HMA
Heads of Medicines Agencies

EMA
EUROPEAN MEDICINES AGENCY

EU Repurposing pilot

Report by the EU regulatory network on the learnings and recommendations from testing a proposal for a framework to support not-for-profit organisations and academia in drug repurposing

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Table of contents

Figures and tables

Executive summary

Repurposing of medicines, i.e. the identification of new therapeutic uses for existing, off-patent, authorised medicines is key to address unmet medical needs where typically there is a lack of commercial incentives for Marketing Authorisation Holders (MAHs). Not-for-profit organisations and academia can play a key role by generating evidence to support new indications.

Repurposing of medicines is a focus in the EMA Regulatory and Science Strategy to 2025. In 2019, the European Commission's STAMP Expert Group, together with EMA, NCAs, and other stakeholders, (patients, healthcare professionals, industry, health technology assessment bodies, and payers), developed a proposal for a framework to support not-for-profit organisations and academia in this space. The framework encourages early engagement with regulators through existing scientific advice (SA) route at national and European levels and promotes collaboration with MAHs to pursue formal authorisation of new indications.

To test this framework, EMA and HMA, through nine EU National Competent Authorities (NCAs) (Spain, Belgium, Sweden, Italy, Ireland, Czech Republic, Finland, Hungary, and Germany) launched a pilot in October 2021. The pilot supported champions in seeking EMA and/or NCA scientific advice free of charge for repurposing medicines and explored MAH or third-party interest in submitting applications based on the generated data.

The overall aim of the pilot was to assess whether the proposed framework could facilitate an application (variation/extension or marketing authorisation application) for a new indication for an off-patent medicinal product. In that regard, it aimed to identify suitable candidates, to characterise repurposing development programmes, to understand impact of the SA, to measure industry engagement as well as to explore the feasibility of using the EMA real-world evidence (RWE) initiatives to strengthen support to the champions.

This report summarises the tailored regulatory support provided and highlights key lessons learned, including the value of scientific advice in shaping evidence generation plans that meet regulatory standards for new indications of well-established medicines.

The report covers the period from the call for repurposing project submissions (October 2021) to the end of the last scientific advice for the selected projects (May 2024) as well as post-SA steps (until December 2024). During this time, nine projects from not-for-profit organisations and academia (termed Champions) were selected: six by EMA and three by AEMPS.

The champions were primarily hospital physicians, and researchers from academia, actively supported by patient and research organisations.

The pilot targeted repurposing projects for new indications for well-established substances in areas addressing important public health and unmet medical needs. On this basis and taking into consideration the level of available evidence, the proposed development plan and the potential benefit to the public health, most selected projects were related to rare diseases (five from EMA, one from AEMPS).

Beyond standard scientific advice processes at EMA and participating NCAs, additional tailored support was provided by regulators to each champion. This included introductory meetings, rounds of review during the briefing document preparation, and debriefing meetings on the SA outcome. Preparatory

meetings allowed not-for-profit applicants to introduce their projects, understand available regulatory services, and prepare comprehensive briefing documents for scientific advice. Follow-up debriefings helped clarifying the SAWP's position, rationale, and expectations as well as guiding champions on next steps.

Despite the limited number of projects and although each project had its own specificities linked to the disease characteristics and the robustness of the existing data, certain scientific issues were frequently encountered such as issues with inclusion/exclusion criteria of the patient population in studies, with the isolation of the effect of the investigational medicinal product when used in combination therapy or when investigated in a trial without an internal control, with the choice of the primary endpoint and with the amount of evidence for the proposed dosing regimen.

Furthermore, while the primary focus of the SA is the development plan, the pilot also tested the value of SA for repurposing projects for which the champion sought regulators' advice on the adequacy of available data for MAA. This specific situation revealed challenges for champions in appropriately describing the available data for the purpose of supporting a regulatory application and outlining the main data to establish the benefit-risk balance. It also posed difficulties for the SAWP in responding to requests for an in-depth benefit-risk assessment of the available data, as such evaluations fall outside the remit of SAWP. Nevertheless, comments were provided on the appropriateness of the study design(s) related to the available data for supporting efficacy and safety claims.

