efpia
European Federation of Pharmaceutical Industries and Associations

POSITION PAPER ON DRUG REPURPOSING

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EXECUTIVE SUMMARY

Drug repurposing[1] can provide avenues to explore new uses of older, off-patent medicines, for example in areas where no treatments are available, or research gaps exist, thus benefitting patients affected by conditions for which limited, or no therapeutic options are approved and/or development is economically challenging.

The COVID-19 pandemic provided numerous examples of repurposing. Even though only a small proportion of drugs proved to be effective[2], these efforts showed the value of repurposing as one of the means to rapidly explore treatment options in an area for which no treatments were available. With the support of digital technologies such as Artificial Intelligence (AI) including Machine Learning (ML), utilisation of register data, data sharing platforms developed under various public-private partnerships, and DARWIN EU, drug repurposing is expected to become more widespread and efficient in the coming years.

In the context of the review of the General Pharmaceutical Legislation (Dir 2001/83 and Reg 726/2004), EFPIA proposes principles for the effective use of repurposing in exceptional situations, e.g. public health crises, or conditions for which no or few medicines are currently authorised. These uses should maintain the highest standards of safety and efficacy for patients, and they should not represent a substitute to the development of novel treatments.

- The EU regulatory system was developed to safeguard public health and patient safety while at the same time encouraging world-class innovation. It sets high scientific standards for quality, safety and efficacy. **Careful consideration is needed to ensure that a specific regulatory pathway for repurposed medicines meets the same evidentiary standards for the authorisation of medicines.**

- **Implementing labelling changes that have not been thoroughly reviewed, discussed and agreed with the marketing authorisation holder (MAH), will not serve the interests of patients.** The expertise and capacity of the MAH as the developer and having the deepest knowledge of the medicinal product, is essential to inform and support the entirety of the scientific ecosystem relating to the medicine for prescribers and patients. Inclusion in the summary of product characteristics (SmPC) and patient information leaflet of new indications based on data generated by a third-party under a repurposing framework necessitates careful consideration and consultation with MAHs.

- **The incentives framework in the EU should equally consider the interests of healthcare systems and the interest of creating a vibrant innovation ecosystem**, where repurposing may play an important part but does not replace the development of novel therapies. The RDP incentive for repurposed products outlined in Article 84 of the proposed Directive would inevitably be subject to the same challenges that impact other indication-specific protections for certain products (e.g. Paediatric Use Marketing Authorisation –PUMAs-), particularly economic off-label ('cross-label') use and pricing and reimbursement hurdles at the national level.

- **The focus of a potential new framework to stimulate repurposing should be on conditions for which limited treatment options are currently authorised or which are associated with high morbidity and/or mortality despite available medicines**[3]. Repurposing solely for economic reasons will discourage innovation. If pricing and reimbursement mechanisms do not incentivise or reward new indications and full development efforts for new molecules, opportunities for innovation will be lost and innovative pharmaceutical companies may decide to move their investments to regions that are willing to incentivise innovation. This would be contrary to the goal, shared by all stakeholders, of improving access to medicines for European patients, and detrimental to the region's strategic autonomy and its capacity to develop and manufacture medicines.

1 - See Chapter I – Definition of Repurposing.

2 - Over 400 drugs were tried, four of them showed established effectiveness and endorsement from professional societies (baricitinib, remdesivir, dexamethasone, and tocilizumab), while others presented mixed or even negative results. Source: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00270-8/fulltext

3 - As it is the focus of the EMA & HMA pilot: https://www.ema.europa.eu/en/news/repurposing-authorised-medicines-pilot-support-not-profit-organisations-academia

DEFINITION OF REPURPOSING

While no common definition exists in literature[4], innovative industry understands 'Repurposing' as the process of bringing on label new therapeutic uses for already known medicines which are out of patent and regulatory data protection, where for example a third party (academia, non-profit organisations, etc.) generates regulatory grade evidence of a potential new use.

This definition excludes abandoned compounds, new uses for drugs in development, and recently approved drugs where development activities are still being carried out by the originator. Particularly the last two are part of the normal life cycle activities of a product and already contemplated in the pharmaceutical regulatory framework in the form of line extensions and new indications.

