# IMI2 JU Scientific Committee recommendations regarding Drug Repurposing

## Introduction and current business models for drug repurposing

*"Drug repurposing is the process of identifying a new use for an existing drug/active substance in an indication outside the scope of the original indication."*[1]

Drug repurposing or drug repositioning involves the use of already existing (on- or off-patent) active substances or medicines for new indications that are different from the registered indication (or original intended indications). Such new indications, especially use in other diagnoses and diseases, could have great value both for patients and stakeholders, public and private. The new indications may or may not be subject to a formal process for obtaining regulatory approval by the marketing authorisation holder.

Examples of repositioned active substances include use of sildenafil, originally developed for hypertension and angina pectoris, for erectile dysfunction based on observations made in the phase I clinical trial [1], thalidomide in multiple myeloma and lepra reactions and retinoic acid for acute promyelocytic leukaemia. Drug repurposing has also become a relevant strategy in the current COVID-19 pandemic. Searching active substances already approved for use in humans with known safety profiles for SARS-CoV-2 antiviral activity or COVID-19 disease-modifying activity could potentially fast-track their progress into clinical trials in humans to assess efficacy in infected patients [2].

New screening technologies, phenotypic screens and other methods have increased the probability of discovering potential new effects of existing medicines. Chemoinformatic approaches based on availability of structures of active substance targets and using supercomputer-based docking of known active substances is another powerful tool that may pave the way for new indications and therapeutic regimens. Pharmacogenomic approaches have improved our ability to understand active substance metabolism and thereby provide a deeper understanding of efficacy and how to individualise dosing.

There are obvious medical needs for new medicines in many small patient populations suffering from rare diseases or requiring an individualised therapeutic regime such as in precision medicine. There are also indications that could benefit from alternative therapies and where there is less development of new medicines because they are either difficult or costly to document or the patient populations are more complicated to work with or cannot be consented (children, psychiatric patients, pregnant women). Lastly, there is need for new applications in emerging infectious diseases.

"Off-label" use may in many European countries[2] be an established practice for some new indications in small patient populations (cancer precision medicine, rare diseases) and in specific domains of medicine such as paediatrics and psychiatry. However, it is generally advantageous if such "off-label" use occurs on-protocol as part of a repurposing process. Documentation of effect and safety are then systematically collected. The repurposing process should next go forward to regulatory approval for the new indication, and regulatory approval is normally a prerequisite for inclusion in clinical guidelines and for reimbursement.

[1] Definition by the European Commission Expert Group on Safe and Timely Access to Medicines for Patients ("STAMP") in their proposal for a framework to support not-for-profit organisations and academia (institutions and individuals) in drug repurposing.

[2] Off-label use may affect the liability with regard to the administration of medicinal products. Usually, the marketing authorisation holder is liable for any adverse effects arising from administration of the product but this is not the case if there is off-label use.

Pharmaceutical R&D of new molecules is costly, the average innovation process of new medicines may cost in the order of billion(s) of EUR, when sunk costs of unsuccessful development projects are also taken into account [3]. However, there is wide uncertainty on the cost of pharmaceutical R&D and consensus on elementary costing principles is lacking in the domain of drug repositioning [4]. Compared to new candidate active substances, there are several potential benefits with repurposed medicines. The preclinical documentation files as well as safety data on healthy humans from the original indication(s) will already be available and depending on the market there may also be extensive post-marketing safety data (real world evidence, RWE). Because of the above, development costs for a new indication is expected to be considerably lower and time to approval shorter. Together, there may be a win-win in research in a public-private partnership context to streamline a path for repurposed medicines for new indications.

Whilst the costs of repurposing are considered to be significantly lower compared to development of new medicines [5] third-party payers (tax-funded national health services and mandatory health insurance funds) may not sufficiently acknowledge the benefits and value of repurposed medicines, because after patent expiry their major objective is to maximise population health for a given budget by facilitating savings and re-allocations in health care budgets through generic price erosion. Furthermore, they may not want to introduce or support an indication-based pricing concept for on-patent repurposed medicines, which might represent a means to leverage the re-investment and expenditure undertaken by the marketing authorisation holder. Thus, the profitability of drug repurposing seems uncertain and this may prevent pharmaceutical enterprises to invest in new and emerging medical needs as observed in other areas of low return on investment such as antibiotics and vaccines.

