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30 Jul 2024 | **Interviews**

Environmental Risk Assessments In The EU Pharma Revision – What You Need To Know

by David Ridley

Marketing authorizations for OTC medicines could be rejected if their environmental risk assessments do not meet new requirements proposed within the EU pharma legislation revision. HBW Insight speaks to regulatory law experts Tine Carmeliet and Eline D'Joos to find out what you need to know about the new rules.

European pharmaceutical companies, including many consumer health firms, are looking at much stricter requirements in terms of environmental risk assessments (ERAs) for their medicines as part of revisions to the region's pharmaceutical legislation.

TINE CARMELIET

Marketing authorization applications could be rejected if their ERAs do not pass muster, the European Commission has proposed, while regulators could impose post-marketing conditions of use relating to environmental considerations, such as prescription-only status.

In this exclusive interview, regulatory law experts Tine Carmeliet and Eline D'Joos outline what ERAs are, what is new in the pharma revision proposals and what might happen to companies that don't comply with the new rules.

Carmeliet and D'Joos – who are senior associate and associate at law firm A&O Shearman respectively – also explain how the proposals relate to other parts of the EU Green Deal, for example with regards to wastewater pollution and to endocrine disruptors within the "one substance, one

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ELINE D'JOOS

assessment" approach within the European Union.

Nothing is happening fast, however. As they point out, the EU Council has not published its negotiating position, so trilogue procedures cannot commence.

And while the European Parliament's position for the trilogues is fixed, new MEPs elected recently may influence these negotiations for better or worse – not that the public will know much about these discussions, as they happen behind closed doors.

The parliament's negotiations on the package are being led by its environment, public health and food safety committee (ENVI), which has a new chair and composition following the parliamentary elections in June.

At its 23 July "constitutive meeting," the ENVI chose Antonio Decaro of the S&D parliamentary group to chair the committee, which will hold its first ordinary meeting on 4 September. The new rapporteurs for the pharma package will also be chosen in the autumn, according to the ENVI secretariat. (Also see "*EU Pharma Reform, SPCs, Compulsory Licensing Among Parliament's 'Unfinished Business'*" - Pink Sheet, 22 Jul, 2024.)

Q **What are environmental risks assessments (ERAs), and what is currently required of pharmaceutical companies operating within the European Union?**

A An ERA aims to evaluate the risks to the environment arising from the use and/or disposal of medicinal products, and, in case of potential risks, propose adequate mitigation measures to minimize the impact and effect of those risks to the environment. This can include measures to minimize the amount of medicinal product released into the environment, specific risk-minimization activities to be taken by the patients and appropriate labelling, to facilitate the correct disposal of the product by patients and healthcare professionals. A risk mitigation measure could be, for example, medical prescription with disposal in special containers. (Also see "*Why Did The European Commission Decide All Antimicrobials Should Be Rx-Only?*" - HBW Insight, 16 Nov, 2023.)

Since 30 October 2005, applicants are already required to include an ERA in their marketing authorization application for all new medicinal products, regardless of the procedural route taken (centralized mutual recognition, decentralized or national procedure). This means that the studies and testing for the ERA should be carried out during the development of the product. The EMA has published technical guidance on how to conduct a stepwise assessment of the potential environmental risks and hazards, and report on the findings.

Q **What are the proposed changes to ERAs within the pharma revision?**

A The current ERA requirement was considered insufficient to address environmental concerns, as the ERA is a one-time snapshot at the time of the marketing authorization application. In addition, there are today no real consequences associated with the (lack of) quality of the ERA or (non-)compliance with the identified risk measures. We therefore expect the existing requirements for the ERA to be supplemented with additional information obligations and responsibilities for pharmaceutical companies, including extending the scope of the ERA to antimicrobial resistance and, if the proposal of the European Parliament is adopted, the entire product lifecycle including manufacturing (as opposed to only use and disposal). (Also see "*Environmental Risk Assessments To Loom Larger In EU Drug Reviews*" - Pink Sheet, 23 Jul, 2024.)