OPPORTUNITIES

EFPIA took part in developing the framework that is currently being tested in a pilot[5] conducted by EMA and a number of NCAs to support the repurposing of products out of data protection and market exclusivity periods, and out of basic patent/supplementary protection certificate (SPC) protection.

The aim of the pilot is to support not-for-profit organisations and academia to gather sufficient evidence on the use of an established medicine in a new indication to have this new use formally authorised (through a relevant MAH) by a regulatory authority, thus making new treatment options available to patients. EMA and the national medicines agencies are providing regulatory support via Scientific Advice, to help clarify with these stakeholders the data requirements to generate a data package robust enough to support a future regulatory application. In the framework, the approached MAHs can decide whether to take the application forward or not.

EFPIA is supportive of this pilot as it is intended to operate: applied to products out of basic IP protection and data exclusivity, on a voluntary basis for MAHs and limited to conditions for which no or few medicines are currently authorised or which are associated with high morbidity and/or mortality despite available medicines. EFPIA believes the STAMP repurposing pilot is key to test the framework for repurposing based on data generation by third parties and the results should be taken into consideration for any policy options related to repurposing.

More broadly, EFPIA considers public and private partnerships may be a further instrument in addressing research gap areas: there might be unexplored potential of current medicines to be developed for more indications that may have therapeutic rationale in rare diseases. Projects such as REMEDI4ALL[6], supported by Horizon Europe funds, highlight opportunities for more systematic and efficient repurposing of medicines.

EFPIA anticipates these efforts will bring more order and structure into the field of medicines repurposing. We recognise the benefit of repurposing efforts as a complement to – not a replacement of – the development of novel therapies and stand ready to be part of these important stakeholder discussions.

4 - Langedijk et al, 2015: https://doi.org/10.1016/j.drudis.2015.05.001

5 - The pilot was launched to test the repurposing framework developed by the Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP), which is composed of representatives of EU Member States; together with EMA and stakeholders from not-for-profit organisations, patients, healthcare professionals, industry, health technology assessment bodies and payers.

6 - https://remedi4all.org/about-us/

PRINCIPLES FOR AN EFFECTIVE APPLICATION OF REPURPOSING

This section expands upon the four principles outlined in the executive summary, understanding repurposing as the process of bringing on label new therapeutic uses for already known medicines which are out of patent and regulatory data protection, where for example a third party (academia, non-profit organisations, etc.) generates evidence of a potential new use.

REGULATORY STANDARDS

The EU regulatory system was established to protect public health and ensure that patients in the EU have access to high-quality, effective and safe medicines. To this end, it enforces high scientific standards and requires robust data from clinical trials to generate reliable evidence.

Real-world data and real-world evidence (RWD/E) are increasingly used by developers along the lifecycle of a medicine and are slowly becoming more broadly accepted by regulators. RWD/E will likely play an important enabling role in repurposing. The innovative industry in Europe welcomes this progress and highlights the need to apply the same high evidentiary and quality standards to repurposed medicines, as to all medicines, so as to avoid the creation of a two-tier regulatory system which may compromise patient safety.

The MAH is responsible and liable for its product and all indications. The MAH is obliged to ensure that all efficacy standards and safety/pharmacovigilance requirements are met, regardless of the origins of its development i.e., whether or not the MAH was provided with external scientific evidence for the repurposed indication in the SmPC. This has significant consequences in terms of the MAH's legal liability position, its regulatory responsibilities and costs, and may be especially challenging if the new, repurposed indication is in a therapeutic area outside of the normal scientific focus of the company.

For the reasons stated above, EFPIA considers any potential policy options that would lead to easing of obligations in terms of evidentiary or quality requirements for non-commercial entities (e.g. academic) inappropriate, given the purpose of these obligations is to safeguard public health. On the other hand, EFPIA considers the policy options that provide increased regulatory support, scientific advice, support schemes to non-commercial entities (incl. reduction/deferrals/waivers of fees) appropriate, as these would positively impact the public health and allow the broad research ecosystem to operate efficiently and in alignment to one another (commercial vs. non-commercial).

