medicines for ireland

value added medicines

a medicines for europe sector group

Advancing **Medicines Repurposing** in the EU

May 2022

Foreword

As Chair of Medicines for Ireland's Value Added Medicines Committee, I'm delighted to present this latest report, 'Advancing Medicines Repurposing in the EU' building on the 2021 published report 'Discussion Document on the Contribution of Value Added Medicines in Ireland' Value Added Medicines (VAMs) offer a wide range of benefits for patients and HCPs – from ensuring better adherence and compliance, to keeping healthcare costs down by reducing the need for patients to be moved to expensive next line therapies.

At Medicines for Ireland, we are committed to improving patient care and delivering value to the HSE and are proud to drive stakeholder engagement on this important topic. We believe that we need a new and simplified regulatory pathway for Value Added Medicines in Ireland – bringing us into line with other major European countries to ensure that our patients and healthcare system is not left behind. We also need a shift in mindset – from one that focuses purely on cost to an outlook that is centred around better outcomes for patients taking a holistic look at the whole patient journey. And we need a system that rewards innovation with appropriate incentives, whilst recognising the potential long-term value and savings that VAMs can bring to the State.

As an organisation, we hope that this report helps set out the steps being taken to advance the debate on this topic, while also helping policy makers recognise the potential long-term value and savings that VAMs can bring to the State.

Clodagh Kevans
Chair, Value Added Medicines Committee
Medicines for Ireland

Executive summary

Repurposing has emerged as an important strategy to address unmet medical need. Yet, there is still significant untapped potential for its application in the EU.

Different approaches can be applied for the generation of data supporting the repurposing of existing medicines, depending on whether the research effort is led by industry or not-for-profit organisations. The STAMP framework was recently proposed by the European Commission to support the latter, but parallel initiatives are still needed to bolster equivalent industry-led efforts.

Regardless of the chosen evidence-generation approach, marketing authorisation holders always play a key role in making repurposed medicines available to patients. Therefore, their importance should be appropriately acknowledged not only in the data generation phase but also in downstream steps, by:

- recognising Value Added Medicines (VAMs), including repurposed medicines, as a separate category of medicines in the EU legislation, with a dedicated regulatory pathway and appropriate incentives
- establishing adequate reimbursement pathways for VAMs.

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Repurposing in the EU

Repurposing (also known as repositioning) is defined as finding a new therapeutic use for an existing medicine. The importance of this strategy to address unmet need in a timely and cost-effective manner has come to prominence during the Covid-19 pandemic and is reflected in the European Commission's Pharmaceutical Strategy for Europe and Europe's Beating Cancer Plan.

There is still significant untapped potential for repurposed medicines to address unmet medical needs and bring relevant benefits to patients and society. To capitalise on this opportunity, we need strategies that bolster all the steps needed to achieve the repurposing of a medicine, starting with the pre-clinical and clinical research that supports the use of a medicine in a new indication. The significant time and resources needed to complete the necessary regulatory steps to include a new indication on the label of an existing medicine as well as the following downstream processes, such as manufacturing set-up and market access assessment, must also be taken into account.

Bringing new indications on label is essential for the success of any repurposing strategy

When a new indication is found for an existing medicine, it is extremely important that this new use is registered on the medicine's label. Failing to do so leads to missed opportunities in the assessment of the medicine in a real-world setting and can have a negative impact on patients both in terms of increased out of pocket costs and standards of care.

The following issues have been associated with off-label use of medicines (Figure 1):

- Lack of official evaluation of the scientific evidence. Use of Real-World Data and Real-World Evidence has allowed an increasingly thorough understanding of the effectiveness of medicines, i.e., their ability to do more good than harm under normal care circumstances. When a medicine is used off-label, these data are not available.
- Lack of data collection systems. When a new indication is registered on the label of a medicine, data collection systems can be put in place to monitor its safety (pharmacovigilance) and effectiveness (e.g., patient registries). This is not possible for indications that are not listed on the label.
- Liability issues. Prescribers have greater liability when administering a medicine off-label, which might prevent some of them from prescribing medicines when the indication is not registered.
- Reimbursement issues. Payers are generally not willing to refund medicines for indications that have not been officially validated by regulators, i.e., added to the label. This may lead to significant out-of-pocket costs for patients, potentially preventing access to medication when patients cannot afford the therapy they are prescribed.
- Supply issues. As the off-label use of a medicine is not quantified through accurate reporting and data collection as done for on-label use, this approach may result in a less accurate prediction of volumes needed, potentially contributing to supply disruption due to underestimation of demand.
- Patients' concerns. Patients may not feel comfortable when using a medicine for an indication that has not been explicitly approved by regulators. This may prevent them from receiving the therapy they need or potentially affect their outcomes through the nocebo effect.