With respect to centralized marketing authorizations, the European Public Assessment Report will include a summary of the ERA and the studies and results submitted by the applicant, and the assessment of the ERA by the EMA (deleting all commercially confidential information). The ERA requirements will also have more teeth and non-compliance can lead to serious consequences with respect to a company's marketing authorization (application) and its medicinal products on the market.

Q **In general, what are consequences of not following these new rules?**

A Under the current legislation, the grant of a marketing authorization is not dependent

on having a complete and sufficiently precise ERA, nor can the competent authorities take away a marketing authorization if the holder does not follow the measures proposed in their ERA. As one of the criticisms on the current ERA obligations was precisely this lack of penalization, the proposed new rules contain several far-reaching consequences that the competent authorities can take. For instance, the marketing authorization may be refused, revoked, suspended or modified, and the medicinal products may be prohibited or withdrawn from the market if the ERA is incomplete or insufficiently substantiated, or there are serious environmental or public health risks which are insufficiently addressed by the applicant. (National) penalties could also be imposed for lack of compliance with the legislation in case the ERA is not updated or post-authorization studies relating to the ERA are not performed.

However, the proposed new rules are not clear on the criteria for assessing the quality of an ERA and therefore seem to leave quite some room for discretionary assessments by the authorities on what is considered "insufficient", leading to uncertainty for companies as to the fate of their marketing authorization and product launch. The EMA plans to develop additional scientific guidelines to support companies in conducting their ERAs, which will hopefully address this industry concern.

Note also that the European Commission and European Parliament are not fully aligned here, and the Parliament has toned down the penalization clause by making the refusal or revocation of a marketing authorization more difficult, in comparison to the Commission's proposal.

Q **How does the pharma review ERA relate to other parts of the Green Deal, for example the Urban Wastewater Directive?**

A With the Green Deal, the European Commission intends to reduce net greenhouse emissions and make Europe the first climate-neutral continent. To achieve this, different legislative measures are being adopted, such as the Water Framework Directive, the Environmental Quality Standard Directive, the Groundwater Directive, the Urban Wastewater Treatment Directive, the Drinking Water Directive and the

Industrial Emission Directive. (Also see "*Infographic: EU Sustainability Legislation All In One Place*" - HBW Insight, 19 Feb, 2024.)

The proposed new rules on the ERA are seen as complementary to the different environmental risk assessments and liability regimes imposed under these other legislations. The pharmaceutical ERA addresses the risks of medicinal products specifically to the environment as a whole (and not just to, for example, water). The reason for this is that residues of medicinal products can enter the environment during their manufacture, use and disposal and have indeed already been found in surface and ground waters, soils and animal tissues across the EU.

Q **What kind of consumer health products might be endocrine disruptors, and what will MA holders of such products medicines need to do under the new rules?**

A There are a variety of consumer health products that may include endocrine disruptors, such as cosmetics, disinfectants, pesticides, natural health products and non-prescription (OTC) medicinal products. But only those consumer health products that qualify as a "medicinal product" are subject to the ERA under the pharmaceutical legislation. Note however that several consumer health products have their own specific legislations, such as the Cosmetics Regulations and the Plant Protection Products (pesticides) Regulation which can include environmental assessments and measures of their own. (Also see "*'The Party Is Over': Green Claims Requirements Among Many Regulatory Changes Coming To EU Cosmetics*" - HBW Insight, 6 Mar, 2023.)

Some OTC medicinal products, such as antifungals and antiseptics, could be considered endocrine disruptors and are therefore subject to an ERA, with specific rules regarding endocrine active substances. The ERA has to identify whether the medicinal product or any of its ingredients or other constituents are an endocrine active substance. The pharmaceutical legislation itself does not include detailed rules on endocrine active substances but the technical guidelines of the EMA include a specific assessment strategy and tailored testing for endocrine active substances.

