Proposal for a framework to support not-for-profit organisations and academia in repurposing authorised medicines

Question and Answers on repurposing pilot project

V. October 2021

1. What is medicines' repurposing and why it is important?

Repurposing of medicines is about identifying a new therapeutic use for an existing medicine/active substance for an indication outside its existing authorised indication(s). It is a way of making new treatment options available to patients.

Medicines, especially off-patent, authorised medicines, are sometimes used in clinical practice outside the terms of the marketing authorisation (off-label use). In other cases, off patent, authorised medicines may be the subject of an investigation for a completely new indication. There are regulatory routes to seek the authorisation of new indications for off-patent authorised medicines by a marketing authorisation holder (MAH). However, for different reasons, these routes are not extensively used for well-established, off-patent medicines by MAH for off-patent medicines. While the latter may carry out such developments, it can happen that they lack incentives and/or commercial interest to pursue the necessary research and development and complete the regulatory process necessary for the authorisation of a new indication. On the other hand, academic institutions and/or patients organisations may be interested in carrying out such development for the benefit of public health; however, these actors may lack the necessary regulatory experience and may have no intention to becoming an MAH themselves.

The absence of a bespoke regulatory route for, off-patent, authorised medicines already on the market to be developed for new uses and reach formal regulatory approval sometimes poses problems to physicians, patients and health systems.

It can result in the absence of new solid and supportive evidence being generated or, that already well-established evidence based on off-label use of such a medicine is not converted into on-label use. These may have negative consequences for patient safety and treatment options. Also, potentially useful new or established non-approved indications will be hampered if the medicine is suddenly withdrawn from the market. Repurposing of well-established, authorised medicines can also contribute to a more sustainable health system.

2. What is the proposed framework to support repurposing?

The Expert Group of the European Commission on the Safe and Timely Access to Medicines for Patients (STAMP) has developed, together with representatives of the Member States, the European Medicines Agency (EMA), and stakeholders from not-for-profit organisations, patients, healthcare professionals, industry, health technology assessment bodies and payers, a *proposal for a framework to support not-for-profit organisations and academia (institutions and individuals) in repurposing authorised medicines* [1].

The goal of the proposal is to facilitate the regulatory recognition of new indications for well-established, authorised medicines that are adequately supported by a data set (e.g. preclinical data, safety data, clinical efficacy data, real world data, …), when these medicines are out of

[1] For more information, consult the website of the Pharmaceutical Committee and STAMP

the protection periods and the MAH does not take the lead in applying for a new therapeutic use for the medicine.

The proposed framework outlines the process to support not-for-profit organisations, including academia, in generating and gathering the required data to support the authorisation of such new therapeutic uses. Such not-for-profit organisation is hereinafter called 'champion'.

The objective of the framework is to help champions present their proposed repurposing activity to regulatory authorities and seek advice. This should then be followed by the engagement of the MAHs/applicant of the concerned medicinal products applying for the new indication through standard regulatory processes.

Thus, the framework builds on existing regulatory tools, namely scientific and/or regulatory advice (through EMA and National Competent Authorities (NCAs)) to provide guidance to champions.

To test this framework, EMA and several National Competent Authorities in EU Member States are launching a pilot project.

3. What is the goal of the medicine repurposing pilot project?

The objectives of the pilot are primarily:

- To assess the clarity and comprehensibility of the core components and milestones of the framework from the not-for-profit organisations' and industry perspective.
- To check that the steps outlined in the process work as intended for all involved stakeholders.
- To check the feasibility of compiling the required information/data for the scientific advice request from the not-for-profit organisation's perspective.
- To identify gaps in the existing guidance available on the EMA/Heads of Medicines Agencies/NCA websites that may be applicable to repurposing, and evaluate the potential need for adaptations (or new guidance documents/ templates for repurposing).
- To monitor the progress of the repurposing programmes beyond scientific advice, i.e. continuation of programme development and compliance with scientific advice outcome.

