifungals and antivirals, and
- medicines containing an active substance which could be deemed concerning for the environment because it is either:
 - * persistent, bioaccumulative and toxic (PBT), or
 - * very persistent and very bioaccumulative (vPvB), or
 - * persistent, mobile and toxic (PMT), or
 - * very persistent and very mobile (vPvM).

Imposing the prescription status will have a negative impact on the accessibility of self-care products and add an additional burden on national health systems. We consider it is a disproportionate measure that would not effectively manage risk.

Prior to the decision to apply any risk mitigation measure to a medicinal product, the supposed risk intended to be mitigated must first be assessed. With this proposal, a blanket worst-case scenario is applied with the application of default preventative measures without first assessing the real risk.

The risk of antimicrobial resistance is already part of the first prescription criteria (as indirect danger) and companies already assess the risk of antimicrobial resistance when considering changing legal status from prescription to non-prescription (switch).

AESGP believes that the existing evaluation that takes place in the context of such a switch should continue. To be able to become a non-prescription medicine, the specific properties of the active substance, combined with the indication, posology, route of administration

and treatment duration as well as the proposed environmental risk mitigation measures are considered. For this reason, **the case-by-case decision that regulatory authorities take on each medicinal product or active substance is a more appropriate and proportionate approach to ensure the objective of safeguarding public health while reducing the environmental impact of medicines.**

Furthermore, mandating prescription status for antimicrobials currently available without prescription should take into account:

- **known differences in scope and scale of resistance for antibiotics, antifungals and antivirals as separate classes;**
- **differences in potential for medicines in these classes to become resistant when used in – self-care indications;**
- **the clinical impact to patients and healthcare systems should access become restricted – and how this could disproportionately affect some demographics more than others.**

Exploration of methods to enhance non-prescription medicines clinical use through patient education (right diagnosis, right product, right dose, right duration) should be explored as a prudent first step in avoiding disproportionate barriers to use. The use of self-care products helps preserve or enhance reductions in morbidity in very common and often distressing conditions.

The prescription status of antimicrobial products (in particular, antifungals and antivirals) or of medicines containing an active substance which is of environmental concern (PBT, vPvB, PMT, vPvM) is, therefore, not an appropriate risk mitigation measure. **To bring prescription status to some of these medicinal products would have a negative impact on the accessibility of self-care products and add an additional avoidable burden on patients, national health system resources and budgets for products where the risk is not present or can be appropriately mitigated.**



Contribution of environmental compartment to AMR

The risk of antibiotic resistance spreading through the environment is currently the subject of many research programmes. Particularly, knowledge on the resistance spreading in the environment and the possibilities of gene transfer of bacterial genome has been reported in a number of studies (see review by Larsson and Flach, 2022) and is part of international research programmes sponsored amongst others by the EU Commission (<https://www.jpiaamr.eu/>). Although the underlying mechanism of this phenomenon is understood, it is unclear how it is influenced by environmental levels of antibiotics, and whether the exchange of resistance genes in bacterial strains in the environment is a major source of pathogenic stress for human health.

Antimicrobials

Directive - Art. 51(e), in connection with Art. 17 and Art. 69

The definition applied to the term “antimicrobial” within Article 4 section 22 is as follows:

“any medicinal product with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals and antifungals”.

The original term “antimicrobial resistance” centres on antibiotics where there is a clear and proven link between resistance development, resistance spread and clinical consequences for the patient. The recent Council recommendations quote that *“more than 35,000 people die each year in the EU/EEA as a direct consequence of an infection due to bacteria resistant to antibiotics. The health impact of AMR is comparable to that of influenza, tuberculosis and HIV/AIDS combined.”*

The broader definition, as proposed, goes beyond antibiotics and drags into scope a broad category of common non-prescription products including, but not limited to:

- **antivirals** (e.g., oral herpes and wart treatments)
- **antifungals** (e.g., dandruff, fungal nail infections, oral and vaginal thrush)

There is clear evidence that antibiotic usage is in many cases inappropriate, which may stem from an absence or lack of adherence to guidelines, insufficient time to manage patients, or a lack of diagnostic utilisation, meaning the causative organism and its sensitivity is not established prior to antibiotic administration.

Misuse and overuse of antibiotics is known to encourage the development of resistance which ultimately can

limit the antibiotic therapeutic value in the treatment of more serious conditions. Therefore, there is a general agreement that antibiotics with a proven risk of “antimicrobial resistance” should be available with prescription-status and linked with definitive diagnostic approach.

It is important to acknowledge that there are non-antibiotic active ingredients with broad multi-point modes of action, such as antiseptics and disinfectants used within medicinal products to treat or prevent infections including in wound care, acne, dandruff, sore throat, oral hygiene and vaginal dysbiosis that, whilst not explicitly mentioned within the antimicrobial definition, could be interpreted as being within the scope of this proposal.

This possible inclusion in the broad definition may lead to confusion as many are used as non-prescription medicines to address infections and as part of achieving *“better hygiene and infection prevention measures to limit the development and spread of antimicrobial-resistant infections and multidrug-resistant bacteria”* as defined with objective 3 of the WHO Global Action Plan on Antimicrobial resistance (1).

AESGP supports the public health goal to contain antimicrobial resistance. However, the major issue in AMR is due to antibiotic resistance in bacteria linked to numerous common infections, and the mis-prescription and over-prescription of antibiotics where they are not effective (e.g. empirical prescribing of antibiotics and use of antibiotics for viral infections). Therefore, there is a general agreement that antibiotics with a proven risk of “antimicrobial resistance” should be available with prescription status and linked with definitive diagnostic approach.

(1) WHO Global Action Plan on Antimicrobial Resistance: <https://www.who.int/publications/i/item/9789241509763>



A few antivirals and antifungals are available without prescription in well-defined conditions when speed of treatment is key to avoid aggravation (e.g. athletes' foot, labial herpes, dandruff, sore throat and vaginal thrush). **Antivirals and antifungals containing non-prescription medicines are usually available at a lower dosage than their prescription (Rx) equivalent or for shorter time treatments.** These products have less units per packaging and treatment is stopped if not exerting a positive effect within a short time frame.

Controversial resistance to topically applied preparations against viral and fungal infections from the non-prescription area has not been sufficiently investigated to draw final conclusions or even restrict the use of these products. **Self-care antivirals and antifungals help people to take timely action and avoid aggravation of the condition. This time-sensitive availability reduces the burden on national healthcare systems, freeing doctors for more important pathologies, and prevents escalation of the infection or its transmission which is wise from a public health point of view.**

Resistance to antifungals

The risk of resistance development to antifungals in humans exists if the antifungals are used inappropriately, especially during long courses of systemic treatment with persistently low drug concentrations in the systemic circulation and tissues (Perlin et al. 2017, Fisher et al. 2022, Carmo et al. 2023). In fact, one of the best methods to avoid acquiring resistance is to take antifungal medication as directed (Hossain et al. 2022). In addition, the widespread prophylactic and empiric prescribing of antifungals to treat suspected invasive fungal diseases in individuals who are chronically at risk, those who are critically ill and in patients with haemato-oncologic diseases remains a concern (Fisher et al. 2022). Antifungal resistance in invasive fungal diseases which are generally not treated with non-prescription medicines, can also be acquired by other factors (e.g., poor patient compliance, when doses are skipped, therapy is stopped too soon, or the dose is too low) (Pai et al. 2018, Hossain et al. 2022, Gupta and Venkataraman 2022, Baid 2022).

