



EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Health systems, medical products and innovation
Medicines: policy, authorisation and monitoring

STAMP 4/20

**STAMP Commission Expert Group
10 March 2016**

Subject: Repurposing of established medicines/active substances

Agenda item 3

The repurposing of established medicines or active substances can allow the marketing of the established medicines for a new indication. Such developments can be important to provide new therapies and therefore contribute to the access to medicines for patients.

The attached background note has been prepared by the UK Medicines and Healthcare products Regulatory Agency to provide a basis for STAMP's consideration of the issue and has raised questions regarding to: the need to establish terminology; barriers to repurposing of established drugs; regulatory routes or incentives; and, whether there are particular disease areas that need support.

Members of STAMP are invited to consider the questions raised in the attached background note and to share the national experience of repurposing of established medicines, in particular, if there are national activities promoting or supporting repurposing of established medicines.

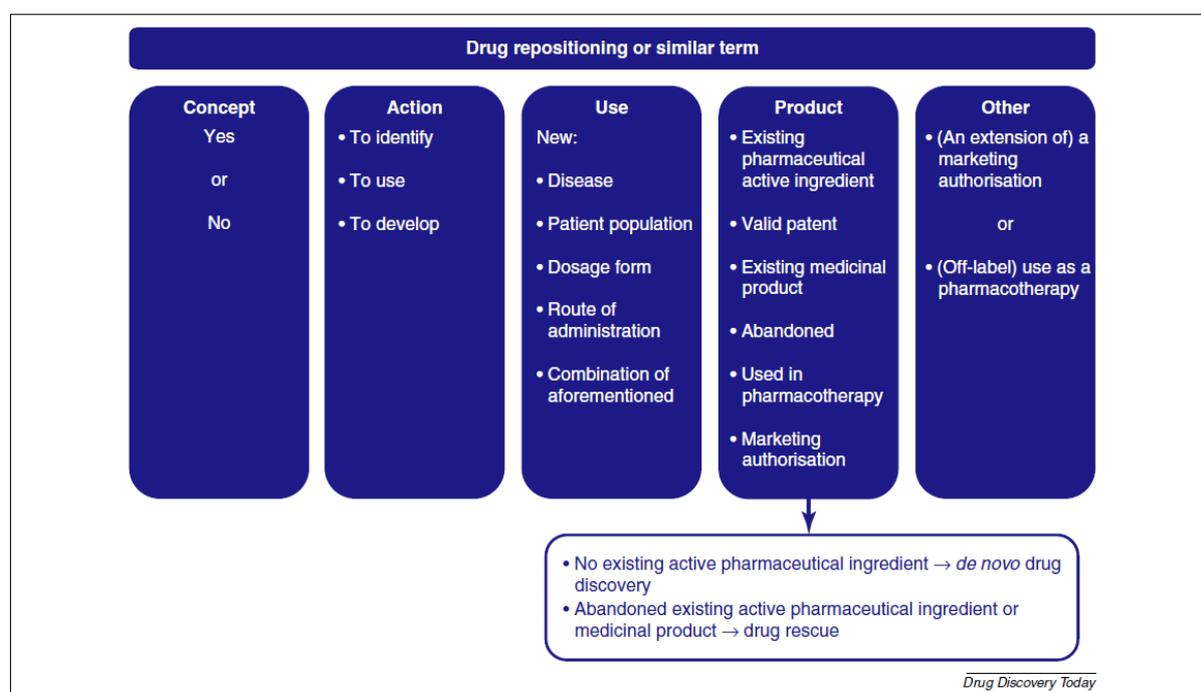
Safe and Timely Access to Medicines for Patients (STAMP)

Background note on re-purposing of established medicines (MHRA)

Introduction

Drug repurposing (also referred to as repositioning, re-profiling) is the process of identifying a new use for an existing drug in an indication outside the scope of the original indication. Drug re-purposing constitutes an emerging and dynamic field of drug development, often led by academic units and medical research charities. Repurposing includes finding new therapeutic uses for already known drugs (repositioning), developing different formulations for the same drug (reformulation), and creating new combinations of drugs previously used as separate products (novel drug combination). Increasingly, established drugs are also being combined with medical devices for novel indications (e.g. embolic beads CE marked for local delivery of chemotherapeutic agents in a variety of tumour settings, but outside the terms of the SmPC). Identifying repurposing opportunities comes from a variety of processes including knowledge mining of existing scientific databases, in silico approaches, in vitro and in vivo experiments, clinical observations, epidemiology and post-hoc analysis.