The ultimate goal of the entire framework is to support progress of the repurposing programme and final regulatory filing for the new indication.

4. Who coordinates the pilot project?

In order to implement and coordinate the repurposing pilot, the STAMP working group has created a voluntary observatory group, so called Repurposing Observatory Group (RepOG). The RepOG is composed of regulatory representatives, the European Commission, Champion interest groups and industry representatives.

The RepOG will report to STAMP and/or the Pharmaceutical Committee on the repurposing pilot project.

5. Who can apply?

The pilot is open to not-for-profit stakeholders (called champions) with a particular interest in repurposing an authorised medicine for a new indication, who has gathered or generated sufficient evidence to support a scientific rationale for their repurposing programme and is willing to seek scientific advice with a regulatory authority, whether it is EMA or an EU national competent authority.

A champion can be, for example, an entity or a person from an academic unit/charity or patient organisations/learned society/research funder or payer (generally seen as not-for-profit organisations).

A champion is typically:

a) a not-for-profit organisation [2] or academic institution [3], collaborative groups and European References Networks (ERNs) [4]

b) able to coordinate and/or foster the research programme up until the point of full industry engagement

c) initially responsible for liaising and leading the interactions with regulatory authorities and industry / other stakeholders such as patient groups

d) transparent regarding interactions with relevant pharmaceutical company(s)

e) in charge of filing the initial request for scientific/regulatory advice on the basis of the available data.

In addition, EMA's policy on the handling of competing interests of scientific committees' members and experts as restrictions or exclusion may apply to the potential involvement of an expert in any Agency activity, including as a member of a scientific committee, working party or other group, when the expert is involved in repurposing**.**

6. Which medicines are eligible?

Candidate medicines are expected to fulfil all the following eligibility criteria:

1) They should be a well-established active substance contained in a medicine with a valid marketing authorisation granted in a Member State or in the European Union.

2) They should be an authorised medicine (containing the concerned active substance) out of data exclusivity and market protection periods and out of basic patent/supplementary protection certificate (SPC) protection.

3) They must target a new indication in a condition distinct from the currently authorised indication(s) listed in section 4.1 of the relevant summary of product characteristics (SmPC) of a medicinal product in the EU (nationally or centrally authorised, including EEA countries).

4) They must target an indication in an area where important public health benefits / Union interests are likely to be achieved. Conditions for which no or few medicines are currently authorised or which are associated with high morbidity and/or mortality despite available medicines, will be the focus of the pilot.

Applicants who are uncertain about the suitability of the repurposed indication could contact the regulatory authority where they intend to seek scientific advice (please refer to the annex).

When submitting their applications, champions should clearly outline how each of the eligibility criteria are met in the Repurposing Submission Form.

In addition , the development, authorisation and safety monitoring of treatments and vaccines intended for the treatment and prevention of COVID-19 is coordinated by the COVID-19 EMA pandemic Task Force (COVID-ETF) and should follow the procedural steps provided in the EMA initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines. Repurposing programmes for medicines intended for COVID-19 will therefore not be considered for this pilot project.

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[2] 'Non-profit organisation' or 'non-profit legal entity' should be understood as a legal entity which by its legal form is non-profit-making or which has a legal or statutory obligation not to distribute profits to its shareholders or individual members; 'Legal entity' should be understood as any natural person, or any legal person created and recognised as such under national law, Union law or international law, which has legal personality and which may, acting in its own name, exercise rights and be subject to obligations.

[3] 'Academia' or 'Academic sector' should be understood as consisting of public or private higher education establishments awarding academic degrees, public or private non-profit research organisations whose primary mission is to pursue research, and international European interest organisations. 'International European interest organisation' should be understood as an international organisation, the majority of whose members are Member States or associated countries, and whose principal objective is to promote scientific and technological cooperation in Europe.

[4] 'Collaborative groups and ERNs' could be understood as virtual networks or associations of people without or with legal personality involving healthcare providers and researchers across Europe. For the purpose of this pilot project, one contact point should be established or act as champion on behalf of the association/network.