Q **How onerous are the ERA requirements for antimicrobials?**

A Special ERA requirements indeed apply to medicinal products with an antimicrobial mode of action. The ERA should (i) indicate whether the medicinal product or any of its ingredients or other constituents is an antimicrobial and (ii) include an evaluation of the risk for antimicrobial resistance selection in the environment caused by the entire manufacturing supply chain both inside and outside the EU, the use and the disposal of the medicinal product. The ERA requirements for antimicrobials therefore are more stringent compared to other medicinal products. Conditional marketing authorizations and post-authorization studies may also require further investigation on antimicrobial resistance.

Q **Will medicines already on the market need to do ERAs, and if so, what if there is insufficient evidence of safety because the evidence is too old, for example (i.e. doesn't meet current standards) or doesn't exist?**

A Medicinal products currently on the market and which were authorized after 30 October 2005 should have already been the subject of an ERA under the current pharma legislation at the time of their initial marketing authorization application. The marketing authorization holder must update this ERA and implement necessary mitigation measures (if any). The proposed new rules extend the ERA obligation to even older products already on the market (authorized prior to 30 October 2005) that have not yet been the subject of an ERA, insofar as they are identified as "potentially harmful to the environment".

The EMA guidelines provide guidance on how to rely on a literature review and use publicly available data for medicinal products that have already been in the market for a while, to avoid repetition of testing. If identified serious environmental or public health risks are insufficiently addressed, the supply of the medicinal product may be prohibited or the product may have to be withdrawn from the market.

Q **How will "potentially harmful to the environment" be assessed?**

A The EMA will determine the scientific criteria for the assessment of "potentially harmful to the environment" using a risk-based approach. No specific details on these criteria are known yet, but the EMA's current technical guidelines provide a set of criteria to be assessed when submitting an ERA and might give some indication as to what the EMA deems relevant.

Q **Once you've done an ERA, is that it? Or is there ongoing work to do?**

A Under the current legislation, there are only few occasions where updates to the ERA are required. For instance, renewals of marketing authorizations do not require a new ERA, but so-called type II variations to marketing authorizations (i.e. major changes affecting the quality, safety or efficacy of the medicinal product) require an update to the ERA in case of an anticipated increase in the environmental exposure of the medicinal product.

Under the proposed new rules, the ERA will have to be continuously updated after the grant of the marketing authorization, for example if new information emerges that could lead to a change of conclusions of the ERA. This means that the potential risks or effects of the medicinal product on the environment and public health need to be monitored during the whole lifecycle of the medicinal product, not just prior to its launch. This includes information on environmental monitoring, new or updated ERAs under other EU legislation, eco-toxicity studies and environmental exposure data. In addition, the competent authorities can make the grant of a new or even existing marketing authorization conditional upon conducting additional post-authorization ERA studies and collecting monitoring data or information on use.

Q **What are the next steps for the pharma review, and specifically ERA – will there be further negotiation around this point? Will the elections impact this area do you think?**

A As part of the legislative process, the European Parliament and the Council of the European Union first adopt and publish their position and proposed amendments to the European Commission's initial legislative proposal. Afterwards, the trilogues

commence until an agreement on the final text is reached.

The Parliament already adopted its position on 10 April 2024, prior to the June elections. As such, the Parliament's going-in position for the trilogues is fixed, but the less or more strict views of the new MEPs might implicitly steer the discussions during the trilogues, which happen behind closed doors with very little transparency for the public. The Council on the other hand has to date not yet provided its position. As the Council's position will have to cover not only the ERA but the entire pharma package, and it is known that certain member state delegations have conflicting views on a number of topics that are part of the pharma package, for instance on regulatory exclusivity, the Council's position is expected around the end of 2024/beginning of 2025. (Also see "*Longer Exclusivity Periods For EU Centralized Rx-To-OTC Switches? Commission Says No*" - HBW Insight, 25 May, 2023.)

The ERA itself might also become a point of conflict as certain delegations within the Council might want to limit the weight of the ERA as a decisive factor in the grant or revocation of a marketing authorization (which is in line with the Parliament's proposed amendments).