EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

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

STAMP 8/37

STAMP Commission Expert Group
8 December 2017

Subject: Repurposing of established medicines/active substances

Agenda item 5

The issue of repurposing of established medicines had been discussed in previous meetings of the Safe and Timely Access to Medicines for Patients (STAMP) Expert Group[1]. During the 7th meeting on 27 June 2017 it was agreed that the small group led by the UK would analyse case studies of the experience of repurposing of established medicines and report back to the STAMP.

Members of the group submitted case studies and these have been summarised in the attached document. Some discussion points and potential recommendations have been included in the document.

Members of STAMP are invited to consider the summary of the cases and the highlighted discussion points and to reflect on whether the STAMP can identify activities that could support the repurposing of established medicines.

[1] STAMP 4/20 (https://ec.europa.eu/health/sites/health/files/files/committee/stamp/2016-03_stamp4/3_repurposing_of_established_medicines_background_paper.pdf)
STAMP 5/26 (https://ec.europa.eu/health/sites/health/files/files/committee/stamp/2016-06_stamp5/3_repurposing_of_established_medicines_reflection_paper.pdf)
STAMP 6/29 (https://ec.europa.eu/health/sites/health/files/files/committee/stamp/stamp6_repurposing.pdf)
STAMP 7/33 (https://ec.europa.eu/health/sites/health/files/files/committee/stamp/stamp_7_repurposing_background.pdf)

8th Commission Expert Group on Safe and Timely Access to Medicines for Patients ("STAMP") meeting

December 2018 - repurposing case studies

Introduction

Drug repurposing is the process of identifying new uses for existing medicines in indications outside the scope of the original approved product information. Drug repurposing constitutes a dynamic field of drug development that can offer real benefits to patients. For background on some of the aspects considered on repurposing so far by the STAMP, please see the documents from the previous meetings[2].

To build on what has already been achieved in the STAMP on repurposing, at the 7th STAMP meeting it was agreed that case studies would be developed by interested Member States and other bodies to highlight by example where barriers / challenges are and what solutions might be identified. This paper summaries the main themes presented in case studies, with some discussion points and potential recommendations that might move the current discussions forward into firm actions and outputs.

Themes from the submitted case studies

1. **Lack of interest from and difficulties in engaging with the pharmaceutical industry**:

Engagement with the pharmaceutical industry is desirable for the efficient and timely generation of the necessary data to conclude on the benefits and risks, and register a new indication. Aside from the need for a marketing authorisation holder (MAH) to vary a product licence, there may be difficulties in gaining access to an active substance / medicine, sourcing all relevant historical non-clinical and clinical data, and challenges in manufacturing a matched placebo if required for clinical studies.

Even if there is data that might support a new indication, non-industry developers often raise the issue of how to proceed to registration if they are not the manufacturer and highlight the lack of regulatory experience and resource needed for filing an application. Thus if a MAH has no particular interest in the repurposing pathway, a new indication cannot be formally considered and approved by regulatory authorities, and the overall clinical development programme maybe more costly and longer than would otherwise be the case with industry collaboration. Therefore existing incentives (e.g. orphan designation [including lack of return on investment criteria], paediatric use marketing authorisation, additional year of market protection) appear to be insufficient to stimulate the commercial interest in many repurposing projects.

2. **Lack of accessible information / data in the public domain**:

There are potential challenges for non-commercial drug developers in sourcing and obtaining all relevant existing historical data for a medicinal product, in particular the non-clinical aspects of a dossier and the data that may support dose finding. The lack of access to data means that there is the potential need to replicate expensive tests and even clinical studies, adding to the costs and extending the timelines for the investigation of the potential new therapeutic indication.