The SA process — including a tailored support with "safe harbour" interactions, reduced administrative burden, and flexible timelines — proved valuable for developing data packages that meet requirements for new indications. However, it was resource-intensive for both regulators and champions, which should be considered in future initiatives also considering that iterative SA is often necessary.

Additionally, the pilot explored the potential of using EMA's RWE generation pathways (in-house, DARWIN EU®, and EMA Framework contract) to complement the champion's dataset. However, this revealed limitations in researching specialised and rare diseases within the primary care databases accessible to EMA, similar to those identified in a previous HMA/EMA review on the experience gained with regulatory-led studies using RWD. Additionally, it was challenging to formulate relevant research questions, and RWE studies could not be completed within the SA procedure timelines.

At the time of this report, the uptake of selected repurposing projects has been limited. Only one project selected by AEMPS successfully achieved on-label approval for the new indication. For one EMA-selected project, uptake by a Marketing Authorisation Holder (MAH) is currently under consideration. However, in most cases, pharmaceutical companies have so far shown little to no interest to submit an extension of indication to their MA.

It is important to note that the majority of the projects (7 out of 9) are still under development, and the situation may evolve as data generation progresses. The pilot initiative foresaw that project champions would proactively engage with MAHs to explore potential interest. As highlighted in the above mentioned STAMP proposed framework, the pilot confirmed that identifying and contacting the appropriate person within a MAH remains a significant challenge for champions as for instance, the R&D team for the product may have been dismantled rendering difficult to establish a relevant contact person. However, despite Academia's effort to reach out to MAHs of existing originators or generics and Industry Associations' support to test a dedicated channel to help champions present their projects to their concerned members, a survey to champions flagged that they continue to face obstacles in engaging MAHs and the lack of interactions / platforms to present their projects to MAH is an issue.

Following the pilot, EMA and the EU regulatory network remain committed to supporting the selected repurposing projects. More broadly, future repurposing initiatives should consider early and iterative engagement with regulators. This includes leveraging scientific advice to support adequate data collection and evidence generation to facilitate downstream the regulatory recognition of a repurposed indication. Not-for-profit organisations and academic institutions are strongly encouraged to seek such advice early in their development process. EMA and National Competent Authorities (NCAs) offer scientific advice free of charge for eligible requests from not-for-profit entities.

Furthermore, in their support to researchers and developers from the academic sector, EMA will continue to offer a suite of measures, as appropriate to each specific case. These may include ad hoc interactions; proactive regulatory strategy development, regulatory and scientific input; review of documentation and briefing materials; debriefings and facilitated meetings with coordinators and Rapporteurs, as appropriate.

To enhance the integration of RWE into repurposing, early collaboration with regulators is essential. This should involve relevant experts from across the European Medicines Regulatory Network, including those in RWE, statistics (e.g. SAWP, EMA, and methodological working parties), to help identify data gaps and evidence needs in a coordinated manner. Additionally, future repurposing projects could benefit from a broader and more diverse range of data sources yet subject to improvement as described in a RWE follow-up report published in July 2024.

Repurposing projects may also require access to specialised support services—such as in statistics, pharmacology, regulatory science, and regulatory affairs. Related financial resources should be considered when establishing the repurposing project, notably as part of funding discussions.

To improve uptake by applicants and MAHs, Industry Associations are encouraged to facilitate connections between not-for-profit organisations and their member companies. EMA and NCAs can also explore multi-stakeholder interactions to support joint discussions between champions, MAHs/applicants, and regulators.

The proposed reform of the EU pharmaceutical legislation (currently in inter-institutional negotiations) introduces new legal measures aimed at supporting repurposing. This entails a regulatory pathway to evaluate evidence submitted by not-for-profit champions, as well as dedicated incentives for MAHs that develop repurposed use of medicinal products.

Finally, it is important to recognise that barriers beyond the level of evidence — such as funding, MAH partnerships, data package preparation, HTA processes, and pricing and reimbursement — require coordinated action from other actors involved in the repurposing ecosystem.