7. What are the benefits of taking part in the pilot?

By taking part in the pilot, not-for-profit organisations will benefit from a clear engagement with regulatory authorities and receive tailored guidance to prepare for scientific advice, in view of supporting data generation for these new uses.

Repurposing candidate projects supported by a mature and robust data set are likely to be provided with scientific advice as they are likely to benefit the most from scientific and regulatory guidance; this support should also help the not-for-profit organisation engage with a commercial company that will then take the project forward until regulatory authorisation.

Projects with less mature data would benefit from regulatory support to increase the robustness of their data set in accordance with the regulatory requirements through earlier engagement and discussions around the evidence base. The regulatory network, through structures already available such as the Innovation Offices, would maintain its support to these projects.

8. How will candidate medicines be selected during the pre-entry phase?

Champions should submit their candidate project(s) to the competent authority of their choice, i.e. the EMA or a National Competent Authority participating in the project (please, refer to Question 10 and the annex). The same Champion should not submit the same project to more than one competent authority.

In order to ensure suitability of the repurposing candidate projects to take part in the pilot (e.g. a different condition, a well-established substance, a valid proof of concept, etc), as well as the likelihood to reach an application for the new indication during the timeframe of the pilot, the concerned competent authority will perform a selection of the candidate projects submitted within a defined period of time as indicated in question 9.

The concerned competent authority will review the eligibility criteria and the level of evidence as provided in the Repurposing Submission Form (please, refer to question 6). Competent authorities will also discuss candidate projects within the European Innovation Network which also involves EMA and that will collaborate by ensuring consistency in the assessment and selection of the applications. Thus, the projects presented will be shared in the context of the regulatory network, and eventually champions might be advised to apply for another kind of support by a given competent authority (for example, to seek directly the centralised advice procedure via EMA or, conversely, to maintain support at national level for a time).

In the event that the pilot is oversubscribed, (i.e. that the number of applications which meet the eligibility criteria exceeds the capacity of the pilot), competent authorities will select candidate medicines based on the likelihood for important public health benefits / union interests to be achieved (see eligibility criterion no. 4 in Q6) and the anticipated timeframe involved. This will be considered based on the information provided in the Repurposing Submission form and therefore applicants should clearly and concisely provide all of the information requested in the Repurposing Submission Form.The final decision as to which applications are accepted for inclusion in the pilot will be a matter for the competent authority to which the application was submitted.

Depending on the completeness of the data, the champion may qualify for full scientific advice when the project development is mature enough to benefit from it or informal guidance may be provided on other types of regulatory support in order to make progress with their projects.

9. What are the steps of repurposing pilot?

The repurposing pilot will follow two main phases (i.e. pre-entry phase and scientific advice phase) as outlined below.

	LAUNCH	Announcement on EMA/NCA (volunteers)/EC	T0 28th of October 2021
	PRE-ENTRY	Champions submit their candidate project(s) to the competent authority of their choice (i.e. EMA or a National Competent Authority participating to the project) using the submission form.	Submission of candidates By 28th February 2022
	SELECTION	Competent Authorities select candidate projects sufficiently mature to benefit from scientific advice (SA), in consultation with the EU-IN and EMA. Less mature projects are allocated to the best available resource to provide ongoing regulatory support.	By 30th June 2022
	Scientific advice (SA) ENTRY	Champions selected for scientific advice submit the full scientific advice data package	Submission of SA package As per the deadline that will be communicated upon review of the candidate projects
		Champions may be invited to a SA pre-submission meeting/teleconference at the discretion of the regulatory authority providing the SA	
		Champions submit the updated SA briefing package and the SA procedure starts.	
	SA START	SA procedure follows standard SA procedure	For EMA SA: 40 or 70 days (in case of meeting with Scientific Advice Working Party (SAWP))
	SA OUTCOME	Outcome of SA	
	POST-SA	Champion takes forward the recommendations and is expected to progress the advice from the regulatory authority.	