Generally, because **invasive fungal diseases are most common in immunocompromised hosts**, host-directed approaches are needed to lessen the pressure on antifungal drugs (Fisher et al. 2022, Rabaan et al. 2023).

The initial concern that the frequent use of non-prescription antifungals for local/topical therapy may promote the development of resistance with cross-resistance to systemically used antifungals (Cross et al. 2000) appears largely unfounded. **After decades of**

use, it can be claimed that, upon appropriate use of non-prescription antifungals in the approved indications, the prescription-free use can be considered safe for humans, as exemplified by clotrimazole, terbinafine and others. Despite its use over decades, resistance to these drugs is rare in the general population, with the caveat that drug resistance has emerged in immunocompromised patients, where immunocompromised patients tend to be under medical treatment anyway because of their immune deficiency. The development of secondary resistance by sensitive fungi has so far only been observed in very isolated cases under therapeutic conditions (EDQM 2017). Susceptibility testing is usually not even recommended for the common non-prescription clotrimazole (Mending et al. 2020).

It is estimated that about 25% of the world's population is affected by dermatomycosis or onychomycosis, 75% of all women suffer from vulvovaginal candidiasis at least once in their lifetime. These fungal infections can substantially impair quality of life (2). Antifungals for the treatment of skin, mucosal or nail fungal infections such as clotrimazole, bifonazole, ciclopirox, terbinafine, or miconazole are available without prescription in the EU. Nevertheless, resistances have not developed as major issue in Europe (3).

The occurrence of resistance in fungi strains is somewhat known in medical treatment but also in context with environmental applications as plant protection pro-

(2) Martinez-Rossi NM, Peres NTA, Bitencourt TA, Martins MP, Rossi A. State-of-the-Art Dermatophyte Infections: Epidemiology Aspects, Pathophysiology, and Resistance Mechanisms. *J Fungi (Basel)*. 2021 Aug 3;7(8):629. doi: 10.3390/jof7080629.

(3) Willems HME, Ahmed SS, Liu J, Xu Z, Peters BM. Vulvovaginal Candidiasis: A Current Understanding and Burning Questions. *J Fungi (Basel)*. 2020 Feb 25;6(1):27. doi: 10.3390/jof6010027



ducts. The pathways of resistance spreading in pathogenic fungi is less well understood than in bacteria. **The mechanism of resistance spreading is fundamentally different from that in bacteria, since genome transfer does not play an important role in resistance acquirement** (Fisher et al., 2022, Cowen et al., 2015). In fact, the absence of fungal capacity to readily take up or horizontally transfer exogenous DNA, such as plasmids, prevents the spreading of resistance by gene transfer (Stevenson et al., 2022). Therefore, the development of resistance is bound to de novo evolution of the resistance mutation in a fungal strain. Additionally, the development of biofilm-related resistance is known for antifungal treatment failure (Chaabane et al., 2019).

The dual use of certain groups of antifungals (e.g., azole fungicides) in agriculture and medicine has caused concerns of resistance in pathogenic fungi, which patients come into contact with. This could result in life-threatening conditions particularly for patients with reduced immunity capacity (Chaabane et al., 2019). So far, reports focus on the resistance acquired in fungi strains of *Aspergillus fumigatus* and *Candida spec.*

Two ways of resistance acquiring can be considered (Jeanvoine et al, 2020):

- The (long-term) use in patients,
- The (over-) use in agriculture.

The observed resistant strains often show cross-resistance with a number of azole fungicides, particularly the triazoles. Jeanvoine et al. proposed that the observed triazole resistance originated first from agricultural use, based on observations of the mutation specifics. The observations also coincided with the authorization periods as plant protection products (PPPs). Overall, the significance of environmental antifungal residues originating from medical use being causative in the selection of resistance relevant to human health may be minor in comparison to those originating from agricultural use. For the UK for example, the use of azole fungicides in plant protection products is reported with 1.300t/a (Garthwaite et al., 2018).

Other groups of fungicides used in medical applications, such as echinocandins and polyenes, can also produce resistant strains, but this is even less studied.

It can be, therefore, expected that the main pathways for antifungal resistance are either driven one-directionally from mutations occurring in the environment by agricultural use or from those occurring in the patient's community itself.

Since the resistance in fungi is not spread and increased through genome exchange as in bacterial strains, a circular resistance pathway from patients to environment and back to patients is less likely. Therefore, if environmental levels of antifungals play a role in the spread of antifungal resistance due to selection processes, it is likely that the use in plant protection products is the main source.

Resistance to antivirals

For the antiviral category mentioned in the definition, the **WHO highlights antiviral drug resistance problems in the immunocompromised, especially in the treatment of HIV, where these drugs are already prescription controlled (4)**. According to the WHO, the underlying problems of HIV drug resistance lie more in the limited access to medication and lack of treatment adherence (5). These are the underlying problems for viral treatments, rather than drug resistance and prescribing-status.

Currently antiviral drugs like acyclovir, penciclovir, valaciclovir, famciclovir and docosanol against

herpes simplex virus (HSV-1) are available over the counter. Recurrent herpes labialis, a very common painful condition, is caused due to the activation of an infection with HSV-1. A study by the World Health Organization (WHO) in 2020 showed a global prevalence of HSV-1 in 66.6% of the world population aged 0-49 years in 2016 (James C et al. 2020). It is estimated that 60 to 90% of adults have experienced herpes labialis (Chuang et al.2013; St Pierre et al. 2009). HSV-1 is typically transmitted from person to person via infected oral secretions during close contact. **Characteristic signs and symptoms allow early detection without the need to consult an HCP. If left untreated, it**

(4) World Health Organization, Fact Sheets — Antimicrobial resistance: <https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance>

(5) World Health Organization, Fact Sheets — HIV drug resistance: <https://www.who.int/news-room/fact-sheets/detail/hiv-drug-resistance>



leads to further complications and morbidity (Gopinath D et al. 2023). For most people, cold sores occur once or twice a year, but about 5-10% of people have more than five outbreaks a year. One essential factor to achieve optimal results is that treatment must be started as soon as possible, ideally at the prodromal stage and no later than 48 hours after the appearance of the lesions (Leung AKC et al. 2013; Vere Hodge R. Anthony et al. 2013). **The earliest treatment start is not only important to lower the viral load, in particular to reduce the probability of infection in babies and small children (risk of meningitis), but also to prevent the risk of the viruses spreading, such as to the eye mucosa (where it can develop to blindness in the worst case).**

Prevalence of resistant strains of HSV-1 has not increased over the more than 20 years that acyclovir or penciclovir were available under prescription, nor in the past decade since they have been available as non-prescription.