1. Introduction

In the context of this pilot, the term "repurposing of medicines" refers to finding new therapeutic uses for existing medicines. Although repurposing of well-established authorised medicines can contribute to address public health and unmet medical needs, the concept is not often used by marketing authorisation holders (MAHs) because of a lack of incentives and commercial interest. However, this does not prevent not-for-profit stakeholders to gather data on off-patent medicines and generate evidence to support a potential future authorisation of a new indication.

Repurposing of medicines was identified as a topic of focus in the EMA Regulatory and Science Strategy to 2025. In 2019, the Expert Group of the European Commission on the Safe and Timely Access to Medicines for Patients (STAMP)[1] developed, together with representatives of the National Competent Authorities, the European Medicines Agency (EMA), 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 drug repurposing of authorised medicines. The proposed framework aims to support not-for-profit organisations, including academia researchers, in gathering data and generating evidence for new therapeutic uses for off-patent medicinal products with the ultimate goal to facilitate the authorisation of such new indications. The proposed framework uses the existing scientific advice (SA) route at national and European level, to help not-for-profit organisations, called champions, present their proposed repurposing project to regulatory authorities and seek advice. This should then be followed by the engagement of the MAHs/applicant of the concerned medicinal products in order to apply for the new indication through standard regulatory processes.

To test this framework, EMA and HMA, through several EU National Competent Authorities (NCAs) (Spain, Belgium, Sweden, Italy, Ireland, Czech Republic, Finland, Hungary and Germany) launched a pilot in October 2021, to support champions in seeking EMA and/or NCA scientific advice (SA) free of charge for repurposing medicines. It also tested on an exploratory basis the engagement of MAHs of the concerned medicinal products (i.e. originators and/or generics) or potential third-party applicants as regard to their interest in particular to envisage the filing of the dataset.

The overall aim of the pilot was to assess whether the proposed framework is able to facilitate an application (variation/extension or MAA) for a new indication for an off-patent medicinal product. In line with the following objectives outlined in the aforementioned document and in the related HMA/EMA Questions and Answers on repurposing pilot project, the pilot more specifically intended:

- To assess the clarity and comprehensibility of the core components and milestones of the framework from the not-for-profit organisations'/academia's and industry's perspective.
- To confirm if 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 organisations/academia's perspective.

This report, which concludes the pilot, reflects on the tailored support in the context of the scientific advice provided by regulators to champions of the selected repurposing projects and presents the

[1] Commission Expert Group on Safe and Timely Access to Medicines for Patients ("STAMP") - European Commission

learnings on the process, including on the added value of scientific advice in developing an evidence generation plan that meets regulatory standards for authorising new indications of well-established authorised medicines. The report also includes recommendations based on these findings.

2. Repurposing pilot objectives and methodology

2.1. Objectives of the pilot

The proposed framework utilises the existing scientific advice (SA) route at National or European level, to facilitate the regulatory recognition of the targeted indication. Hence, the pilot aimed to identify suitable candidates, to characterise repurposing development programmes, to understand impact of the SA, to measure industry engagement as well as to explore other existing tools to strengthen support to the champions.

The main objectives and additional exploratory objectives of the pilot are presented in the report as follows:

Objective 1: Identification and characteristics of the projects

To identify suitable projects with adequate evidence and scientific rationale for a new indication that fit the core components of the targeted repurposing projects as identified in the STAMP proposal for a framework to support not-for-profit organisations and academia (institutions and individuals) in repurposing authorised medicines and listed in the below section 2.2.

In that regard, key features of the submitted and selected repurposing candidates such as number of projects, champions status, therapeutic area, rare disease target, references in EU treatment guidelines, type of available data were analysed.

Objective 2: Regulators' tailored support

To check the clarity, comprehensibility of the framework and how feasible it was for champions to compile the required information.

In that regard, regulator's support provided and readiness of not-for-profit organisations to follow the SA procedure were assessed through measurement of:

- Timeframe of the preparatory phase.
- Analysis of the type of support provided by regulators.