For candidate project(s) that have been selected for scientific advice, the procedure will take place according to the standard scientific advice process of the respective competent authority champions applied to. The champion will be informed of the timelines for the scientific advice phase.

In cases where a scientific advice procedure is considered premature in the light of the proposed data set, champions will be informed of the available regulatory resources through which they can receive orientation for their projects in order to be future candidates for scientific advice.

10. How to apply and what information to submit to enter the repurposing pilot?

Champions interested to take part in the repurposing pilot and whose project meets the criteria (please refer to question 6) should submit the following documentation for the pre-entry phase and then subsequently for the scientific advice if their project is selected for scientific advice.

1) Pre-entry phase

Champion should use the dedicated Repurposing Submission Form in order to provide an overview of the evidence gathered from identified data sources and/or own data to demonstrate proof of concept, to establish the public health interest in terms of unmet medical need in the targeted population and to provide an indication of the progress made to date.

Moreover, the champion is expected to show its ability to move the repurposing candidate project forward in terms of development, in case more data need to be generated to support bringing the concerned new use on-label based on the scientific advice provided.

Champions should submit the completed Drug Repurposing Submission Form to the competent authority of their choice, i.e. either EMA or a National Competent Authority participating in the project to the electronic address provided in the list (see annex), within the given timelines.

Before submitting their form, interested champions can seek clarifications regarding their potential project with regulatory authorities. Points of contact are provided in the annex.

In case of projects which fulfil the criteria for entering the pilot and are based on more than one authorised medicines, a single Repurposing Submission form should be completed including authorisation details for each one of the medicines.

2) Scientific Advice phase

Once a champion receives feedback from regulators that they can engage with regulators for the scientific advice phase, the champion is expected to expand the information included in the Drug Repurposing Submission Form and to turn it into a comprehensive briefing package for the scientific advice.

In particular, in order to receive feedback on their project, champions should formulate specific questions within the scope of the scientific advice (e.g. relevant to the proposed non-clinical and/or clinical development) and should provide further background information as per the relevant scientific advice guidance from the Competent Authority where the project is planned to be submitted. This will allow the regulators to provide appropriate advice on the current data set and potential next steps of the development.

The type and number of potential questions may vary from case to case depending on issues such as the availability and amount of clinical data, but examples of topics that can be presented in the repurposing scientific advice are outlined below (non-exhaustive list):

(a) Whether the evidence based on the available data set indicates a potential to fulfil an unmet medical need.

(b) Whether the available data set on its own or combined with additional studies could be sufficient to support the targeted indication and a benefit risk assessment.

(c) Whether the proposed post-authorisation measures are appropriate

(d) Whether the proposed study design and key elements are appropriate to generate efficacy/safety evidence for the targeted indication.

For more details regarding the briefing package to be submitted to the scientific advice, please refer to the respective webpages of the competent authorities listed in the annex.

11. What happens after the scientific advice?

Further to scientific advice, champions are expected to progress the advice from the regulatory authority which could include the generation of additional data and the champion may consider to hand-over the data and/or seek a partnership with (an) MAH(s), since it is the MAH who will

apply, for example, for a variation, an extension or a new market authorisation application (MAA).

When an MAH decides to pursue a change to their marketing authorisation (MA), the champion will need to provide the MAH with the relevant data to enable it to prepare the necessary update to the dossier and file the amendment to their MA. As needed, the champion may assist in responding to questions from the regulatory authority. Likewise, the champion may act as a link to the clinical trial site(s) and investigator(s) when the Good Clinical Practice (GCP) inspections are deemed necessary.

A champion that wishes to find an MAH with whom to engage for the repurposing of a given substance should first consult the Article 57 database on the EMA website:

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/public-data-article-57-database

The Excel spreadsheet shows the names of all MAHs that hold a marketing authorisation for a product containing a given active substance across the MSs of the EU. The champion can select the MAH(s) he wishes to contact. If the MAH has set up a specific mailbox for repurposing queries, this should be used. Alternatively, when there is no general contact point for repurposing, the champion should contact the MAH via the Medical Information desk in the country.

