Proposal for a framework to support not-for-profit organisations and academia (institutions and individuals) in drug repurposing

Prepared by a working group of the Safe and Timely Access to Medicines for Patients (STAMP) expert group

Members of the working group:

- Member States (Belgium, the Netherlands, Norway, Spain, Sweden, the United Kingdom)
- European Medicines Agency (EMA)
- Anticancer Fund
- European Society of Paediatric Oncology (SIOPE)
- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- Medicines for Europe
- European Patients' Forum
- European Organisation for Rare Diseases (EURORDIS)
- European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
- Association Internationale de la Mutualité (AIM)
- European Commission representatives

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Abbreviations

EMA: European Medicines Agency
GCP: Good Clinical Practice
IP: Intellectual property
MAA: Marketing Authorisation Application
MAH: Marketing Authorisation Holder
NCA: National competent authority
SA: Scientific advice
SmPC: Summary of product characteristics
STAMP: Safe and Timely Access to Medicines for Patients
SPC: Supplementary protection certificates

PROPOSAL FOR A REPURPOSING FRAMEWORK

1. Introduction

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. Normally a marketing authorisation holder (MAH) initiates variations and extensions within the company's development plan to an approved medicinal product, alternatively a marketing authorisation application may also be submitted for a new medicinal product with the repurposed indication. This document considers the circumstances when a not-for-profit party (defined below in section 3.1) has an interest in an indication of an already authorised medicinal product that is off-patent and out of regulatory protection. Such initiatives are important, often innovative in their approach and are continuously ongoing. However, these projects may have low visibility and awareness within the regulatory framework and wider drug development community. Thus, repurposing of approved medicines that is not led by a MAH constitutes a dynamic field of drug development that can span from the very innovative to already accepted non-approved practises in medical care, often led by clinical and academic units and medical research charities.

The issues surrounding the challenges of repurposing of established medicines has been discussed in meetings of the European Commission's Safe and Timely Access to Medicines for Patients (STAMP) Expert Group. A working group including representatives from Member States, the European Medicines Agency (EMA) and stakeholders from industry, not-for-profit organisation, patient, healthcare and payer representative organisations was formed to consider a framework for repurposing. STAMP observations were that the main rate-limiting steps and disincentives for not-for-profit organisations in repurposing projects concerned the lack of knowledge and resources in terms of understanding the regulatory routes and requirements, what additional data may exist or needs to be generated de novo, how to access industry non-published clinical and non-clinical data and how to find a MAH of the finished product to collaborate with to bring the indication on label. Such not-for-profit organisations are normally not equipped, do not have the resources or do not have the intention to legally take the role as applicant/MAH when seeking approval or for fulfilling post-marketing responsibilities. However, they are often involved in generating data and in analysis of data from different sources.

2. Scope

In order to address some of the barriers and hurdles identified by STAMP, the aim of this proposal is to provide a visible supportive framework to a not-for-profit stakeholder (termed Champion), who has evidence and scientific rationale for a new indication that fits the criteria below, with the aim of bringing a new indication on-label.

In this regard, the working group proposed a targeted scope to support not-for-profit organisations, taking into account the following considerations:

- The repurposing framework is the process of facilitating data generation and/or data gathering in accordance with regulatory standards of a new therapeutic use for an authorised active substance – outside the scope of the original authorised indication(s) - with the purpose of seeking its authorisation.

- The repurposing framework uses existing regulatory tools and, as applicable, may run in parallel with other regulatory processes. The elements discussed below cover only one possible

scenario of repurposing of medicinal products, namely the one where medicines are already out of basic intellectual property (IP)/regulatory protection.

3. Key-features of STAMP repurposing framework

The framework for repurposing of a medicinal product (MP) without basic IP protection and data exclusivity may be described as voluntary steps within the existing regulatory framework. The framework is open to Champions and applicable to both EMA and national competent authority (NCA) interactions. However, it should be noted that individual Member States (MS) may have different policies and resources. Some key milestones of the repurposing framework are not regulatory activities, e.g. the repurposing Champion (see definition below) finding an interested marketing authorisation holder and concluding on the necessary agreements and ensuring that IP and exclusivity rights are not infringed. However, Champions may lack experience with conducting registration trials and scientific advice is needed at an early stage to ensure that the regulatory requirements are understood and applied. The European Medicines Regulatory Network (EMRN) may also offer relevant training opportunities / advice for Champions that may also be considered depending on their needs (for example Good Clinical Practice (GCP) compliance training, project on strengthening training of academia in regulatory sciences and supporting regulatory scientific advice (STARS), contact with innovation offices, etc).