(6) W.C. Summers, "Virus Infection", National Center for Biotechnology Information, National Library of Medicines: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7149757/>

HSV strains that are resistant to acyclovir occur naturally at a very low frequency (~0.3% in immunocompetent and in < 10% immunocompromised patients) (Schalkwijk HH et al. 2022). A unique combination of virus-, host- and drug-related factors explains why resistance has not emerged in the general population.

The consequence of antivirals in the environment on resistance is clearer as all viruses by nature are obligate intracellular parasites, meaning they can only replicate within a living cell (6). Therefore, outside the body, viruses are inactive and not replicating and, as such, are unable to develop resistance mechanisms as a consequence of any potential environmental exposure. The concentration of topical antivirals within non-prescription medicinal products is low (e.g. 5% for acyclovir and 1% for penciclovir) and applied in small volumes. This means the quantities that could potentially enter the environment from therapeutic use are vanishingly small.

Self-care use of antifungals and antivirals

In conclusion, there are fundamental differences in the potential spreading of resistance in bacteria, viruses and fungi through pathways in the environment. In contrast to AMR spreading in bacterial pathogens, antifungal resistance is not thought to increase by genome transfer but only by the development of resistance *in situ*.

It seems unlikely that the environment is a major source for resistance spreading originating from medicinal use of antifungals. Therefore, the change to prescription-only use of antifungals and the assumed reduction of environmental levels by medical use has no influence on the overall occurrence of resistant strains of fungi.

Observed **antiviral resistance has overwhelmingly preponderance in immunocompromised patients**, where a unique interplay of factors including prolonged infection, higher viral replication, increased drug exposure and reduced innate immune control to eliminate resistant strains are likely to operate. Such patients will be under the care of healthcare professionals where usage will be most tightly scrutinised and controlled. In

contrast, concerns that more general availability without HCP prescription could accelerate or aggravate resistance is not supported by the observed rates in immunocompetent patients.

Potential delay in the start of antifungal or antiviral treatment due to the need for an HCP visit and prescription could therefore have an extremely negative impact on the success of treatment. The availability of antifungal and antiviral medicines without prescription is therefore of crucial importance, and to restrict rapid access to medicines would be detrimental to treat all these cases.

Community pharmacists are often the first healthcare professional a patient will talk to about their conditions. **Pharmacists can deliver easily accessible and trusted healthcare advice meaning they are perfectly positioned to promote the responsible and rational use of antimicrobials through health literacy campaigns in community pharmacies and ensure non-prescription antimicrobial medicines are appropriate for a patient's condition and need, offering alternatives when this is not the case, and onward referral where required (7).**

(7) S Essack, J Bell, A Shephard, "Community pharmacists-Leaders for antibiotic stewardship in respiratory tract infection", National Center for Biotechnology Information, National Library of Medicines: <https://pubmed.ncbi.nlm.nih.gov/29205419/>



In addition, from a socio-economic angle, significant healthcare costs would be generated if a physician consultation and prescription were required to treat all these cases. **Just in 2022, Germany, The Netherlands and Austria combined sold 8,35 million packs of topical antivirals for treatment of herpes, and 47,3 million packs of topical antifungals for nail, vaginal or oral fungal infections. The number of packs sold represents the potential number of additional medical consultations if these medicines**

were subject to a medical prescription. Due to the growing scarcity of doctors, this could result in significant undertreatment and overload of health systems. **Also, if a medicine requires prescription many patients with common conditions might not treat them until they are serious enough, due to the time and financial constrictions incurred with a doctor appointment. This would disproportionately disadvantage people who are already in communities with underserved health needs.**

Recommendations

AESGP believes that the new criteria for a **blanket prescription legal status should be restricted to antibiotics for which an AMR risk has been proven.** Such a restriction applied to all antimicrobials will not necessarily reduce environmental exposure, as patients should ultimately receive the same products. **It could, instead, significantly slow down patient access to those products and result in a requirement for higher dosages and longer-term usage due to the delay in treatment, also increasing the potential for transmission.** It would also mean significant rise in healthcare costs and significant load on health services as millions of people would have to consult a physician to obtain a prescription.

In cases where the additional barriers result in patients opting not to seek treatment, or to use unproven or unsafe alternatives, there could be a significant detrimental health impact on those patients and their quality of life.

Active substance of environmental concern – PBT, vPvB, PMT, vPvM

Directive - Art. 51(f)

Parameters such as PBT or PMT are hazard-based classifications, which do not necessarily indicate an environmental risk. Since a risk assessment is required by law for all new APIs, the risk can be determined through the established environmental testing and assessment procedures. **Therefore, automatic restrictions for compounds with PBT/vPvB or PMT/vPvM are not in line with the environmental risk assessment goals.**

Should an environmental risk be assessed and identified that requires risk mitigation, the **medical prescription is not appropriate to mitigate such an environmental risk, because the individual assessment would be out of the qualifications scope of the healthcare professional who prescribes.** The prescription status of medicines containing an active substance which is PBT, vPvB, PMT, vPvM, is, therefore,

not an appropriate risk mitigation measure to reduce the environmental exposure.

Residues of active pharmaceutical ingredients found in the environment are used in prescription-based and non-prescription products. Moreover, shifting to prescription-only could result in a shift to other non-prescription alternatives which, in turn, would increase use of similar medicinal products and result in a greater risk in the environment.

AESGP believes actions should be based on risk evaluation to avoid incurring in public health burdens without achieving the intended concomitant benefits intended (i.e., risk reduction). In that context, medical prescription is not appropriate to reduce an environmental risk and should be removed from the proposal.

Recommendations

A pre-requisite before authorizing a medicinal product is to provide scientific data showing a lack of threat to environment and public health.

Accordingly, AESGP believes that the new criteria for an automatic prescription legal status for medicines containing an active substance which is PMT, vPvM, PBT, vPvB should be removed.



ENVIRONMENT

The pharmaceutical industry, including the non-prescription medicines sector, recognizes and understands concerns regarding the presence of pharmaceuticals in the environment (PiE). The industry is committed to playing its part to address these concerns and is actively engaged in managing and controlling the impact of PiE. To this end, the Eco-Pharmaco-Stewardship (8) framework (that applies the widely accepted principles of product stewardship) was developed and is being implemented. Furthermore, companies are implementing appropriate controls and wastewater management (9) throughout the manufacturing process to address concerns.

Non-prescription medicines are often the first choice for patients/people because they enable them to manage symptoms of a wide range of common illnesses. However, an inevitable consequence of patients taking their treatments (whether prescription or non-prescription), traces of pharmaceuticals can find

their way into the environment. It is therefore essential to assess the potential impact that pharmaceuticals can have on the environment. This is why, since 2006, producers must include an environmental risk assessment (ERA) when seeking approval for human medicines.

The ERA is indispensable in assessing the potential environmental risk of pharmaceuticals and we support proportionate efforts to strengthen ERA requirements. For that reason, we propose an extended ERA to proactively address and manage the environmental risks associated with the patient use of human medicinal products (10).

We do, however, have significant concerns about the proportionality and potential for negative unintended consequences of the environmental provisions in the Proposal for a Directive on the Union code relating to medicinal products for human use. These concerns are outlined below.