Choices regarding what to include and exclude in a definition of drug repositioning or a similar term. (Figure 3: Langedijk J et al., 2015)



Re-purposing of older drugs in areas of unmet medical need could lead to faster development times, reduced costs and risk for pharma, as drug repurposing commonly starts with compounds that have already been tested in humans and many have demonstrated an acceptable level of safety and tolerability. In addition, in the field of nanotechnology, products that have previously had their development discontinued for safety concerns in particular indications may now be considered as potential candidate molecules for further study and eventual human use. Current regulatory incentives for re-purposing of established medicines include:

New therapeutic indication for a well-established substance

Paragraph 5 of Article 10 of Directive 2001/83/EC states that where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication. This provision has been under-utilised, at least in the UK, presumably due to either the lack or the perceived lack of benefits to the pharmaceutical industry.

Paediatric-use marketing authorisations (PUMA)

Introduced by the Paediatric Regulation (Article 30 of Regulation (EC) No 1901/2006), PUMA is a type of marketing authorisation covering indication(s) and appropriate formulation(s) for the paediatric population. It was designed to promote paediatric development of already authorised products which are no longer covered by a supplementary protection certificate (SPC) or a patent qualifying for a SPC. A PUMA benefits from the 8+2 year period of data and market protection. However, since launch there have been only been a handful of successful applications (e.g. Hemangirol (propranolol) used to treat children with proliferating infantile haemangioma) and the provision is under-utilised.

Orphan drug designation

The EU offers a range of incentives to encourage the development of medicines intended for small numbers of patients and this includes a 10-year period of market exclusivity for orphan designated products. To qualify for orphan designation, a medicine must meet a number of criteria including that the prevalence of the condition in the EU is not more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development. There are numerous examples of established drugs given orphan designation in a 're-purposed' setting based on the prevalence criteria and these include:

- Ibuprofen solution for patent ductus arteriosus
- Ciclosporin (inhaled) for graft rejection after lung transplantation
- Heparin for treatment of idiopathic pulmonary fibrosis
- Hydrocortisone (MR) for treatment of congenital adrenal hypoplasia
- Sodium valproate for treatment of 5q muscular atrophy
- Doxorubicin (liposomal) for treatment of soft tissue sarcoma
- Ciprofloxacin (inhaled) for treatment of CF
- Metronidazole (PR) for treatment of pouchitis

However, the vast majority of orphan drugs are designated on the basis of the prevalence criteria and the provision to support development in more common conditions and based on 'sufficient returns to justify the investment' criteria is under-utilised by both industry and academia.

Other initiatives

A new model for translational research and drug repositioning has been established based on three-way partnerships between public funders, the pharmaceutical industry and academic investigators. Two initiatives — one involving the Medical Research Council in the United Kingdom and one involving the National Center for Advancing Translational Sciences of the National Institutes of Health in the United States have been established. The MRC Mechanisms of Human Disease Initiative is a partnership between the MRC and AstraZeneca that was launched in 2011 and has provided academic researchers with unprecedented access to a high-quality collection of clinical and preclinical AstraZeneca compounds in order that they could propose new research into human disease mechanisms and the development of potential therapeutic interventions.

Challenges

Research in the field of repurposing can happen slowly as it is generally under-resourced compared to more commercially funded research, and it is often perceived that there is no financial incentive for industry to seek licences for off-patent indications. In this regard, as an example, it is reported that the off-label use of oncology drugs is estimated to be around 50%, and is particularly widespread in paediatric oncology. In addition, 'preventative' indications are also under represented in licensed indications e.g. the use of tamoxifen for primary breast cancer prevention in high risk women, aspirin for colorectal (and other) cancer prevention. Therefore, there is concern that off-patent drugs for which there may be a strong evidence base for a new indication are not licensed because the originator company perceives little commercial value once they have lost exclusivity rights. Furthermore, national policy makers may not produce commissioning

guidance on off-label drugs and thus prescribers may not have the opportunity to prescribe useful drugs to patients outside of the terms of the marketing authorisation. Of concern, if medicines are used off-label based on published evidence of safety and efficacy, information on the optimal use in the 'off-label' condition is not included in summary of product characteristics or the patient information leaflet and thus denied to both health professionals and patients.

Points for discussion at STAMP:

The aim of the questions listed below is to stimulate discussion between STAMP members regarding the issue of re-purposing established drugs:

1. Is there a need to establish specific legal or regulatory terminology and definitions?
2. What are the barriers to re-purposing established drugs for industry and non-profit organisations in terms of: (a) the development programme, (b) adding new indications to existing marketing authorisations
3. Could existing regulatory routes be used better and in what way e.g. PUMA, orphan designation including the returns to justify the investment criteria?
4. Is there a need for new regulatory incentives and/ or pathways (non-legislative) to support industry and non-profit organisations?
5. Are there particular disease areas that need specific support e.g. neurodegenerative diseases, anti-microbial resistance, rare conditions?

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