3.1 Core components of the targeted repurposing projects

The following attributes should be considered for the repurposed medicinal product(s) targeted under this proposed framework, in particular, for a future repurposing pilot:

1 The proposed new indication for an authorised active substance should be in a condition distinct to the currently authorised indication(s) listed in section 4.1 of the relevant summary of product characteristics (SmPC) of a medicinal product in the European Union (EU) (nationally or centrally authorised, including EEA)countries)

2 The targeted indication should be in an area where important public health benefits / Union interests are likely to be achieved

3 There should be a valid MA granted in a Member State or in the European Union for the medicinal product containing the concerned active substance

4 Relevant authorised medicinal products containing the concerned active substance should be out of basic patent / supplementary protection certificate (SPC) protection, and data and market exclusivity periods

5 A Champion takes the initiative and is willing and able to take forward the roles and responsibilities required of the framework whose goal is to facilitate the bringing of the new indication to a label. A Champion can be for example a person or entity from a charity or patient group/academic unit/learned society/research funder or payer (generally seen as not-for-profit organisations) with a particular interest in repurposing an authorised medicinal product for a new indication, and who has data evidence/scientific rationale to do so. In principle, Champions based both within and outside the EU are eligible.

A Champion is typically characterised by the following:

a. Is not a pharmaceutical company or is not financed or managed by private profit organisations in the pharmaceutical sector ("PPO"), nor has concluded any operating agreements with any PPO concerning their sponsorship or participation to the specific research project at the time of entry into the framework
b. Is able to coordinate and / or foster the research programme up until the point of full industry engagement
c. Is initially responsible for liaising and leading the interactions with regulatory authorities and industry / other stakeholders such as patient groups
d. Is transparent regarding interactions with relevant pharmaceutical company(s)
e. Files the initial request for scientific/regulatory advice on the basis of the available data

f. Where feasible and appropriate, provides information to the MAH during the MAA submission / process (e.g. regarding GCP compliance of the clinical trial(s), responses to questions from regulatory authorities)

6 There should be some supportive clinical evidence. It could include documentation from clinical trials, off label use, registry data, or reported case studies.

In summary, the repurposing framework is defined by the aim to foster the authorisation of a new indication to unprotected off-patent medicinal product where some data have already been generated.

3.2 Regulatory engagement (Scientific or regulatory advice)
Scientific Advice (SA) and/or regulatory advice (through EMA and NCA) are the main tools that are considered important to support repurposing projects. Guidance can be provided to the Champion on the regulatory and scientific aspects of the project (and with joint health technology assessment (HTA) advice as appropriate). The advice will be instrumental for regulators and Champions to discuss the data package in relation to regulatory requirements, and available regulatory routes. The outcomes of the SA could be made available under due diligence in the context of encouraging engagement with MAH(s), but the timing of this will remain at the discretion of the Champion. A data package generated in accordance with the regulatory requirements and compliant with the scientific advice is of utmost importance to facilitate the uptake by a business company.

The future full assessment by regulators of the data in support of a new indication will follow an existing pathway for an application to the EMA, or NCAs e.g. variation, extension or new MAA by either the originator or a generic/biosimilar MAH/applicant, whereby it could allow the granting of a new indication if successful or other amendments to the product information.

If the Champion has not identified a company partner, other regulatory or MS-specific measures might apply, as appropriate.

3.3 Industry engagement
Industry engagement in the pathway can be envisaged in two stages:

3.3.1 Before the Champion seeks Scientific Advice
At this point, the Champion may choose to contact one or more of the existing MAH(s) for the product or active ingredient of interest, in order to seek their views or input on the proposed new use. Identification of the MAH(s) will be facilitated through the EMA's Article 57 database, and MAH companies will be encouraged to create a dedicated e-mail address for repurposing enquiries to be included on their websites. The originator of the product, if identifiable, will often be best placed to provide input; however other MAHs may equally have relevant insights, experience or interest in relation to the proposed use.