LABEL UPDATES

As part of the lifecycle management of a medicine, innovative companies update the SmPC and the patient information leaflet when new efficacy or safety evidence is generated or collected. The MAH is and remains fully responsible for their product in use for all its authorised indications, regardless of the origin of the data supporting them.

Implementing labelling changes which have not been thoroughly reviewed, discussed and agreed with the MAH, will not serve the interests of patients. The expertise and capacity of the MAH as the developer and having the deepest knowledge of the medicinal product, is essential to inform and support the entirety of the scientific ecosystem relating to the medicine for prescribers and patients.

Additionally, repurposing a medicine in a new indication outside of a company's therapeutic focus is a high-risk and costly endeavour, and the imposition of new obligations in this respect would weaken the ability of innovative pharmaceutical companies to manage their portfolios and to set their own medical and commercial priorities. The inclusion of new data or indications developed by a third-party under a repurposing framework necessitates careful consideration and consultation with marketing authorisation holders.

For the decision on the addition of a new indication, MAHs will have to consider a multitude of factors, including expertise in the therapeutic area, critical liability issues and pharmacovigilance responsibilities, potential impacts on HTA and payer discussions, and manufacturing and supply chain constraints.

Externally generated evidence may be useful or valuable to a MAH in support of the development of a new indication. However, in most cases, obtaining regulatory approval for a new indication still requires significant additional investments, for example to generate the volume and quality of data necessary to support such approval. Therefore, the MAH must be involved in the process for scientific assessment of the evidence for repurposing, and only the MAH can finally determine whether it should apply for a variation to authorise the new indication, taking into account all of the above c ritical factors.

MAHs are in any event obliged to keep their product labels up to date with the current scientific knowledge, in accordance with Directive 2001/83/EC[7], and the proposal for the revised Directive[8]. Any additional obligation to include new indications based on data generated externally by a third-party is not justified but rather disproportionate. For these reasons, we strongly advocate for a non-binding system for scientific assessment of the totality of evidence for repurposing.

INCENTIVES

The incentives framework in the EU should have the objective to create a vibrant innovation ecosystem. Repurposing may play an important part of this ecosystem as a complement, and not a replacement, of the development of novel therapies.

Current EU law provides the opportunity for the innovator MAH to be granted a one-off additional year of marketing protection (8+2+1), if they add a new indication bringing significant clinical benefit to patients (as determined by the regulator) within the first 8 years after the original MA. This possibility is retained in the proposed revised legislation, within the data protection period for the product concerned. Since repurposing (as defined in the STAMP pilot) applies to older products with no remaining patent-based protection or RDP, these are not eligible for this +1 year of RDP.

The RDP period outlined in the proposed Article 84 (Directive), providing four years of data protection in the case of repurposing products no longer under patent/SPC or RDP, may be valuable in some cases. However, it would be subject to challenges such as economic off-label use of competitor/ generic/biosimilar products, and difficulties in obtaining pricing and reimbursement for the new, protected indication.

IMPACT ON INNOVATION

Repurposing can provide avenues to explore new uses of off-protection medicines, for example in areas where no treatments are available, thus benefiting patients affected by conditions for which no therapeutic option is approved, and for which development is economically challenging. However, the value of this type of innovation needs to be recognised in pricing and reimbursement decisions.

In addition, the value of differentiated innovative medicines and the accompanying evidence needs to be recognised and rewarded in order to incentivise relevant R&D efforts in areas of unmet need. If payers predominantly prefer to reimburse older medicines for economic reasons, these may become price references in cost-effectiveness analysis for new medicines in an area. As a consequence, opportunities for innovation will be lost, with repercussions for patient access, jobs and the research ecosystem[9].

Repurposing can be a useful instrument to benefit patients affected by conditions for which limited, or no therapeutic options are approved, by exploring new uses of older, off-patent medicines. For an effective implementation, it is key that high scientific and regulatory standards are met, marketing authorisation holders are involved along the process, the right incentives are in place, and repurposing is not used as an economic replacement for the development of novel treatments. EFPIA stands ready to be part of shaping the regulatory framework to support repurposing efforts.

7 - See Directive 2001/83/EC – Art 23.3

8 - See Directive proposal – Art 90.3

9 - https://www.politico.eu/sponsored-content/dropping-the-dogma-europe-can-support-patients-and-innovation

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