Definition of 'risks related to the use of the medicinal product'

Directive - Art. 4

The definition of 'risks related to the use of the medicinal product' has been extended to include '*undesirable effects on public health due to the release of the medicinal product in the environment, including antimicrobial resistance*'. This is a move that, we believe, could potentially have an **indirect negative impact on citizens,**

if medicines are refused solely because of environmental concerns (without also considering positive human health benefits) and if no opportunities are given for actions to be taken to mitigate potential environmental risks.

Recommendations

AESGP believes the **extended definition is too broad** and, if implemented, could threaten the core benefit-risk approach of the human medicinal products' authorisation system, which goes against the objective expressed by the legislator with the new legislative package.

Decisions to minimise the environmental impact should always lead to proportional risk mitigation measures, with due consideration of clinical priorities and positive benefit/risk assessments that ensure EU citizens get access to the healthcare products they need.

(8) AESGP, EFPIA, Medicines for Europe, "Eco-Pharmaco-Stewardship" Brochure : https://aesgp.eu/content/uploads/2022/01/EPSC-BROCHURE_CARE-FOR-PEOPLE-OUR-ENVIRONMENT.pdf

(9) AESGP, EFPIA, Medicines for Europe, Technical Guidance Document "Responsible Manufacturing Effluent Management": https://aesgp.eu/content/uploads/2023/04/Responsible_Manufacturing_Effluent_Management_Technical_Guidance_updatedV04-20012023.pdf

(10) AESGP, EFPIA, Medicines for Europe, "Proactively managing the environmental risks associated with the patient use of human medicinal products: an extended Environmental Risk Assessment (eERA) proposal ": https://aesgp.eu/content/uploads/2023/04/EFPIA-eERA_BROCH_V08.pdf



Article 22 of the Commission's proposal foresees the following elements of concern:

1. The ERA indicating whether the medicinal product or any of its constituents is PBT, PMT, vPvB, vPvM or are endocrine active agents (Paragraph 2)
2. Risk mitigation measures in the ERA to avoid or limit emissions to air, water and soil of pollutants listed in Directive 2000/60/EC, Directive 2006/118/EC, Directive 2008/105/EC and Directive 2010/75/EU (Paragraph 3)
3. The ERA extension to the manufacturing stage of the production of antimicrobial substances (Paragraph 4)

Regarding **paragraph 2**, the inclusion of CLP criteria to define the scope of the ERA, the ERA guideline that EMA currently implements is sufficiently tailored to the anticipated environmental exposure scenarios for APIs. The data that is submitted under other legislation requirements, needs only to be consulted when filing for dual - or multi-use APIs. This results in a richer database for the API than would otherwise be available under the EMA guideline. **The expansion of ERA scope will be difficult to implement beyond the APIs.**

Regarding **paragraph 3**, the risk mitigation measures in the ERA to avoid or limit releases of substances listed under specific legislation should clearly state that **MAHs and MAAs can account for risk mitigation, in addition to other measures, through the implementation of advanced wastewater treatment, currently proposed under the Urban Wastewater Treatment Directive.** This is imperative so as not to unreasonably restrict patient and consumer access to medicines, further burdening healthcare systems, whilst wastewater treatment plant upgrades are implemented.

Regarding **paragraph 4**, the reason behind the ERA covering the entire life cycle is justified by the possibility of antimicrobial leakage, thus contributing to the current

global threat of antimicrobial resistance (AMR). Nonetheless, we would like to draw attention to the possibility of unintended consequences arising from the implementation of Article 22.

There are consequences of extending environmental protection requirements to manufacturing for antimicrobials. This expansion would be difficult to implement and would lead to an increase in the resource burden on regulators, reduce flexibility in the supply chain, have potential impacts on global manufacturing, whilst negatively impacting patients' access to medicines. The risk to human health from traces of antimicrobials in the environment (from manufacturing or any other source), germs resistant to them and genes that cause resistance traits can currently not be quantified (see Box **"Contribution of environmental compartment to AMR"** in previous chapter, page 7).

A recent publication (11) states that "Currently, there is no agreed-upon method for how to develop regulatory values such as EQS and PNECs protective against AMR". Without a standardised method for the derivation of resistance based Predicted No-Effect Concentration (PNECs) for all antimicrobials, we believe a robust regulatory evaluation of the risks caused by AMR cannot currently be conducted in a scientifically reliable way.

We would like to prevent the negative impact of implementing a hazard-based approach in the absence of sufficient risk-based science that would further hinder access to medicines for patients. To avoid this, we suggest including an environmental management system and a risk-based approach to assessing and controlling manufacturing waste streams focusing on antibiotics.

Over the last decade, the AMR Industry Alliance has developed an antibiotic manufacturing standard (12) including science-based PNEC targets for risk assessments to effectively control antibiotic releases from operations and supply chain networks. It requires an environmental management system and risk-based ap-

(11) Marlene Ågerstrand, Henrik Josefsson, Ann-Sofie Wernersson & D. G. Joakim Larsson, "Opportunities to tackle antibiotic resistance development in the aquatic environment through the Water Framework Directive": <https://link.springer.com/article/10.1007/s13280-022-01828-7>

(12) AMR Industry Alliance, "Minimizing risk of developing antibiotic resistance and aquatic ecotoxicity in the environment resulting from the manufacturing of human antibiotics": https://www.amrindustryalliance.org/wp-content/uploads/2022/06/AMRIA_Antibiotic-Manufacturing-Standard_June2022.pdf



proach to assessing and controlling antibiotic manufacturing waste streams, and adherence to the Alliance's published Predicted No-Effect Concentrations (13).

We would welcome the opportunity to share the learnings from the AMR Industry Alliance before extending the ERA to the manufacturing stage of other antimicrobials than antibiotics.

Recommendations

The industry proposes a different approach to strengthening the ERA requirements: an **Extended Environmental Risk Assessment (eERA)** (14) should be the main regulatory tool for assessing environmental risks of APIs, as it is crucial to not only consider environmental risks at the **point of a market application but also post-authorisation and across products containing the same active pharmaceutical ingredient (API)**.

The proposed changes to ERA will not address known issues such as repetition of studies, inconsistent and conflicting ERA conclusions and non-equitable testing burdens on individual companies which are unforeseen at the point of application unlike the eERA approach.

ERA of medicinal products authorised before 30 October 2005

Directive - Rec.71, Art. 23

The pharmaceutical industry welcomes the proposal to establish a programme for the submission of ERAs for legacy human medicinal products which would use a risk-based approach to prioritise ERAs for the pharmaceuticals most likely to present a risk to the environment.

We believe that the Innovative Medicines Initiative (IMI) projects **iPiE** (15) and **PREMIER** (Prioritisation and Risk Evaluation of Medicines In the Environment), two European-funded research projects, can play an important role in the prioritisation programme.

The IMI **PREMIER** (16) project aims to improve models that can predict the exposure and the effects of APIs. The outputs may also be applied to screen new APIs to advance drug candidates for development that are less likely to be problematic from use and disposal perspectives. For drugs already in development the project can predict environmental testing needs. **PREMIER** will also increase the transparency and accessibility of environmental data to all stakeholders.