The input provided may range from none at all, if the MAH has no relevant knowledge or experience, to commentary from the MAH as to what they know, or have learned, or can hypothesise about the proposed new use from their own development and/or post marketing experience, and may extend to data sharing or exchange and even collaboration with the Champion in seeking Scientific Advice. The nature of the input provided will depend on the individual circumstances of the product and proposed new use and the available knowledge, experience (including known off-label use), data and capacity of the MAH. However, at this stage, the Champion is the project lead and is responsible for deciding whether to proceed with the interactions with regulatory authorities.

3.3.2 After the Champion has obtained Scientific Advice
This is the key point for industry engagement in the repurposing pathway. The Champion should contact the MAHs (originator and/or others, as described above) and consider sharing with them the output from the Scientific Advice, at the Champion's discretion and subject to appropriate terms of confidentiality as the Champion may require, with a view to establishing the potential for at least one MAH to obtain regulatory approval for the new indication via an MA variation. For its part, the MAH may wish to consider:

- whether they have expertise in the therapeutic area of the new indication;
- whether further trials or measures are required to support the variation;

- the practical and economic feasibility of:
    - generating further data;
    - manufacturing/formulation changes that might be required;
    - preparing for, submitting and maintaining the variation;
- the likely post-marketing, risk management and pharmacovigilance requirements which the MAH would have to support.

In general terms, one or more MAHs are more likely to be interested in pursuing an MA variation for the proposed new indication when the scientific basis and unmet medical need are convincing and the practical, economic and legal burden is manageable.

When a MAH decides to pursue an amendment to their MA, the Champion will need to provide the MAH with the relevant data to enable the MAH to (i) prepare the necessary updates to the dossier, (ii) file the amendment to their MA and (iii) respond to questions from the regulatory authority(ies). If Good Clinical Practice (GCP) inspections are deemed necessary, the MAH will need the Champion to act as or provide a link to the clinical trial site(s) and investigators.

3.4 Incentives – disincentives

Both legal and non-legal incentives may be important to different stakeholders. There are incentives within the European regulatory framework (e.g. orphan designation, additional protection periods) and other types of incentives may also exist in different MS. Barriers may include the costs involved in generating / gathering data and for the scientific advice meeting, and difficulties in finding a willing and supportive MAH. For industry the nature of the business case will be important as well as minimising the perceived barriers (ease / feasibility of MA submission, additional pharmacovigilance requirements).