Objective 3: Added value of the scientific advice to the projects

To understand whether the SA procedure brings value to the repurposing development and data package as proposed by the champion to meet the scientific and regulatory requirements for filing a new indication. To also help identifying gaps in the existing guidance and need for adaptations.

This was assessed through:

- Analysis of the frequency and topics of questions posed by the champions to SAWP and NCAs and the extent of divergence between the champions' proposed development plan and the respective SAWP position.

- Analysis of the SA outcome reflected in the report as short narrative for each selected repurposing project.

Other exploratory objectives

- **Objective 4**: **The feasibility of using the EMA real-world-evidence (RWE) initiatives** in the context of the repurposing pilot.
- **Objective 5: The engagement by a marketing authorisation holder (MAH) of a concerned off-patent medicine** to claim the new indication based on the champion's data package.

2.2. Eligibility criteria for the targeted repurposing projects

Candidate repurposing projects were expected to fulfil all the following eligibility criteria:

- The project should concern authorised **medicines containing a (well-established) active substance** contained in a medicine with a valid marketing authorisation granted in a Member State or in the European Union and no longer subject to data exclusivity, market protection and out of basic patent/supplementary protection certificate (SPC) protection.
- The proposed **new indication should be in a condition distinct to the currently authorised indication(s)** listed in section 4.1 of the summary of product characteristics (SmPC) of the medicinal product in the European Union (EU) (nationally or centrally authorised, including EEA countries) to be repurposed.
- The **targeted indication must be in an area where important public health benefits / Union interests are expected** (except for the treatment or prevention of COVID-19). The pilot will prioritise conditions for which no or few medicines are currently authorised, or which are associated with high morbidity and/or mortality despite available medicines.
- The sponsor of the repurposing project, so called **'champion' is a not-for-profit organisation including academia** with a particular interest in repurposing an authorised medicinal product for a new indication, and who has data evidence/scientific rationale to do so. They are expected to be able to take forward the roles and responsibilities required by the framework, whose goal is to facilitate the bringing of the new indication to a label (see further details in below section 2.3).

2.3. Parties involved

Champions

In the context of the repurposing pilot, a champion was expected to be:

- A not-for-profit organisation[2], an academic institution[3] or a collaborative group such as a European Reference Network (ERN)[4].

[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.

[3] "Academia" or "Academic sector" should be understood as consisting of public or private higher education establishment awarding academic degrees, public or private non-profit research organisations whose primary mission is to pursue research, and international European interest organisations.

[4] "Collaborative groups and ERNs" should be understood as virtual networks or associations of people without or with legal personality involving healthcare providers and researchers across Europe.

- Of note, to be eligible from the EMA SA fee waiver, a champion could not receive funding or management from private profit organisations ("PPO")[5] in the pharmaceutical sector.
- Able to coordinate and willing to seek funding for the research programme until uptake by a pharmaceutical industry.
- Responsible for initiating and leading the interactions with regulatory authorities and MAHs / other stakeholders such as patient groups.
- Transparent regarding interactions with relevant pharmaceutical company(s).
- In charge of filing the initial request for scientific/regulatory advice based on the scientific rationale underpinning their repurposing programme for the targeted new indication on the evidence underpinning their repurposing programme for the targeted new indication.