The consortium in **PREMIER** will establish a public database of environmental information that uses studies of existing APIs and science-based tools to identify APIs with potential risks to the environment.

The industry strongly supports the introduction of a transparent web portal for environmental data and risk assessments. Such data sharing is considered imperative to increase the transparency of ERA decisions and the relevant data.

The prioritisation of testing of legacy APIs and the development of intelligent testing methods (to decrease animal use) continues to be a priority for the pharmaceutical industry and the European Commission through the IMI. IMI **PREMIER** is also working towards delivering an optimized set of tools for testing and assessing environmental exposure without relying on animal testing.

(13) AMR Alliance Science-Based PNEC Targets for Risk Assessments: https://www.amrindustryalliance.org/wp-content/uploads/2023/02/AMR-Table-1-Update-20230222_corrected.pdf

(14) AESGP, EFPIA, Medicines for Europe, "Proactively managing the environmental risks associated with the patient use of human medicinal products: an extended Environmental Risk Assessment (eERA) proposal": https://aesgp.eu/content/uploads/2023/04/EFPIA-eERA_BROCH_V08.pdf

(15) iPiE—Intelligent Assessment of Pharmaceuticals in the Environment: <https://www.imi.europa.eu/projects-results/project-factsheets/ipie#:~:text=The%20goal%20of%20iPiE%20is,the%20>

(16) **PREMIER**—Prioritisation and Risk Evaluation of Medicines in the Environment: <https://imi-premier.eu/>



Recommendations

AESGP believes that the **IMI PREMIER project**, scheduled to end in 2026, would be instrumental to help prioritize legacy compounds presenting a risk and should be taken on board.

Inter-agency cooperation and increased interlinkage across non-pharma legislations

Directive - Rec. 69, Rec. 71, Art. 22, Art. 23

We are seeing legislation linked to environmental, food, chemical and climate issues increasingly impacting the development, manufacture and supply of medicines. **It is important to note that the legislative dossiers mentioned in the draft proposal are all presently under revision and the interlinking impacts are unclear.**

It is important not to unnecessarily increase the burden on data generation or the ERA methodology. We support that other EU legislations offer opportunities to compensate shortcomings in ERAs. However, the phrasing of the text indicates that a submission will be automatically refused if the ERA does not meet certain, yet unidentified criteria.

Our industry does not oppose the ‘one substance - one assessment’ (OS-OA) concept, in principle. However, it is our perception that the impact on medicines has not been fully considered yet. The OS-OA concept must not have a negative impact on ensuring access to safe, efficient human medicines to citizens in Europe. **The uncompromised safety, efficacy and quality of a medicine should remain the most important criteria for benefit-risk based product approval.** An assessment of the risk to patients will differ strongly depending on the dose, amount, formulation and use of a pharmaceutical ingredient. The impact on simplification of the EU regulatory framework is reasonably expected to result in the removal and replacement of chemicals also used in healthcare products.

Recommendations

The industry supports **alignment across agencies and legislative dossiers** as long as **risk-based approaches are considered and all legislative dossiers are subject to the same standards**, based upon high-quality scientific data, with clear requirements for the inclusion or exclusion of studies.

The EMA should maintain overall control of the ERA for human medicines and closer collaboration with industry should also be kept.

System of ERA monographs of the ERA data of active substances

Directive - Art. 24

The commission proposal would implement a review system of ERA data (‘ERA monographs’) for authorised medicinal products. An ERA monograph shall include a comprehensive set of physiochemical data, fate data and effect data based on an assessment of a competent authority.

The industry believes that when considering Monograph systems for APIs posing risk to the environment, it will be beneficial to rely on deliverables from the IMI iPiE and PREMIER projects, which are already developing a prioritisation framework which will identify APIs contained in medicinal products authorised before 2006 that are most likely to present a risk to the environment.



Recommendations

We ask for **more clarity in the updated data requirements**, and we think that the ERA **monograph must be based upon high-quality scientific data** (Klimisch and CRED quality approach), with clear requirements for the inclusion or exclusion of studies.

Finally, we advocate for closer collaboration between the industry and the competent authorities in assessing the data.

Refusal of a Market Authorisation

Directive - Art. 47, Art. 195, Art.196

In the proposal for a Directive, the European Commission introduces the possibility to refuse, suspend, revoke, or withdraw a marketing authorisation, or prohibit supply, based on:

- environmental grounds, or
- incomplete or insufficiently substantiated ERA, or
- risks identified in the ERA that have not been sufficiently addressed.

The proposal to strengthen the ERA by introducing options for refusal and other measures on market authorisation (post approval) is a new and potentially far-reaching enhancement of the use of the ERA. As elaborated in relation to **Article 22**, the industry proposes a different approach to strengthening the ERA requirements: an **Extended Environmental Risk Assessment (eERA) should be the main regulatory tool for assessing environmental risks of APIs**. It is crucial to not only consider environmental risks at the point of a market application but also post-authorisation and across products containing the same active pharmaceutical ingredient (API).

The proposal in **Article 47** is contradictory to the **European Parliament resolution of 2020 that highlighted that marketing authorisations cannot be delayed nor refused solely on the grounds of adverse environmental impacts (17)**. In light of this EP resolution, it is concerning and inappropriate that a marketing authorisation shall be refused due to environmental concerns without considering benefit-risk considerations.

Industry agrees that an ERA is essential, however, we have concerns regarding these bases for refusal or withdrawal of an authorisation. We believe that such a measure threatens the long-lasting authorisation system of medicinal products and would negatively impact patient access to medicines for one-sided reasons. Moreover, the general option or, even worse, the requirement to suspend, revoke or vary a marketing authorisation for environmental reasons alone appears disproportionate and unjustified if not limited to major short-comings and without providing options for post-approval commitments. From our perspective, any actions taken should focus on bolstering the ERA without restricting market access based on formal deficiencies that can be appropriately addressed.

In addition, it is our opinion that these updates need to consider and align with timelines for other important legislation undergoing revision, such as the UWWTD and the implementation of WWTP upgrades across the EU. These proposals will significantly reduce the environmental exposure of pharmaceuticals in the environment and reduce the need for such stringent measures. **To this end, we ask for Article 47, Article 195 paragraph 2, and Article 196 paragraph 1(f) to be amended to state that these provisions are not applicable until 100% of all urban wastewater entering collecting systems is subject to quaternary treatment before discharge, for all agglomerations of between 10 000 p.e and 100 000 p.e [or final equivalent agreed target from the UWWTD].**

The industry agrees that in most situations, **a complete ERA should be submitted with the marketing authorisation application (MAA) and would be supportive of steps to ensure that this occurs**. However, there are certain, critical instances where, despite best inten-

(17) European Parliament, MOTION FOR A RESOLUTION on a strategic approach to pharmaceuticals in the environment: https://www.europarl.europa.eu/doceo/document/B-9-2020-0242_EN.html



tions, it is not possible to provide a complete ERA or an ERA without an identified risk. Clarifications are required on what would constitute an incomplete dossier, insufficiently substantiated ERA or acceptable mitigation risks.