There are also incentives to overcome market failure. For example, the business models for orphan indications gives both exclusivity and pricing that recognises small market size[3]. In the US there is also the Competitive Generic Therapy Approvals programme by the FDA that gives a 6-month exclusivity for the first generic use of an earlier branded on-patent medicine[4]. However, industry-led repurposing has in some cases driven prices of repurposed medicines very high while previously used off-label at low costs and may not be the only viable business model. A number of countries also have purely public initiatives set out to document use of generic drugs, biosimilars and off-label use where there is public but not private interest[5]. Also, the STAMP Expert Group has discussed a framework for drug repurposing and the involvement of not-for-profit stakeholders in their meetings from 2017 to 2019[6] and specific pilot projects are being investigated. There may also be good basis to explore public-private partnerships for repurposing, and there are examples of such partnerships such as by UK MRC Technology, Cancer Research UK and industry or the New Therapeutic Uses programme under the NIH Centre for Advancing Translational Sciences with eight pharma partners[7].

## Scope: Medical need and disease areas of relevance for repositioning on-patent and off-patent medicines

There are many fields where repurposing and expansion of indications are relevant. Notably, this is an issue that should already be considered when a medicine is approved. For example, many antibiotics are developed only for a few specific indications whereas rare and more severe infections that would require complicated clinical trials are omitted because the trials are considered to be too costly, time consuming and difficult to pursue. Thus, many antibiotics are used off-label in regards to indication and dosage

[3] https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview
[4] https://www.fda.gov/drugs/generic-drugs/competitive-generic-therapy-approvals
[5] https://kce.fgov.be/en/content/what-is-kce-trials
[6] https://ec.europa.eu/health/documents/pharmaceutical-committee/stamp_en
[7] https://ncats.nih.gov/ntu

because there is no mechanism that would account for a change in indication as long as it is not initiated by the marketing authorisation holder. Next to financial prospects there may also be other biases of what is investigated and evaluated[8] [6].

In some cases, large prescription databases have been used as a viable byway to detect potential effectiveness for repurposing agents e.g. within psychiatry. However, this has not been followed up systematically nor evolved to state-of-the-art or generally used to inform pharmaceutical policies although some European countries use such data to evaluate safety and inform changes in clinical practice[9].

## A role for public-private partnerships in this context

In views of the difficulties, it is obvious that public-private partnerships such as IMI can contribute to innovative solutions via research in this specific area of medicine. A few examples may illustrate this.

The IMI project iABC showed that bronchiectasis patients are at disadvantage because most active substances have not been tested in this population and extrapolation from cystic fibrosis might not be sufficient. Of further note, the IMI projects STOPFOB and PD-MIND also support drug repurposing efforts where there is medical need.

Additional contextual information is gathered on pathway biology through 'omics' approaches. Pathogenic activity in particular pathways are now increasingly associated with a particular disease. The IMI projects AETIONOMY and PRECISEADS strives to redefine disease taxonomy based on pathway biology which illustrates the movement from disease taxonomy shifting from an organ focus to a pathway biology focus [7].

Similarly, real world evidence, the focus of the IMI project GETREAL, may play an increasing role in the collection of data for new indications for approved medicines.

## Further solutions

The existence of registries and use of patient-reported outcomes could constitute an important basis for the evaluation of efficacy and safety of medicines in small populations in rare diseases where there are incentives but also in somewhat higher prevalence indications, particularly if data aggregation could happen across Europe or worldwide to facilitate rapid data aggregation and to quickly adapt to novel concepts. Active scouting for new indications and extraction of data on their actual off-label use could also become relevant.

A specific and emerging example that mainly concern on-patent medicines would be in the area of precision cancer medicine. Increased knowledge of the biology driving cancer development and progression in the individual patient has led to sub-stratification of previous large patient groups. Genomic medicine with identification of hot spot mutations, tumour mutational burden, overexpression, gene amplifications and inversions in the tumour compared to patient germ line forms a basis for the current practice in molecular tumour boards used at present in clinical trials to match the right active substance or medicine to the patient.

[8] There may also be clinical trial biases such as in selection of patient populations (e.g. gender, age) that limit the indication of investigated drugs.