Outline of key components of the proposed framework

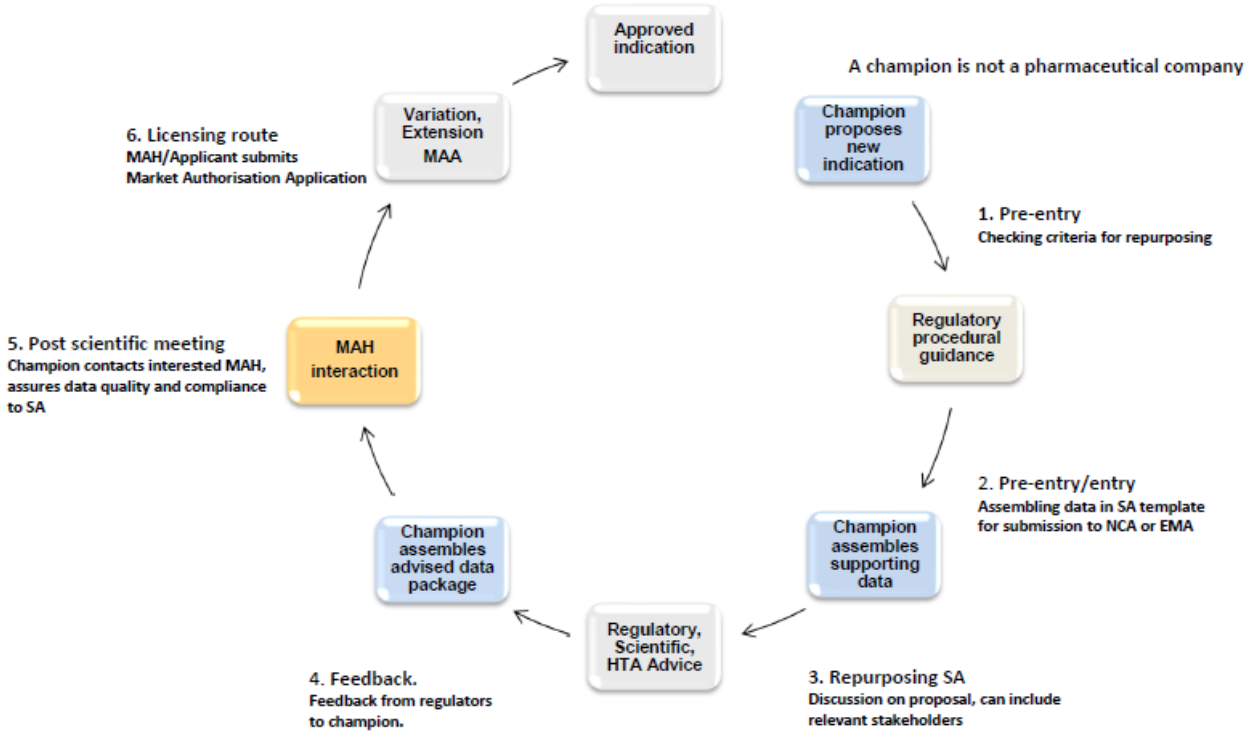
	Phase / activities	Description
1	Pre-entry	Champion identifies and has an interest in a new indication. Champion to approach EMA and/or NCA after cross checking the suitability of the project against the scope criteria (see section 3.1 for details)
2	Pre-entry / entry	Using identified data sources and / or own data, the Champion submits the proposal to enter the framework to a regulatory authority (EMA or NCA) for a repurposing scientific or regulatory advice meeting using the relevant template and topic check list that might include (but not limited to) the following aspects: - Medicinal product - Proposed repurposing indication (prevention, treatment or diagnosis of disease) - Description of the existing supporting data for indication and proposals for future data generation /development plan and questions to regulators - Scientific rationale - Discussions on available incentives as appropriate - Approaches for accessing data - Considers industry collaboration (use Article 57 database[1] to determine list of MAH, Co-ordination Group for Mutual

[1] Article 57 database on all medicines authorised in the European Economic Area (EEA) - https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/public-data-article-57-database

		Recognition and Decentralised Procedures – Human (CMDh) MRI[2] Product Index[3], access to list of industry contacts). The Champion may choose to contact one or more of the existing MAH(s) for the product of interest, in order to seek their views or input before scientific advice
3	Repurposing SA	Regulatory authority conducts meetings according to their practice with the Champion and as applicable other relevant stakeholders (MAHs, patient groups, HTA bodies, clinical investigators, other). Discussion on the proposals.
4	Feedback	Regulators provide feedback on the current and future development programme, taking into account the overall proposals and the available data. Regulators can signpost to different existing regulatory routes and incentives where appropriate.
5	Post scientific meeting	Champion takes forward the recommendations and is expected to follow the advice from the regulatory authority. The Champion considers the timing for engaging with a potentially interested MAH, if no collaboration has previously been sought or been successful – the Champion is encouraged to take forward the development programme with or without the support of a specific MAH as far as possible. The Champion may make the scientific advice feedback available to other partners to stimulate interest in the repurposing project. At the time of linking the project development programme to a collaborating MAH, the Champion acknowledges compliance alignment with the advice given by the regulatory authority, e.g. additional clinical trials or non-clinical studies conducted, data analysis (or is expected to provide justification for any deviation). If the repurposing project is left without company partner, other regulatory or MS-specific measures might apply, as appropriate.
6	Licensing route	Existing MAH holder(s) or another applicant take(s) forward the data package and submits a variation/extension/MAA to EMA or relevant NCA.

[2] MRI - mutual recognition information
[3] http://www.hma.eu/mriproductindex.html

Repurposing of medicinal products out of data & patent protection by Not-for-Profit organisations



Summary

- A Champion can be a person/entity from a charity or patient group/academic unit/learned society/research fund/payer, with a particular interest in repurposing an authorised medicinal product for a new indication and who has data evidence/scientific rationale to do so.

- A Champion puts forward sufficient supporting data for a new indication to an unprotected off-patent MP to be discussed in a repurposing regulatory scientific advice meeting.

- The repurposing regulatory scientific advice provides comments and feedback on the presented data package components, and the requirements of any future data generation (if required).

