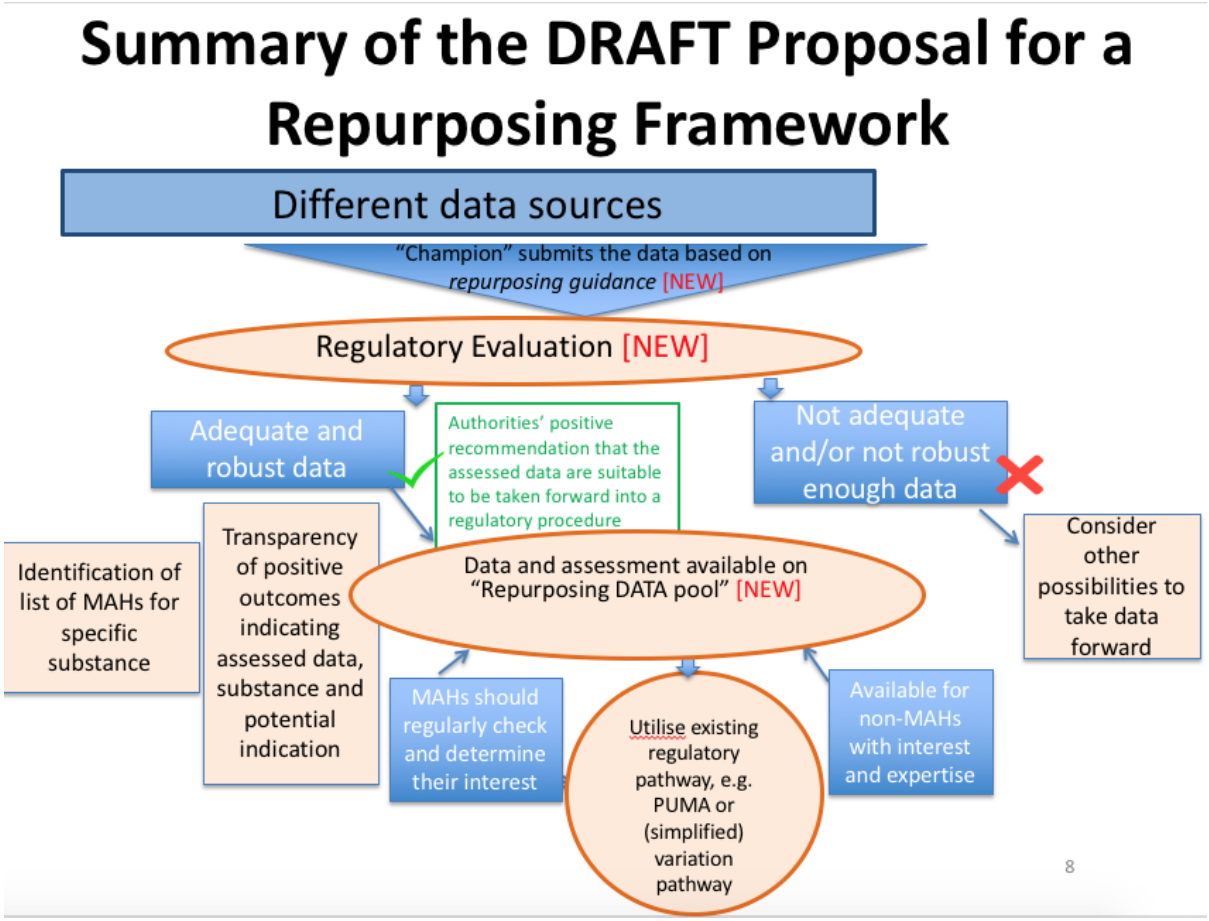
Clarification Paper – Repurposing

For the purpose of the further discussion with the STAMP, this paper provides further clarification to address the points raised by the European Commission and EMA on the draft proposal of a Repurposing Framework presented by EFPIA and Medicines for Europe, representing the innovative and the generics and biosimilar industries in Europe, respectively. This document should be read together with the accompanying PPT.presentation.

Proposed pathway:

The aim of the proposal is to provide a clearer framework and pathway to any stakeholder who has evidence and scientific rationale to support a new indication for an off-patent substance/product already on the market.



Definitions:

- **Champion roles and responsibilities**

  A Champion can be a person/academic unit/learned society/research fund with a particular interest in repurposing a compound/product for a new indication.

  A Marketing Authorisation Holder who is seeking a new indication for an already existing licence that they hold as part of their product lifecycle management is not regarded a champion here. There already exists a clear regulatory pathway for this kind of product development scenario.

  The Champion puts forward a repurposing proposal for regulatory evaluation.

  - Standard format data package according to the guidance provided by regulators, including information such as:
    - Compound (or product if it exists)
    - Proposed repurposing (prevention, treatment or diagnosis of disease)
    - Description of the existing supporting data for indication (in vitro, in vivo, clinical)
    - Any new data that has not been used before for a regulatory submission and would support the application for a new indication

- **Regulators (EMA and / or Competent Authority) roles and responsibilities**

  Regulator notifies the affected marketing authorisation holder(s) of a repurposing proposal at the start of the evaluation. This facilitates at the early stage the identification of the MAHs and increases their readiness to make an eventual regulatory submission after the evaluation results are made available.