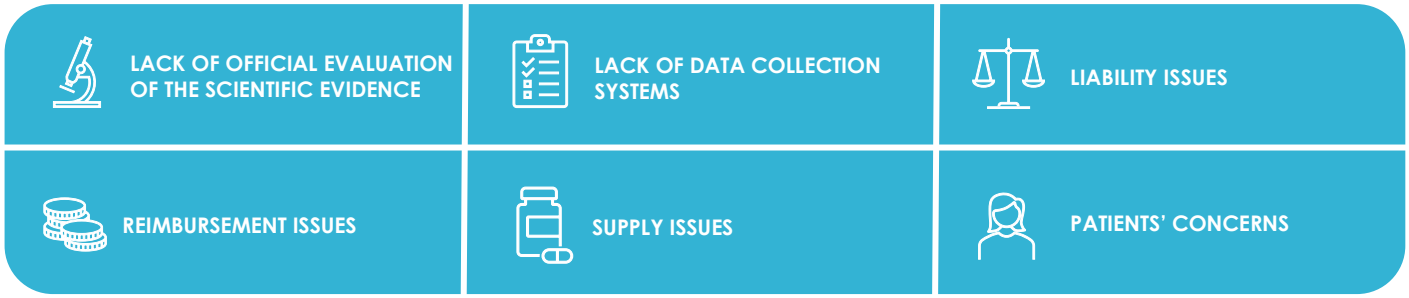

Figure 1: Downsides of off-label medicines use

Importantly, only the marketing authorisation holder (MAH) can request that a new indication is added to the label of a given existing medicine. The MAH is also responsible for pharmacovigilance.

Different stakeholders can contribute to data generation efforts for repurposing

Marketing authorisation holders (MAHs) are frequently involved in the early stages of repurposing, but research efforts may also be led by other stakeholders such as not-for-profit and academic organisations. Depending on when industry engagement starts, different approaches can be implemented to generate the data that inform the repurposing of a medicine in the EU:

a) Late industry involvement: the STAMP pilot project and the possibility of creating an indications pool can enable champion-driven data generation

Academic and not-for-profit research initiatives aimed at finding new indications for existing medicines can contribute significantly to the identification of therapies that meet unmet medical needs or provide improvements over existing treatments for certain medical conditions. EMA and the Heads of Medicines Agencies (HMA) launched the STAMP pilot project to support the repurposing of medicines. This initiative aims to support not-for-profit organisations and academia to gather or generate sufficient academia to gather or generate sufficient evidence on the use of established medicines in new indications, to have this new use formally authorised by a regulatory authority.

Within the STAMP pilot, a champion (not-for-profit organisation or academic institution) that is interested in bringing a new indication on the label of an off-patent medicine available in the EU and has obtained data to back this initiative can:

- Directly contact an EU-based MAH for the medicine they intend to repurpose as soon as the evidence supporting the use for a new indication has been generated. This process will be facilitated by EMA or a National Competent Authority (NCA) through access to the EMA article 57 database.
- Contact an EU-based MAH after having received regulatory and scientific advice to support appropriate data generation and analysis, including to fill gaps that would preclude regulatory approval of the new indication. Through the STAMP pilot, scientific advice fees can be reduced or even waived. Each organisation is then responsible for disclosing relevant scientific advice to the MAH.

As the first initiative addressing the repurposing of medicines initiated by not-for-profit and academic organisations, the STAMP framework represents a significant step towards more efficient strategies for the repurposing of medicines in the EU. By supporting champions in their data generation and analysis efforts, it facilitates the development of evidence that is fit-for-

purpose for regulatory assessments. Therefore, this initiative can help bridge the gap between research and its translational applications.

Building on the current STAMP framework and lessons learnt from the Covid-19 pandemic, a possible further improvement would be the creation of an "indication pool" for repurposed medicines, where the information generated by not-for-profit and academic organisations would be centrally collected upon submission to a regulatory authority. This approach would be implemented in a similar way to what was done in the assessment of dexamethasone for use in Covid-19 patients on oxygen or mechanical ventilation, when the EMA's human medicines committee (CHMP) reviewed the Covid-19 RECOVERY trial data.

With the indication pool approach, there would be less burden on champions to actively seek an industry partner, as the evidence they generate would directly be made available to all developers who have the concerned medicine in their portfolio (or wish to do so), upon submission to a regulator.

This would result in a simpler and even more efficient process, reducing the amount of effort and resources that should be invested by champions within the STAMP framework to develop a partnership with a MAH.

b) Early industry involvement: consortia- and industry-led data generation can bring further optimisation of repurposed medicines

Involvement of industry in the early stages of the repurposing process is not incompatible with the engagement of academic, patient and not-for-profit organisations. Pooling of resources and expertise in the form of a consortium can facilitate partnerships between stakeholders and favour the exchange of information on medicines repurposing.

What differentiates such consortia from the STAMP or "indication pool" approaches is the early involvement of MAHs in the process, as opposed to research driven uniquely by non-industry partners who only later share relevant information with the MAH.