Repurposing Observatory Group

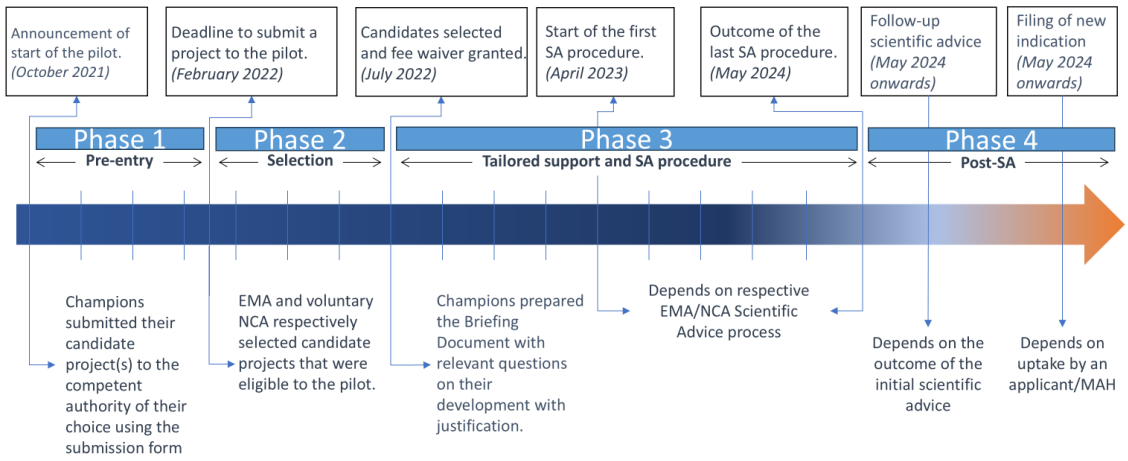
To oversee the pilot implementation, the STAMP working group created an observatory group, the so-called Repurposing Observatory Group (RepOG) composed of regulatory representatives, representatives from the European Commission, Champion interest groups and industry. RepOG is co-chaired by the Spanish Agency of Medicines and Medical Devices (AEMPS) and EMA and reports to the Pharmaceutical Committee. As foreseen, the group was not involved in selecting Champions or medicines for the pilot, nor had it any decision-making role for the individual pilot projects. Any regulatory decisions and support were provided by the regulators through existing mechanisms.

2.4. Methodology

The EU repurposing project pilot comprised 4 main phases, which are illustrated in Figure 1.

[5] They also cannot have agreements with these organisations to sponsor or participate in the specific research project under the repurposing pilot. The applicant must not be under the direct or indirect control of any PPO, which could mean that the PPO owns more than 50% of the applicant's share capital or has majority voting rights or decision-making power in the applicant.

Figure 1. Phases of the EU repurposing project pilot



2.4.1. Phase 1 – Pre-entry - Submission of applications

The submission phase lasted from October 2021 to the February 2022.

At the launch of the pilot, the following materials were published to guide non-for-profit organisations on how to apply for this pilot:

- The HMA/EMA Questions and Answers on repurposing pilot project
- The submission form

Furthermore, EMA and AEMPS organised a "walk-in-clinic" webinar for non-for-profit organisations and academia to explain the pilot and answer potential questions from stakeholders.

In order to apply, the champions first had to submit the completed submission form to the competent authority of their choice, i.e. to the EMA or to a participating NCA, to provide an overview of the data already gathered (i.e. literature references or own generated evidence), and their plan for any additional non-clinical and/or clinical studies to be conducted as well as their willingness and ability to conduct additional pre-clinical and clinical studies. This detailed information was expected to demonstrate the proof of concept for the repurposed product in the targeted indication, establish the public health interest, provide preliminary proposals for the evidence to be generated and give high-level information on resources available or needed by the champion to conduct the repurposing project.

2.4.2. Phase 2 – Selection of repurposing projects

The selection phase lasted from March 2022 to July 2022 and followed a 3-step approach.

As a first step, EMA and NCAs reviewed the eligibility of the champions *as per* the criteria described in section 2.2. and excluded applications that did not meet the selection criteria (such as applications on medicines still covered by regulatory protection, or without a marketing authorisation (MA) in the EEA).

As a second step, EMA and NCAs categorised the applications respectively submitted to them according to the following indication index:

- High: a new indication in a different condition than the authorised indication based on a different mechanism of action.
- Medium: new indication in a different condition but based on a common mechanism of action.
- Low: new indication in the same condition.

As a third step, the projects with a "High indication index" were ranked based on a scoring of the below eligible criteria developed in collaboration with the RepOG:

- Potential benefit to public health (scored as 0, 1, 3 for each criterion):
  - Life expectancy of condition
  - Quality of life
  - Current treatments
  - Availability of the treatment
  - Expected treatment effect
- Level and quality of the preclinical/clinical evidence (scored as 1, 2, 3).