  The regulator decides whether proposal is supported and the evidence is robust enough:

    - Standard evaluation (based on existing EC/EMA guidances -> *repurposing procedural guidance* is needed)
      - Scientific rationale for repurposing
      - Status of proposed indication (unmet need, population, etc)
      - Suitability of data to be taken forward into a regulatory procedure (orphan designation, MA, PUMA, variation etc)

  NOTE:
  - An inspiration for what the guidance could include can be sought by looking at the already existing guidances (e.g. guidance for orphan designation) and could be developed by the multi-stakeholder manner addressing the various needs of a champion.
  - The specific process for submission and evaluation needs to be worked out. Particular considerations are needed on how to manage the possible “queue” of proposals, as the evaluation is dependent on regulators’ resources, and on how to secure the completeness of packages before the evaluation is initiated (ie. technical validation, proper utilisation of Scientific Advice).

  If the regulatory evaluation is positive, it is placed in a ‘repurposing Data pool’ to be picked up by the applicable MAH(s). The intention is to not to resubmit data by each MAH but rather to refer to positive recommendation issued by the authorities.

If the regulatory evaluation is negative, information and rationale for the negative recommendation is also placed in a 'repurposing Data Pool" to inform the stakeholders of the shortcomings or other reasons why the opportunity should not be pursued.

- **Industry roles and responsibilities**

  Industry already has a responsibility to respond to enquiries regarding products for which it has a marketing authorization. (Item 2.4.5: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/2016-01-01_caps-human_rev12.pdf

  In this repurposing proposal industry would have the following responsibilities:
  - Collaborate where possible with champions in the process of assembling a repurposing proposal to enable e.g. re-use of/cross-reference to already submitted data (especially for quality)
  - Perform a regular review of the Data Pool to identify opportunities to progress for a submission of an application of a new indication; e.g. make an effort to amend the labelling of the medicinal product with a repurposed active substance referring to the positive recommendation from the data pool
  - Respond to any enquiries from other organisations who have identified opportunities in the Data Pool which they wish to pursue.
  - To progress with applications that are of interest which have been identified from the Data Pool.

Q&As

Could the data pool be regarded as off-label promotion?
The data pool is a key part of the proposal. Allowing companies to have access to information about new evidence which meets regulatory standards, and are suitable for taking forward into a regulatory procedure, will mean that companies can elect to take up opportunities which they would otherwise be unaware of. Safeguards to prevent unintended off-label use that could potentially be triggered before the assessment has been made or when the positive assessment is made available before the regulatory procedure has been started could include restriction of access to the Data Pool with applicable Terms of Use/Access to commercial organizations and researchers. In addition, indicating and making that information available in the data pool that a repurposing proposal has been rejected for lack of plausibility can help to stop existing off-label use.

Can earlier engagement between academia and companies be supported?
Academics are able to engage with companies at any stage in this process and an earlier identification of the existing Marketing Authorisation Holders for the substance in question will also facilitate this. One outcome of the data pool will be the ability to foster collaborations which otherwise wouldn't have been possible, through identification of new opportunities. Encouraging engagement to generate data to support repurposing is beyond the scope of this proposal. Although the Repurposing Data Pool as suggested in this proposal won't replace other types of research platforms, which could be utilised for repurposing proposals where data is not adequate nor robust enough, it has the potential to foster the collaborations.

Will requests from "champions" block the system (ie. Regulatory evaluation)?
Clear guidance will be needed on the regulatory framework and evidentiary standards required for the approval of new indications, for stakeholders who are not familiar with these. Some criteria of prioritisation could be also defined to avoid blocking the system.
This could be provided as part of the ongoing work within the Framework of collaboration between the European Medicines Agency and academia, possibly linked to part 4., section 6 in the framework.

What specific incentives would help?

- A combination of the provision of incentives and the removal of disincentives will be particularly important; neither alone is likely to be sufficient.
- There would need to be enough incentive in any particular off-patent setting with multiple manufacturers, as the others in the current system would be able to "free ride" on the efforts made by the champion. "Free ride" in this context means for example that there is no incentive for the champion to spend resources in order to come up with the repurposing proposal package.
- Suggestions include:
    - free scientific advice to support Champions to take proposals to regulatory evaluation (to avoid low quality and insufficient data packages to be submitted)
- lower fees/fee waiver/fee voucher for the needed regulatory applications (eg. Variations) made by the MAH(s) associated with the change in variation's category (i.e. type IB instead of type II)
- Set up a (public) repurposing fund that could grant funding for a project accepted in the pool
- There is a proposal set out in the UK, which aims to provide incentives for the developer whereby the developer has the opportunity to recoup investment through R&D tax credits.

One advantage is that this type of incentive would certainly support SMEs and companies with limited capital risk upfront.

What disincentives need to be removed?

- To remove disincentives for repurposing, the following major issue needs to be addressed:
  - the encouragement (by payers, health authorities etc) of off-label use for economic purposes

Further context

The UK Association of Medical Research Charities published a Report "Facilitating adoption of off-patent, repurposed medicines into NHS clinical practice" in December 2017. The report includes recognition of the need to provide results of expert assessments on evidence which may support a new use of a medicine.

DATE: 22nd May 2018