[9] https://www.oecd.org/health/health-systems/Using-Routinely-Collected-Data-to-Inform-Pharmaceutical-Policies-Analytical-Report-2019.pdf

Development of repurposed drugs for use in precision medicine is, in general, hampered by the fact that the development process to evaluate new indications becomes costly and inefficient when a whole array of diagnostics is required to select which patients should receive a particular drug. Furthermore, strong selection criteria can ultimately lead to small cohorts treated with each drug and slow patient recruitment into clinical trials. However, the efficacy may potentially be very good in such small strata of patients (thus yielding good "return on investment" from a health cost perspective) [8].

## Recommendations of the IMI2 Scientific Committee

The IMI2 Scientific Committee recommends strategic discussions and research on how to improve the business model for drug repurposing and how to advance such strategies for on-patent and off-patent medicines. Furthermore, for both types of medicines there may be distinct benefits of promoting research in public-private collaborations to facilitate drug repurposing and evaluation and approval of new indications. However, the path forward may be different in the two areas of on-patent and off-patent medicines because of the IP issues and the economic interests; special caution may be required in the on-patent area because aligning public and private interests may require innovative concepts to be developed.

Repurposing of generic and on-patent terminated drugs may be applied for small patient populations, rare diseases or neglected diseases where there are no other treatment options and *de novo* development of new costly drugs is not profitable. It may also be used to address global health issues such as the current search for drugs with SARS-CoV-2 antiviral activity as mentioned above where a rapid response is required and repurposing of safe available medicines for a new indication could advance faster than *de novo* drug development. However, systematic efforts in this area may require the establishment of public-private joint efforts and a defined path or platform to bring projects forward and promoting and incentivising drug owners to provide access to already available data.

On this background, a number of topics could be explored through research, policy-making and establishment of guidelines that may facilitate further development of repurposed drugs:

- Clinical trial designs and systems that are scalable in Europe and allow for aggregation of safety and efficacy data.
- **Collaborative efforts where development and evaluation of innovative molecular diagnostics and screening for recruitment into clinical trials of suitable precision medicine designs are arranged and payed for (as screening goes before inclusion). ***
- **High quality and in-depth research on patient cohorts to understand responses and resistance patterns and find additional biomarkers for optimal stratification. ***
- **Harnessing real-world evidence (RWE) and registry data as well as access to electronic health records and other real world drug use data for long-term effectiveness assessment, for arranging control cohorts for precision medicine studies (that cannot be randomised) and for retrospective analysis and validation of biomarkers versus clinical outcome using established biobanks. Digital avatars would also potentially be useful in this context. ***
- Systems implemented to gather RWE data that allows long-term follow up of patients and health technology assessment (HTA) methodological approaches to assess effectiveness both at the level of individual drugs and at the level of the algorithms and clinical decision support systems used to select optimal treatments.

- Merge existing or establish electronic prescription databases and health registries to investigate whether agents with *a priori* preclinical or theoretical evidence base may have beneficial effects when applied in indications previously not tested. Data-driven approaches could also be used to identify subgroups of patients responding to different combinations of treatment.
- **The full implementation of precision cancer medicine with molecular diagnostics available to all patients, will produce huge amounts of data. These data, fed into the appropriate algorithms and clinical decision support systems, will make possible the selection of the best combination of cancer medicines for each individual patient, with a potentially huge impact on cancer treatment. ***
- Development of more effective HTA assessment processes that take into account small cohorts and that put out a predictable path to approval for reimbursement. For example: could data be aggregated on-line world wide (viewable for investigators, sponsor and regulators) and approval/HTA assessment processes initiated at a time a threshold is reached? Such a framework might need to be adapted to potential solutions found to resolve how to tackle repurposing. If left to the conventional procedures and to the marketing authorisation holders alone, the potential of some substances could otherwise be missed due to lack of financial incentives and for regulatory reasons.
- Pilot on the level of evidence to be provided and acceptable for HTA of premium priced repurposed medicines in different areas. Set out a predicable path to reimbursement as a recommendation to national authorities.

For some of the above items there may be joint interest among public and industry stakeholders and a public-private partnership could be beneficial or prove added value (indicated in bold and by *). Other topics may be more suited for public research, analysis and policy making.

On behalf of the Scientific Committee

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