Taking into account the definition (**Article 4**) for an ERA to cover risk prevention, limitation and mitigation mea-

asures, these new provisions will lead to the possible delay or prevented access of patients to medicines that could be appropriate for their medical needs. Furthermore, the extended definition of the 'risks related to use of the medicinal product' threatens the core benefit-risk approach of the medicinal product authorisation system for human use, which is driven primarily by protection of human health.

Recommendations

When an ERA based on worst-case assumptions indicates a potential risk, **appropriate binding and time constrained post-authorisation measures should, instead, be used** to give applicants the opportunity to address the potential concerns without delaying patient access to medicines.

Imposed post-authorisation studies

Art. 87

The proposal for the Directive is considering the implementation of a post-authorisation environmental risk

assessment study when a concern about environmental or public health risks has been raised.

Recommendations

Clear criteria on what constitutes a valid environmental concern should be established to minimise unnecessary post-MA obligations. In doing so, the industry calls for clearer provisions on what constitutes permissible use of post-authorisation commitment periods to be able to provide additional data where an updated ERA is required due to the identification of data which suggest a medicinal compound may present a serious risk to the environment.



SHORTAGES

Regulation - Art. 116, Art. 117, Art. 121,
Art. 130, Art. 132

The pharmaceutical industry, including the non-prescription medicines sector, are committed to avoid medicine shortages and, whenever unavoidable, mitigate the effects on end-users in close collaboration with regulators and healthcare professionals. Shortages are of particular concern when they affect medicines for which no or limited alternatives are available, and where interruption of supply will result in a potential risk to public health.

The European Commission's structured dialogue on medicines supply has showed that shortage mitigation and management measures need to be adapted to the specifics of each situation, such as therapeutic area, category of product and presence of alternatives on the market, among others.

AESGP therefore calls for future legislation to build on these findings and look for proportionate solutions for each specific situation in order to ensure the availability of medicines. Priority should be given to critical products, with high potential medical impact (i.e., life-threatening conditions), no alternatives on the market and with a potential risk of shortage.

In the case of non-prescription medicines, because substitution is possible (even if assisted by a pharmacist) and because alternatives exist in most situations (with the same or another active principle for the same indication), any shortage of a product will have little to no impact on the outcomes of self-treatment. Shortages of non-prescription medicines only happen in rare circumstances, such as during the recent coronavirus pandemic. Due to a variety of supply chain strategies, companies have usually been able to manage a shortage in supply of a particular ingredient.

Currently only a few European countries monitor shortages of non-prescription medicines proactively (notice period currently is 2 months), because of the low risk and impact of shortages. For example, in countries where such data is available, like in Belgium, only 1% of the medicine shortages reported to the Belgian Medicines Agency correspond to products with non-prescription status. Likewise, in Spain, reported shortages of non-prescription medicines are under 5% when compared to medicines subject to medical prescription. Consequentially in the vast majority of the cases of non-prescription medicine shortage reports no action is taken by regulators given the variety of alternatives available on the market.

AESGP believes that notification of shortages of non-prescription medicines should be done no later than 2 months prior to occurrence and should be limited to those medicines that are included on the critical medicines list, either national or EU-wide. It is projected that the vast majority of potential disruptions to non-prescription medicines supply that would be reported six months in advance would be resolved before they manifest. The proposed six-month notice and shortage mitigation plan would generate a significant amount of information traffic to authorities and would significantly increase workload to MAHs, for no material gain in non-prescription shortage risk reduction or elimination.

Most non-prescription medicines have alternatives on the market and are easily substitutable by a pharmacist at the point of dispensing. Therefore, **the new requirement for Shortages Prevention Plans (SPP) should be restricted to non-prescription medicines that are listed in the critical medicinal products list.** This would ensure efficient use of resources by regulators and MAHs. Further, MAHs must be able to determine commercially confidential information when submitting both SPP and Shortage Mitigation Plans. Information identified by MAHs as commercially confidential must be treated as such by the Competent Authority.

In case a critical non-prescription medicine is at risk of supply shortage, we are concerned with the explicit power of MSSG to recommend inventory management and diversification of suppliers. Supplier networks are carefully built to ensure that non-prescription medicines are always available. Diversification of suppliers, if mandated by MSSG, would be a complex undertaking, as this would require not only sourcing and integrating new suppliers but also the ongoing engagement of these new suppliers to create a sustainable business relationship with them.

AESGP is of the view that regulators should not direct MAHs to enter specific business relationships. Similarly, with respect to inventory management, increasing stocks above the necessary levels especially in the case of seasonal non-prescription medicines eventually increases the cost and is associated with significant risk of products in stock expiring. Expired stockpiles would have negative economic, and sustainability impacts due to the cost and effect of disposal.



Recommendations

In general, AESGP believes that notification of medicine shortages and shortages prevention and mitigation plans should be based on a **criticality assessment of a medicinal product from a patient outcome and health system perspective** and consequentially aimed at medicines on critical medicines lists that do not have any alternatives:

- In case of a suspected shortage of a non-prescription medicine included on the critical medicines list either nation- or EU-wide, marketing authorisation holders should report it to concerned national competent authority concerned no later than 2 months prior to occurrence.
- Shortages Prevention Plans (SPP) should be required for those non-prescription medicines that are listed in the critical medicines list.
- In case of critical non-prescription medicines, MSSG should NOT have a specific power to mandate inventory management and diversification of suppliers. There is a wide variety of supply chain strategies that companies deploy when mitigating shortages and they should be further empowered to adopt the most appropriate strategy in each individual case.



INCENTIVES FOR SWITCHING FROM PRESCRIPTION TO NON-PRESCRIPTION STATUS

The change of legal status of medicines from prescription to non-prescription legal status (switch) is a significant form of innovation in the non-prescription medicines sector that plays a major role in patient care by expanding the range of self-care treatments available.

Non-prescription status makes it easier and quicker to access treatments that are effective and safe, empowering people to manage their own health, with or without the support of health care professionals, or medical appointment. **By freeing up HCPs time, away from managing ailments that can be appropriately self-diagnosed and self-treated, switch allows refocusing on conditions that require their support and the exercise of their professional judgment.** This efficient use of expert qualified resources, in turn, helps ensure the long-term sustainability of EU healthcare systems.

The Commission proposal does not contain adequate measures to incentivize switch to unlock the benefits for all EU stakeholders and create a vibrant, stimulated environment to attract further innovation and investment within the EU. The proposal for a Directive maintains the provision of the current legislation, which awards one-year of data exclusivity “*where a change of classification of a medicinal product has been authorized on the basis of significant pre-clinical tests or clinical trials*”. **One year of data protection is insufficient in a sector where the typical delay between the marketing authorization approval and launch is several months, and this is even more true in cases of seasonal conditions.**

Furthermore, the current provisions only cover “**significant pre-clinical tests or clinical trials,**” ignoring the value of other types of evidence, such as behavioural studies or real-world evidence, that can be material in assessing (and reaching a conclusion on) a switch’s safety, effectiveness, and healthcare contribution. It’s worthwhile noting that since the introduction of data exclusivity for switch, it has only been granted twice, in the context of the tamsulosin switch in the UK and the one for ulipristal via the centralized procedure. In the case of the ulipristal switch, the medicinal product was still under the original data and market exclusivity from the prescription MA and therefore did not benefit from the additional data protection.