Some of the projects were not considered appropriate for receiving SA since they would require additional proof of concept (PoC) studies to strengthen the rationale for repurposing, or projects where a clinical study had already started, and consequently could not have a protocol amended.

The candidate projects with the highest score were selected taking into account available SA resources (from EMA and network) and financial aspect on number of SA fee waiver which can be offered.

If a project was withdrawn from the pilot by the champion, e.g. after a partnership with a company could be found, the next project in line would be selected.

Upon selection, champions were given a timeframe of 6-months to initiate the SA process.

Based on submitted and selected candidate repurposing projects, the following features were analysed: number of projects, champions status (type of organisation), therapeutic area, rare disease target, references in EU treatment guidelines, type of available data *(objective 1 - Identification and characteristics of repurposing projects in the pilot).*

2.4.3. Phase 3 – Regulators' tailored support and scientific advice

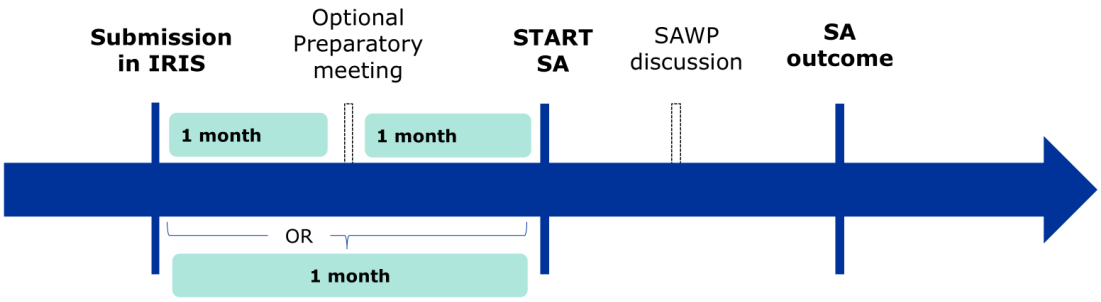
The scientific advice phase lasted from August 2022 to May 2024.

Scientific advice followed the standard processes already existing at EMA and participating NCAs, as applicable, in terms of the required documentation and timelines.

Additional **tailored support** was provided to each champion to ensure the process was well understood, the briefing document was complete enough to start the SA procedure, and the outcome delivered by the SAWP and CHMP or NCAs was well understood.

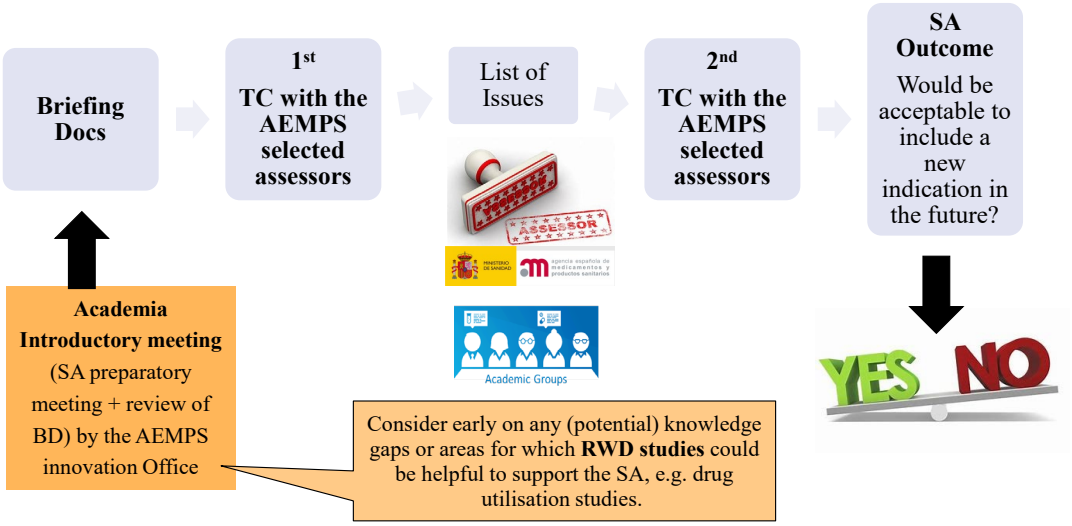
In a standard SA procedure to EMA, sponsors submit their briefing documents directly through IRIS. They can indicate if they would like a SA pre-submission meeting with EMA staff to review the briefing document. In case of a SA pre-submission meeting, sponsors have then 1 month to submit an updated version of the briefing document through IRIS, which is followed by the start of the SA procedure (Figure 2). Also, there is no foreseen debriefing meeting after the SA procedure.