- On the basis of the advice, the Champion conducts further development and/or consolidation of the available data.

- The Champion seeks an immediate or future partnership with (a) MAH(s) depending on the stage of the development.

- For the purpose of filing the data to support a new indication, the Champion / MAH confirms that the available data are in compliance with the advice given by the regulatory authority (or is expected to provide justification for any deviation).

- The MAH(s)/applicant seek(s) an extension or variation or a MA using the existing regulatory pathways if the data package is considered sufficient.

Conclusion/ next steps
In order to test the framework, it was agreed that a pilot should be conducted to test the proposals, learn from the practical applications of candidates in the framework and build on the concepts identified. The context and the objectives of the pilot are summarised below.

PILOT OF THE STAMP REPURPOSING FRAMEWORK

Objectives and deliverables

The overall aim of the pilot is to assess whether the proposed framework is able to facilitate an application (variation/extension or MAA) for a new indication for an unprotected off-patent medicinal product.

From a regulatory perspective, the proposed framework utilises the existing scientific advice (SA) route at national or European level, in order to discuss existing evidences as well as evidence generation packages. Other elements like identification of suitable candidates, uptake of scientific advice, industry engagement and opportunities for fee incentives and regulatory designations as well as other existing tools will be explored. It is expected to be a learning exercise providing insight into the characteristics of repurposing development programmes in order to support champions in generating and/or gathering a data package that can meet the scientific and regulatory requirements.

Therefore, the following aspects will be addressed:

- Assessment of the clarity and comprehensibility of the core components and milestones of the framework from the champion's and industry perspective.
- Assessment of the steps followed by the champion to enter the repurposing framework and other complementary tools also discussed and/or used.
- Identification of gaps in the existing guidance available on the EMA/HMA[4]/NCA websites that may be applicable to repurposing, and evaluation of the potential need for adaptations (or new guidance documents/ templates for repurposing).

[4] Heads of Medicines Agencies

- Feasibility of compiling the required information/data for the scientific advice application from the Champion's perspective.
- Applicability of the Article 57 database and/or the CMDh MRI product index for identifying the MAHs and indirectly the originator, where applicable
- Opportunities for identification of potential candidates for repurposing.
- Assessment of proposed framework from the perspective of attractiveness/ fit for purpose for the industry.

Deliverables

Short term:

- Identification of list of specific candidates for repurposing (active substance, target indication) and the respective potential Champion(s).
- Application(s) for SA, compliant with applicable requirements and understanding of scientific advice scope and outcome letter.
- Project progress further to SA i.e. continuation of programme development and compliance with scientific advice outcome.
- Adjusting the framework and the roles and responsibilities of the Champion, regulatory authorities and industry in the framework according to experience gained.

Long term:

- Uptake of a repurposing candidate by one or more business companies or consider lessons learned in case of no uptake of the project by any business company.
- If appropriate, an application for a variation by a MAH or a new MA with the repurposed indication.
- In case of no uptake by industry and appropriate evidence generated by Champion in compliance with SA explore, where possible, what might be the next steps.

Identification of suitable Champions and candidates for the pilot

To be confirmed by the Repurposing Observatory Group – see next section.

'REPURPOSING OBSERVATORY GROUP' DURING THE PILOT PHASE

In order to learn from the process and conclude on the operational aspects of the repurposing framework, the STAMP working group concluded that it would be important to create a voluntary virtual observatory group. This Repurposing Observatory Group will report to STAMP and/or the Pharmaceutical Committee and will be composed of Champion interest groups, industry and regulatory representatives (and other stakeholders as appropriate).

The group will be on a voluntary basis and drawn from interested members of the STAMP and/or members of the innovation network. The Observatory Group will conclude on the practical aspects of the implementation of the pilot and report on the challenges, successes and opportunities of the framework, and can make recommendations for adaptations to facilitate the cooperation between the different parties. This group will be initially chaired by Spain, supported by a small core group of representatives from regulatory authorities. The group will act as a contact point for Regulatory authorities and other stakeholders who have been approached by potential Champions. The group may help with guiding the process across the different existing regulatory structures, establishing the necessary links, coordinating development of the practicalities for the pilot and additional guidance documents as required / appropriate.

The group will not be involved in selecting Champions or medicines for the pilot nor any individual decision making role for the individual pilot projects. The specific decisions and support will be provided through existing mechanisms of the regulatory authorities running the pilot projects.