Extending data protection period from one to three years

AESGP believes broadened access to effective therapies with well-established safety profiles through non-prescription legal status is a major contributor to patient self-care and sustainable health systems, and therefore the level of data protection (for switch innovators) needs to be proportionate to the value to EU society.

Improving patient care through better self-care is a clear EU priority, and one avenue for achieving this is by enhancing access to medicines available as non-prescription. First-in-class switches represent a major opportunity to contribute to better patient care by improving future access to innovative treatments. However, these switches often involve complex considerations and industry may need to generate additional data or develop new tools to sufficiently demonstrate safe selection, usage and risk mitigation measures, necessitating substantial investments by the applicant.

The lack of adequate incentives in the EU to support switch innovation is clearly evident when compared with other markets, such as the United States and Japan, where three-year data protection is granted and puts the EU at disadvantage for ensuring continued focus on innovation and investment by the self-care sector. The consumer healthcare sector operates in a healthy competitive environment, with strong competition between brand and generic companies, and the ability of other players to quickly enter the off-patent market after the originator. This rapid market entry can increase the commercial risk of investing in development and being a first mover, particularly when there is a high level of commercial investment involved in switch applications and market launches.

Extending data protection to major contributions to patient care supported by real-world evidence

As mentioned above, a change in classification always requires significant assessment and investment by the applicant, including in additional studies. These studies may be “traditional” non-clinical or clinical studies, but could also include observational studies, pharmacy-based studies and other types of real-world studies, appropriate for confirming the benefits of broadening



access and mitigating any incremental risk(s) of non-prescription use to ensure the benefit/risk balance remains positive. This is particularly valid for innovative switch applications. **Safety and efficacy in the target indication and patient population has already been well established and thus generally no new non-clinical or clinical studies are needed.** Thus, the criteria applied for consideration of market exclusivity apply an unfair and disproportionate threshold.

The utilization of real-world data, notably patient-generated health data, has the potential to yield novel evidence to substantiate the feasibility of a

switch. It is therefore imperative to expand the scope of eligible data for granting data protection, particularly considering the transformative potential of digital advancements and the evolving data landscape.

A legislative framework that lays out the broad nature of the acceptable data and evidence, and the conditions for data protection, to both switch sponsors and subsequent applicants, would help ensure legal certainty in the EU market for both innovators and followers and help to incentivize legal status “switch” applications.

Recommendations

Incentivizing switch is crucial for improving access to new non-prescription treatments and advancing the self-care agenda in the EU.

AESGP believes that a **longer data exclusivity period** should be considered in cases where new, pivotal evidence is generated that is material to the switch approval. This **period should be extended from +1 year to +3 years**, to ensure continued stimulation and attractiveness of EU innovation in line with other global markets such as USA and Japan.

Extending the protection period to three years and **broadening the nature of acceptable data would encourage switch investment and broaden EU citizen’s access to innovative non-prescription medicines.** Introducing these measures can enhance the environment for self-care, benefit citizens, and ensure the sustainable use of healthcare resources while keeping pace with international standards.



PRODUCT INFORMATION

Directive - Art. 62, Art. 63, Art. 64, Art. 65

The new legislative package provides for Member States to decide whether medicinal products should include a paper or an electronic leaflet, or both.

AESGP believes that the future of product information is digital due to many of its benefits (e.g., facilitating quick updates, multiple language availability and readability, accessibility to information, addition of multimedia and other tools to help increase medication and health literacy). Therefore, AESGP recommends that an orderly and harmonized approach to transition to digital product information is taken, and that the access to essential information for responsible use of a medicine is ensured at all times to aid self-selection of non-

prescription medicines and self-treatment. This should be done by a step-wise approach, for example, by **shortening and simplifying the current paper patient information leaflet and introducing a more detailed digital information support as the first step.**

The “Member State by Member State” implementation phase should be as short as possible and consider pragmatic implementation needs such as in the case of multi-country packs. **Having a common EU harmonised introduction of the digital product information across all Member States will reduce access asymmetries for the users of medicines and avoid overburdening regulators and companies.**

Recommendations

When fully implemented, digital technology will enable industry to **communicate product information timelier and more effectively to users of medicines.**

AESGP believes that **legislation should pave the way for the transition to the digital leaflet** and aim to always ensure the continuous access to essential product information. This should be done by shortening **and simplifying the current patient information leaflet** and **introducing a more detailed digital information support as the first step** and ultimately by removing the paper leaflet.



REGULATORY AGILITY

Streamlining of procedures

AESGP welcomes that there are no substantial changes to marketing authorisation procedures access and related requirements. In addition, **we welcome the proposed changes aiming to reduce regulatory burden, with marketing authorisations now granted for an unlimited period and the sunset clause removed.**

AESGP also welcomes the **proposed modernization and digitalisation of the Variations system.**

AESGP welcomes the **shortening of the procedure for granting a marketing authorisation** for medicinal products is completed within a maximum of 180 days (from 210 days) in application of Article 30. AESGP emphasise the need for a swift validation of the application.

Mutual recognition Procedure (MRP) and Decentralised Procedure (DP)

Directive – Art. 34(3), Art. 36(4)

With regards to the Mutual Recognition Procedure and Decentralised Procedure, we noted the new requirement proposed in **Article 34(3)** and **Article 36(4)** for MAHs to inform all countries that a procedure is starting. **We believe this new notification will create additional burden for both industry and authorities and a lot of background noise for countries being notified of all new procedures in addition to those where National Competent Authorities are already involved as Concerned Member State or Reference Member State.** It also defeats the principle of the MRP and DCP where Member-States are chosen to best fit the launch of the specific product.

In case of opt-in for public health reasons, as further laid out in **Articles 34(3)** and **36(4)**, the additional 30 days will delay the procedure. **In case additional national required documents must be added to the dossier this will slow down even further the procedure. We believe this new measure is disproportionate and burdensome since there are already existing mechanisms, such as the Zero-Day MRP and Repeat Use Procedure (RUP) which enable the ability to expand national marketing authorisations to new Member States who need these medicinal products.** It is also not in line with the goals of simplification and agility.

Recommendations

AESGP proposes to **remove the requirement to notify all Member States at the start of a decentralised or mutual recognition procedure** as well as the member state opt-in provision.

As mentioned, there are other mechanisms available which would improve access and availability.



Change of Summary of Product Characteristics (SmPC) by Competent Authority without Marketing Authorisation Holder (MAH) involvement

Directive - Art. 43(4) - Regulation - Art. 166

The **Article 43(4)** of the Commission proposal for a Directive and **Article 166** of Commission proposal for Regulation state that the competent authority of the Member State or EMA *may consider and decide upon additional evidence available, independently from the data submitted by the marketing authorisation holder. On that basis, the summary of product characteristics shall be updated if the additional evidence has an impact on*

the benefit-risk balance of a medicinal product. We believe that the proposed change completely flips the paradigm of the European Marketing Authorisation system where the MAH is responsible for the content of the MA and update. AESGP considers it is essential to involve the MAH(s) or applicant(s) in this process as it already is established in practice.