Figure 2. EMA standard scientific advice



Below figure 3 shows the SA procedure followed at AEMPS for researchers.

Figure 3. SA procedure followed at AEMPS for academia and not-for profit organisation



The tailored support consisted of:

- An **Academia introductory meeting** before start of SA with submission of the SA briefing document to EMA via IRIS. This was in addition to the existing SA pre-submission meeting; thus, the champion could benefit of 2 preparatory meetings with regulators. For an application submitted to EMA, the introductory meeting was held with EMA staff from various functions: Academia workstream, scientific advice office, RWE workstream, methodology workstream and regulatory affairs office. The objective of the meeting was to clarify and explain the SA process to the champions and to address aspects of the data package and proposal for evidence generation that required further elaboration in the briefing document. When the application was submitted to the NCA the introductory meeting was held with the staff of the NCA innovation office.
- **Rounds of review of the draft briefing document** to ensure its readiness to start the SA procedure.

- A **debriefing meeting on SA outcome** was also offered to the champion after the SA outcome letter was issued by EMA. This meeting aimed to address questions that the champions may have on the SA advice and to discuss the potential next steps. The meeting was held by EMA staff and the SAWP coordinators appointed for the procedure.

The tailored support and the added value of scientific advice to the selected repurposing projects in the pilot were analysed under *objectives 2 and 3*.

Exploration of feasibility of using EMA RWE initiatives (*exploratory objective 4*): For each project selected by EMA, consideration was made whether additional data could be provided by EMA to support the pilot during the selection and the SA phases. All of the three existing pathways available to EMA for RWE generation were examined: (i) studies conducted in-house by a team within EMA of pharmacoepidemiologists and data scientists using six real-world data (RWD) sources containing mainly primary care medical records from different European countries (e.g. IMS Germany, IMS France, THIN Spain and IMRD UK); (ii) studies conducted via DARWIN EU®, a federated network of data, expertise, and services initiated in February 2022 which has access to a growing list of data partners; and (iii) studies commissioned to one of eight research organisations and consortia via the Agency's research framework contracts.

For the 23 'high-indication index' repurposing projects, EMA performed a search in available RWD sources. This search aimed to estimate the number of patients with the targeted diseases, and gather information on the use of the medicines subject to the repurposing SA, to support the assessment of the evidence provided by the champions.

In addition, it was explored whether a research question could be identified whereby use of the DARWIN EU® and EMA framework contract routes could be tested.

2.4.4. Phase 4 – Post-Scientific Advice and MAH's engagement

Exploration of MAH's engagement (exploratory objective 5): In parallel with and/or after the SA (until December 2014 for the purpose of the report), the champion reached out to the MAHs of the repurposed medicine to explore their interest to partner on their repurposing project and to apply for a new indication on the basis of the dataset they had gathered and/or will generate.

This phase could not be tested to a full extent as data generation by the champions is still ongoing for most of the projects and depends on the willingness of the MAH to file for that new indication when the data package is considered mature.

Post-SA, a survey to collect feedback from the champions on their experience with the support and process was also conducted. It also included questions on their potential interactions with MAHs, Health Technologies Authorities (HTA), payers, their plan for funding and next steps and finally biggest challenges they faced with their repurposing project. It was then complemented by a focused survey to champions to understand reasons provided by MAHs, if any, for their lack of interest in the concerned repurposing project.