12. How is the Industry engaged in the repurposing pilot?

After the scientific advice, when approached by champions, if the scientific basis and the unmet medical need are convincing it is expected that MAHs of existing medicinal products (e.g. originator, generics, biosimilars) will be interested in pursuing an MA variation or a new applicant would submit a new marketing authorisation application.

The MAHs are encouraged to create a dedicated e-mail address for repurposing enquiries to be advertised on their websites.

13. For how long will the pilot run?

It is foreseen that the pilot will run until the completion of scientific advice for the selected repurposing candidate projects and optimally up to the filing of an application for the new indication. The exact period of operation of the pilot will depend on the degree of accomplishment of its objectives, which will be assessed within the first 2 years of its operation, and in particular after the scientific advice milestone.

14. What fee will be applied?

There is no fee for the pre-entry phase submission when the champion submits its project for first consideration. However, as the project progresses there may be fees associated to specific procedures, notably the scientific advice procedure.

In general, the fee will follow each competent authority's fee structure for a scientific advice procedure. More complete information on fees (when applicable), possibilities for fee reductions or fee exemptions can be found in the annex and, in case of doubt, please contact the relevant regulatory authority, using the contact details provided in the annex.

15. What information on the selected medicines will be made public?

In general, the same rules of confidentiality that guide medicines agencies in their respective regulatory procedures will apply. Furthermore, publishing scientific advice may have the unintended consequence to encourage off-label uses. The scientific advice provided will not be made public by the competent authorities prior to the submission of an application for a marketing authorisation or during the assessment of such marketing authorisation. In case a marketing authorisation is granted centrally, reference to the scientific advice will be made in

the European public assessment report (EPAR). However, nothing prevents a champion from sharing their data or giving their consent to make them public, either totally or partially.

In addition, in the context of the pilot, candidate projects information and scientific advice outcomes will not be shared completely with the RepOG. Only high-level and anonymised information (e.g. type of product, the intended indication, the type of data supporting the scientific advice request, the type of champion, etc.) will be extracted and aggregated to perform an analysis of the repurposing pilot, resulting in a public report.

Annex 1

Contact points and submission mailbox for candidate projects in national competent authorities and EMA

Institution	Country	Participation in the repurposing pilot? (yes/no)	Contact Point (including email Address and/or others if applicable)	Type of advice provided (only formal, only informal*, both formal and informal)	Fees applicable for champions for informal meetings (yes/no)	If yes, amount	Fees applicable for champions for formal meetings (yes/no)	If yes, amount	Possibility of transfer** to National Scientific Advice? (Yes/No)
State Institute for Drug Control (SÚKL)	Czech Republic	YES	innovation@sukl.cz	Both formal and informal	NO		NO	N/A	YES
Finnish Medicines Agency Fimea	Finland	YES	innovation.office@fimea.fi	Only formal	NO		No fee (for non-profit Champions)		YES
AEMPS	Spain	YES	innov_spain@aemps.es	Only informal	NO	N/A	NO	N/A	YES
National Institute of	Hungary	YES	tanacsadas@ogyei.gov.hu	Both formal and informal	NO	N/A	NO	N/A	YES

Pharmacy and Nutrition									
Italian Medicines Agency - AIFA	Italy	YES	innovation.office@aifa.gov.it	The Agency will not release a formal advice. Requests will be handled by the Innovation Office, and a f2f or TC meeting will be scheduled to discuss the issues raised. There will be minutes of the meeting.	NO	N/A	NO	N/A	National Scientific advice temporarily suspended. As soon as the activity will be restarted, this will be promptly communicated.
Paul-Ehrlich-Institut	Germany	YES	Bettina.Ziegele@pei.de	Both formal and informal	NO		YES	Depending on scope of advice	YES
FAMHP	Belgium	YES	innovationoffice@fagg-afmps.be	Formal (1)	Not applicable (cfr 1)	Not applicable (cfr 1)	Yes (2)	Different fees (2) exist depending on the type of advice request / type of questions and	YES