Recommendations

AESGP proposes that the proposed provision include the **requirement to consult MAH on any changes to the SmPC** as MAH remain responsible for the content and update of MA.

Well-established use application (WEU)

Directive - Art. 13

The well-established use (WEU) route of obtaining a marketing authorization in the EU is defined by Article 10a of Directive 2001/83/EC. **This route may be used when the applicant can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least 10 years, with recognized efficacy and an acceptable level of safety in which case test-and-trial results shall be replaced by appropriate scientific literature.**

Currently, if there is a reference product available in the EU for the proposed medicinal product, an applicant can choose to follow the generic application route or the WEU route.

The Commission proposals removes the current Article 10a and replaces it with article 13. **The new Article 13 allows the bibliographic route to be used only under specific conditions:**

- No established reference product is available, and
- Active substances have been in well-established use within the Union for at least 10 years, with recognized efficacy and an acceptable level of safety, and for the same therapeutic use and route of administration.

According to the current requirements, the WEU route require the applicant to demonstrate relevance of the proposed product, to those described in the literature. **Given that for non-prescription medicinal products, a reference product is likely to exist, the proposed change in legislation will force companies to follow the generic (including hybrid) route.** This means an obligation for companies to perform bioequivalence studies on active ingredients that have been used widely for many years and have therefore an established safety and efficacy profile.

As a result, registration of a new non-prescription medicinal product in the EU may become significantly more limited for the following reasons:

- Product development timings and costs will be significantly higher, driven by the cost and timeline of bioequivalence studies.
- The development of new pharmaceutical forms or combinations of known active substances will be associated with substantially increased resource efforts, potentially analogous to the development of new active substances.
- Reference product may not be marketed anymore, even if a registration can be traced, making it impossible to follow the requirements led out in this article.



- Any modernization of old formulations will most likely be limited to changes that do not alter bioequivalence.

Aside from the above, the ethical aspects of conducting unnecessary clinical trials on substances that already have proven efficacy and safety, need to be considered. Although non-prescription products are generally very safe and efficacious, taking part in a clinical trial is ne-

ver risk-free and can cause avoidable inconvenience to both trial participants and medical professionals.

Overall, it is anticipated that the proposed legislation change will, as a result, decrease the range and availability in the future of important self-care products that meet the evolving needs of patients and consumers.

Recommendations

AESGP proposes to **maintain the well-established use application route** as it is enshrined in the current legislation to allow for continued innovation in the self-care sector.

This would furthermore avoid any unnecessary clinical trials.



REAL-WORD DATA AND REAL-WORLD EVIDENCE (RWD/RWE)

Directive - Art. 4

AESGP believes that the new legislative package lacks fit for purpose definitions of RWD and RWE for all types of medicines (innovative, generic, non-prescription) that are not restrictive in terms of data sources.

Non-prescription medicines are indeed not prescribed nor reimbursed and therefore have no routinely collected data (outside of pharmacovigilance data). **RWD should therefore be defined as “data used for deci-**

sion making that are not collected in conventional randomized controlled trials”.

RWE has the potential to inform authorities decision on medicinal products, notably on the change of legal status, safety, and effectiveness. **RWE should therefore be defined as “evidence regarding the usage and potential benefits or risk of a medical product derived from analysis of RWD”.**

Recommendations

AESGP believes that the new legislative package should **introduce fit for purpose definitions of RWD and RWE which recognise all data sources and therefore is also suitable for non-prescription medicines.**

RWD definition:

“data used for decision making that are not collected in conventional randomized controlled trials”

RWE definition:

“evidence regarding the usage and potential benefits or risk of a medical product derived from analysis of RWD”



The Commission proposal for Directive in **Article 21** removes the obligation to submit Risk Management Plans (RMP) for generics and biosimilars, provided that there are no new risk minimisation measures for the reference product, and provided that the marketing authorisation of the reference product continues to exist at the time of the new application submission.

For other product categories, a risk-based approach should be applied to the Risk Management Plan (RMP) based on existing API safety informa-

tion and indication. Requirement for an RMP should, for these categories, be delinked from the legal basis to minimise unnecessary work for both authorities and industry. For instance, a full marketing authorisation application based on an off-patent API should benefit from the same waiver as a generic application that is no longer required to provide an RMP. Even in the absence of a reference product, the safety profile of medicinal products of well-established use are monitored in a risk-proportionate basis through the PSUR process.

Recommendations

AESGP welcomes the proposal to remove Risk Management Plans obligations for some medicinal products, which, we believe **should be extended to medicinal products of well-established use where there are no existing or new significant safety concerns** and where there is no additional pharmacovigilance plan or risk minimization in place.

We consider that in these cases, any safety concern are already sufficiently followed-up or addressed in PSURs.

MANUFACTURING AND QUALITY

The scope of the Directive extended to include starting material

Directive - Art. 1(3)

In **Article 1, sentence 3** of the Directive, the scope of the Directive is extended to include starting materials, with a particular reference to Chapter IX “Manufacture and Import”. In **Article 188, sentence 5(e) and (f)**, the supervisory authorities are also given the option of inspecting manufacturers and importers of starting materials.

We consider that supplier qualification is sufficiently regulated in the Good Manufacturing Practice (GMP) Guide (in *Active Pharmaceutical Ingredient Manufacturing EU GMP Guide Part 2, Chapter 16* and in *Finished Pharmaceutical Ingredient Manufacturing EU GMP Guide Part 1, Chapter 7*). We propose to adapt the mentioned articles accordingly and to delete “starting materials” from the scope of application.

Recommendations

AESGP proposes to **remove starting material from the scope of the proposed Directive**, so that specifically Chapter IX “Manufacture and Import” does not cover starting material.

The requirement to have a Wholesale Distribution Authorisation (WDA) expanded to include obtaining medicinal products by financial transactions

Directive - Art. 166(1)

In **Article 166, paragraph 1(c) and (d)**, the scope of “obtaining” and “supplying” medicinal products – and the corresponding need for an EU wholesale distribution authorisation – is expanded to include also financial transactions. **This seems to be an unnecessary shift from current practice and not in the least would cause serious and unnecessary inefficiencies.** The current focus on physical flow, disregarding financial flow, was recently confirmed in the latest version of Annex 21 to the EU GMP Guidelines, applicable since August 2022. The proposed shift towards including financial transactions, would mean that a currently allowed

model of financial flow via Switzerland or UK and physical flow within the EU/EEA is no longer possible because such ex-EU and EEA entities cannot get an EU WDA. **Requiring financial and physical flow to be aligned would create huge inefficiencies as well as concerns from a sustainability point of view.**

AESGP considers that the current rules, disregarding the financial flow, sufficiently safeguard the safety and quality of medicinal products in the EU/EEA.





About

The Association of the European Self-Care Industry (AESGP) is a non-profit organisation which represents the manufacturers of non-prescription medicines, food supplements and self-care medical devices in Europe, an area also referred to as consumer healthcare products.

Contact

Association of the European Self-Care Industry (AESGP)

Avenue de Tervueren 7, 1040 Brussels (Belgium)

+32 2 735 51 30 | info@aesgp.eu | www.aesgp.eu