[2] STAMP 4/20 (https://ec.europa.eu/health/sites/health/files/files/committee/stamp/2016-03_stamp4/3_repurposing_of_established_medicines_background_paper.pdf)
STAMP 5/26 (https://ec.europa.eu/health/sites/health/files/files/committee/stamp/2016-06_stamp5/3_repurposing_of_established_medicines_reflection_paper.pdf)
STAMP 6/29 (https://ec.europa.eu/health/sites/health/files/files/committee/stamp/stamp6_repurposing.pdf)
STAMP 7/33 (https://ec.europa.eu/health/sites/health/files/files/committee/stamp/stamp_7_repurposing_background.pdf)

3. **Lack of a regulatory framework that recognises the challenges faced by non-industry researchers**:

Investigator-initiated researchers may have little experience with conducting registration trials and scientific advice is needed in an early stage to make sure the trials meet regulatory requirements. Limited regulatory awareness can hamper developments or result in clinical trial or regulatory failures. It is a challenge to know who to speak to and how to gather evidence for prescribers and to channel the data collection to have the benefit of indications within a marketing authorisation. Regulatory authorities do offer small and medium sized enterprises (SME) support and fee waivers, but these are not provided to the same level for the not-for-profit community. Innovation offices /innovation task forces appear to focus mainly on new innovative drugs and not necessarily innovative ways of using older active substance / medicines.

Greater advice and support is needed for organisations and individuals who may want to make use of an authorised, off-patent, medicine in an indication outside its authorisation where research has shown value for treatment of identified conditions. This should include explaining how medicines can be repurposed through the authorisation system or exploring under what circumstances / procedures medicines can be made available on an off-label basis.

Clinical trials investigating new uses for off-patent drugs are often non-commercial, so there should be a way to apply for label extension by third parties or to ask for another type of official evaluation of the evidence by the competent authorities.

A wise use of the flexibilities offered by the new clinical trial regulation regarding low interventional clinical trials can also be helpful for evidence generation.

The undefined legal and financial responsibilities associated with using repurposed medicines often lead to increased off-label use, which could entail safety and data collection issues, legal liability issues for the prescriber, reimbursement issues, and supply issues when medicines are withdrawn for their approved uses.

4. **Potential advantages of access to real world data not realised:**

Some not-for-profit organisations potentially have access to extensive data sets generated in registries in the 'real world'. It is not clear how regulatory authorities and others could use this data which is an untapped and valuable resource. There needs to be a formal framework to bring this data into the drug development arena / regulatory setting with or without an identified marketing authorisation holder, to support appropriate use of the products.

Points for discussion and potential recommendations

- Discussion with industry on the specific incentives and motivation needed to support the development and uptake of new indications to innovator medicinal products and whether new rewards are required e.g. fee exemptions. However, incentives and pricing should be proportionate, particularly for known and well established indications

- If an innovator company is not interested in a repurposing pathway, how to identify, engage and incentivise a manufacturer of a generic or biosimilar who could be interested in applying for the new MAA

- Regulatory framework, tools and support considerations

    - Determine the viability and desirability of a public health referral to ensure product information is up to date (see example of a USA proposal from the Friends of Cancer Research in links below) or consider another regulatory route to formally review existing data on the benefits and risks by the CHMP / competent authorities, and include the indication as a 'soft' recommendation (outside SmPC) or to include relevant information in sections other than 4.1 of the SmPC

      https://www.focr.org/sites/default/files/PANEL%203.pdf

https://www.focr.org/sites/default/files/pdf/Development%20and%20Use%20of%20RWE.pdf

https://pink.pharmaintelligence.informa.com/PS122019/Labeling-Updates-For-Old-Drugs-Could-Be-Faster-Under-Streamlining-Proposal

- Generate guidance on how to access available data, freedom of information requests, where data could be located /requested

- Development of a regulatory and product development 'handbook' that explains how and who to contact with relevant links for specific issues (European Medicines Agency (EMA) & National Competent Authority (NCA) guidance, HMA EU-Innovation Network) and available incentives including designation opportunities (e.g. orphan designation, PRIME)

  Introduction of a voucher reward system, similar to the US FDA priority review voucher, to incentivise companies in taking forward key indications in the repurposing pathway.

- Investigate mechanisms to encourage uptake of regulatory advice and scientific advice/protocol assistance to ensure that the data generated can be submitted and serve the purpose of an authorisation for a new indication. Alignment between academia, hospital and patient associations, with regulatory requirements should be facilitated, wherever possible

- Consider if the EMA's registry pilot and or HMA/ EMA Joint big data task force can offer some form of consensus regarding data collection in the real world setting

  http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/03/WC500224262.pdf

  http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/02/WC500221618.pdf