								workload involved.	
EMA	EU	YES	SArepurposing@ema.europa.eu	Formal	No	N/A	Yes	Applicants from the academic sector are eligible to receive free scientific advice (i.e. protocol assistance) for developing orphan medicines – See EMA explanatory note on general fees payable and EMA decision as regards to Academia definition For other medicines than orphans, standard fees for SA apply, taking into account any applicable fee reduction (e.g. orphan, paediatric). On a case by case basis, SA	N/A

								fee waiver will be granted by the Executive Director to a subset of selected applications taking into account the extent of the expected public health benefits and the strength of the evidence to substantiate the promise held by the proposal, in accordance with Article 9 of fee regulation (EC) No 297/95 - (EMA will inform champion of successful candidates regarding the process for	

								applying for SA fee waiver)	

(1) For several reasons non-commercial applicants/academics that would apply as "champion" for a drug repurposing pilot would not be eligible for the type of informal (free of charge) advice mechanism currently available at FAMHP's innovation office (i.e. the "project info meetings" concept is strictly limited to highly innovative drug products), see also point 2 below.

(2) A 75 % reduced fee for national scientific-tehnical/regulatory advice (STA) is possible in Belgium for SME's, universities, certified hospitals, foundations for the public good and statutory administrations that request a national scientific and/or technical regulatory advice (i.e. STA type I, II or III) on all aspects related to research into and the development of a medicinal product eg. in view of a potential future application for marketing authorisation or registration of a medicinal product or a request for a variation or line extention, request for a CUP/MNP, etc . In order to be eligible for the 75% fee reduction the following conditions should be met :Universities, certified hospitals, foundations for the public good and statutory administrations should be formally recognized by the FAMHP as sponsor of non-commercial studies as defined by art. 31 of the Law of 7 May 2004 in order to be eligible for the 75% reduced STA fee. This recognition should normally be in place prior to applying for a formal STA request according to the reduced STA fee concept or should at the latest by initiated by the Applicant in parallel with the national STA request submission. In the latter case, the Applicant should be aware that in case the FAMHP would not recognize the Applicant as a sponsor of non-commercial studies the standard fee for the related STA request will be owed to the FAMHP and therefore charged retrospectively to the Applicant (or it's legal representative).

75% REDUCED FEES for SME, universities, certified hospitals, foundations for the public good and statutory administrations:	
• STA Type I	563,96 €
• STA Type II	3.383,78 €
• STA Type IIIa/b	4.511,70 €

More info on scientific advice procedure

1. European Medicines Agency: 'Scientific Advice - How to submit a request'

Annex 2

List of abbreviations

AEMPS: Spanish Agency of Medicines and Medical Devices

AIFA: Italian Medicines Agency

CUP: Compassionate use programs

EMA: European Medicines Agency

EPAR: European public assessment report

ERNs: European References Networks

EC: European Commission

EEA: European Economic Area

EPAR: European public assessment report

EU: European Union

EU-IN: European Innovation Network

FAMHP: Federal Agency of Medicines and Health Products

FIMEA: Finnish Medicines Agency

GCP: Good Clinical Practice

HMA: Heads of Medicines Agencies

MA: marketing authorisation

MAA: market authorisation application

MAH: Marketing Authorisation Holder

MNP: Medical need programs

MS: Member States

NCAs: National Competent Authorities

RepOG: Repurposing Observatory Group

SA: Scientific Advice

SAWP: Scientific Advice Working Party

SME’s: Small and medium enterprise

SmPC: Summary of Product Characteristics

SPC: Supplementary Protection Certificate

STA Scientific-technical/regulatory advice

STAMP: Safe and Timely Access to Medicines for Patients

SÚKL: State Institute for Drug Control