The full remit and working methods will be discussed at the first meeting of the Repurposing Observatory Group. The observatory group has five main activities:

1. To observe and to report on the pilot on behalf of STAMP and/or the Pharmaceutical Committee.
2. To stimulate regulatory authorities to bring the pilot phase of this framework to attention of academic groups and other non-commercial organisations that have shown interest in drug repurposing or have already requested or received scientific advice.
3. To serve as contact point for procedural help for participating Champions. For example, to explain the framework when the Champion faces issues or has questions. The regulatory agencies should be asked for regulatory help.
4. To document the experiences of all involved stakeholders (e.g. regulatory agencies, Champions and industry)
5. To promote interactions with the EU Coordination and Support Action on Strengthening training of academia in regulatory sciences and supporting regulatory scientific advice (STARS) and the EU Innovation Network.

By executing these activities, the Observatory Group stimulates the pilot and helps to reach the deliverables of the pilot phase, while not being in a decision-making position.

Annex I: Useful resources, contacts and information on incentives in the EU

Resources	Description
EMA SCIENTIFIC GUIDELINES	The European Medicines Agency's Committee for Medicinal Products for Human Use prepares scientific guidelines in consultation with regulatory authorities in the European Union (EU) Member States, to help applicants prepare MAAs for human medicines. Guidelines reflect a harmonised approach of the EU Member States and the Agency on how to interpret and apply the requirements for the demonstration of quality, safety and efficacy set out in the Community directives. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines EMA's brochure 'From laboratory to patient': https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf
Scientific advice / Protocol Assistance (for orphans)	The European Medicines Agency (EMA) can give scientific advice and protocol assistance to medicine developers. For human medicines, scientific advice and protocol assistance are given by the Committee for Medicinal Products for Human Use (CHMP) on the recommendation of the Scientific Advice Working Party(SAWP). Scientific advice is when the Agency gives advice to a developer on the appropriate tests and studies in the development of a medicine. This is designed to facilitate the development and availability of high-quality, effective and acceptably safe medicines, for the benefit of patients. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance
EMA's Innovation Task Force (ITF)	The ITF is a multidisciplinary group that includes scientific, regulatory and legal competences. It was set up to ensure coordination across the Agency and to provide a forum for early dialogue with applicants on innovative aspects in medicines development. Amongst ITF objectives is to establish a discussion platform for early dialogue with applicants, in particular micro, small and medium-sized enterprises (SMEs), academics and researchers, to proactively identify scientific, legal and regulatory issues of emerging therapies and technologies. https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines
INCENTIVES	
Orphan designation	About 30 million people living in the European Union (EU) suffer from a rare disease. The European Medicines Agency (EMA) plays a central role in facilitating the development and authorisation of medicines for rare diseases, which are termed 'orphan medicines' in the medical world. Orphan designated medicinal products authorised for marketing in the EU are eligible for 10 years' market exclusivity for the orphan designated indication. https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview

Paediatric Use Marketing Authorisation	Products which are authorised for a paediatric use pursuant to a paediatric investigation plan agreed by the EMA are eligible for a separate period of data and marketing protection (8+2 years) for that paediatric indication
1 year data protection for well established substance	Well established substances authorised for a new indication are eligible for a non-cumulative period of one year of data exclusivity provided that significant clinical or pre-clinical studies were carried out in relation to the new indication
CONTACTS	
Member States, national competent authorities	The NCAs in the Member States can provide scientific or regulatory advice. A list of the NCAs is available on the Heads of Medicines Agency's (http://www.hma.eu/) webpages: http://www.hma.eu/nationalcontacts_hum.html
EU Innovation Offices The links to the documents made available by individual Member States are:	A network of EU Innovation Offices work on matters relating to emerging therapies and technologies that aim to make the regulatory support for medicines developers currently available at national and EU levels more visible. There is a list of contact points: https://www.ema.europa.eu/documents/other/eu-innovation-network-e-mail-addresses-users_en.pdf
	Spanish Office for Innovation (in English) https://www.aemps.gob.es/en/medicamentosUsoHumano/ofi-innova-conocimiento-med/home.htm UK Innovation office https://www.gov.uk/government/groups/mhra-innovation-office