Removing the need for a champion to actively seek out potential industry partners would not only streamline and simplify the process, but also increase the chances of successfully bringing new indications on label by automatically involving multiple MAHs that would all be able to add the new indication on the label.

The early involvement of industry, either as the sole driver of data generation efforts or as part of a consortium, allows to better design the medication for its intended purpose by not only focusing on adding a new indication, but also planning needed manufacturing capacities and potentially introducing further optimisation. This can include adjusting the delivery form, changing the dosage and combining different therapies to better meet the needs of the patient community.

How repurposing can be promoted

The STAMP pilot has the potential to significantly promote research into the repurposing of established medicines. However, it alone will not suffice to realise the full potential of repurposing initiatives in the EU, as it only focuses on data generation programmes that are driven by academic and not-for-profit champions. It should therefore be complemented by parallel initiatives that bolster industry-led innovation. In practice, this means not only supporting industry-led data generation efforts but also ensuring that the role of MAHs is recognised throughout the process.
Regardless of the data-generation strategy that is applied to the repurposing of an existing medicine, MAHs play an essential role. They are irreplaceable in some of the necessary regulatory steps as they are ultimately responsible for adding a new indication on the label and they drive all downstream steps after regulatory approval.

The Value Added Medicines Group with Medicines for Europe has compiled figures illustrating the regulatory costs of repurposing, which are detailed in Annex 1 of this document. It is also important to highlight that the generation and validation of research data informing the repurposing of a medicine and completion of regulatory processes are not sufficient to make a medicine available to patients in the EU. Once regulatory approval is obtained, MAHs invest further resources and budget in downstream steps, such as manufacturing set up, commercialisation costs and applying for market access assessments. Due to the complexity and variability associated with post-regulatory processes, costs can vary greatly, making it difficult to obtain representative and widely applicable figures.

For more repurposing projects to come to fruition, we need to adapt the EU pharmaceutical ecosystem, starting with recognising the need for a tailored development approach for so-called Value Added Medicines (VAMs), including repurposed medicines. VAMs should be acknowledged as a separate group of medicines in EU legislation.

The legislative recognition of VAMs should lead to the creation of a dedicated regulatory pathway and the possibility of appropriately rewarding the investment and resources dedicated to developing a medicine based on a well-known substance, including by introducing proportionate regulatory incentives as suggested in the Value Added Medicines Group's report "Creating a European ecosystem for safe, timely and affordable patient-centric innovation" and in the Centre de Politique Européenne's recommendations for "Incentivising Pharmaceutical Off-Patent Innovation in the EU".

Creating an EU environment that appropriately recognises the importance of VAMs, including repurposed VAMs, also requires the development of fit-for-purpose reimbursement processes that consider and value the effort and commitment of MAHs in developing these medicines.

Annex 1: estimating the regulatory cost of repurposing in the EU

Marketing authorisation holders (MAHs) are frequently involved in the early stages of repurposing, but research efforts may also be led by other stakeholders such as not-for-profit and academic

organisations. Depending on when industry engagement starts, different approaches can be implemented to generate the data that inform the repurposing of a medicine in the EU:

Estimated figures for repurposing: European Medicines Agency process (CP)

Activity	Agency/Company responsible for the activity	Costs [€]	Notes
Preparation for EMA scientific advice meeting	MAH or academic/not-for-profit research institution	10-50k	
EMA scientific advice meeting	EMA (with fees paid by MAH or academic/not-for-profit research institution)	90-180k (50% meetings requiring follow-up)	These costs can be waived/ reduced if research is carried out by academics or not-for-profit organisations seeking advice within the STAMP pilot
Regulatory dossier preparation	MA holder	30-120k (generally 30-50k)	
Pharmacovigilance and RMP	MA holder	20-100k (plus development of educational materials connected with PhV and RMP up to 100k)	
Update of product information, leaflet and pack with new indication, VAM readability	MA holder	20-90k (major type II variation or line extension) + 12k translations	

Estimated figures for repurposing: National Competent Authority process (MRP/DCP)

Activity	Agency/Company responsible for the activity	Costs [€]	Notes

Preparation for NCA scientific advice meeting	MAH or academic/not-for-profit research institution	10-50k	
NCA scientific advice meeting	NCA (with fees paid by MAH or academic/not-for-profit research institution)	4-10k	Fee reductions and waivers may apply if research is carried out by academics or not-for-profit organisations seeking advice within the STAMP pilot[13]
Regulatory dossier preparation	MAH	30-120k (generally 30-50k)	
Pharmacovigilance and RMP	MAH	5-100k	This example considers Denmark or Germany as Reference Member States. Low end figures refer to 5 countries, high end figures to 20 countries
Update of product information, leaflet and pack with new indication, VAM readability	MAH	Type II variation: 25-60k Line extension: 120-210k + 2-12k translations depending on set of countries involved in DCP/MRP	This example considers Denmark or Germany as Reference Member States. Low end figures refer to 5 countries, high end figures to 20 countries. Average cost per translation ranges between 400 and 600€

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