3. Results

This section of the report reflects the key-findings for the 3 main objectives and 2 exploratory objectives. Objective 1 reflected on the submitted and selected projects and the other objectives only focused on the selected projects which proceeded to SA.

3.1. Objective 1: Identification and characteristics of the projects

EMA received 35 applications for repurposing projects from not-for-profit organisations and/or academia.

NCAs received 5 applications for repurposing projects from not-for-profit organisations and/or academia:

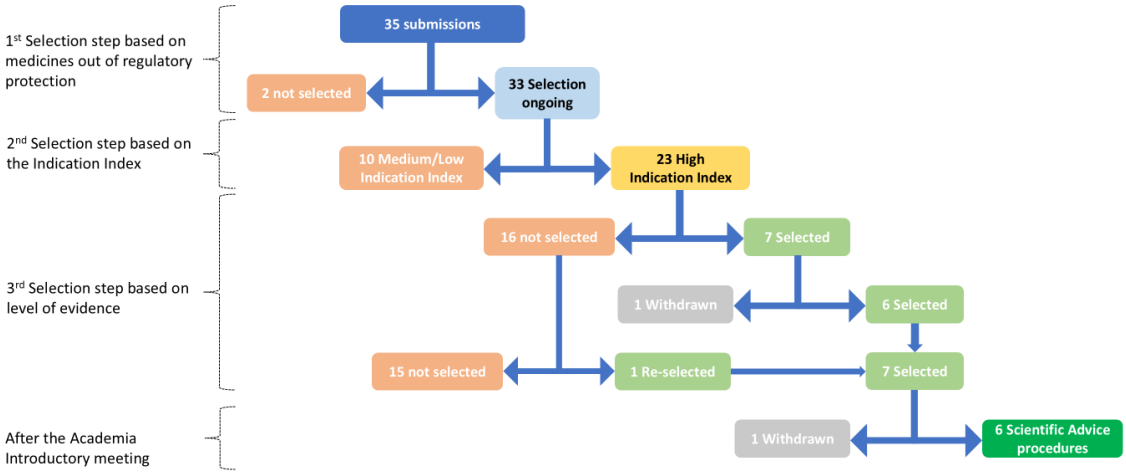
- **AEMPS (ES)** received 3 projects directly through their Innovation Office[6]. AEMPS also took over 2 projects initially received by EMA. So AEMPS processed in total 5 applications.
- **PEI (DE)** received 1 project through their innovation office[7] that they directed to EMA and therefore was part of the pool of submitted applications to EMA.

It should be noted that this was the choice of the not-for-profit organisations and academia champions to submit to EMA or any of the 9 participating NCAs.

3.1.1. Selection by EMA

Of the 35 applications submitted, 7 projects were selected, of which 6 ultimately proceeded to the SA procedure. The numbers of projects which went through each selection step can be found in Figure 4, with explanations provided underneath on the respective steps.

Figure 4. Selection steps



[6] Office for support of Innovation and knowledge of medicinal products | AEMPS

[7] Innovation Office - Paul-Ehrlich-Institut (pei.de)

Of the 35 submitted projects, all met the criteria for eligibility of the champion. However, 2 were excluded as they did not meet the criteria for eligibility of the medicine to be repurposed: in one case the concerned medicine was still covered by a regulatory protection and in the second project the product had no longer a MA in the EU.

Twenty-three of the remaining 33 projects were categorised with a "High" indication index, 4 were considered "Medium" and 6 "Low" (see description in section 2.4.2.).

Finally, based on the scoring of each sub-criteria related to the potential benefit to public health and the quality of the preclinical/clinical evidence (see section 2.4.2., third step) of the 23 "High" index projects, the first 7 projects with the higher scoring were selected for the repurposing pilot.

Of these 7 projects, one was withdrawn from the pilot by the champion after they found a pre-existing partnership with a company. Thus, the next project in line was taken on board. However, one of these 7 selected projects did not proceed to SA following the EMA-Academia introductory meeting due to methodological issues with the study design. As a result, 6 projects proceeded to the SA procedure in the context of the pilot.

3.1.2. Selection by NCAs

Among the 5 projects received by AEMPS, only 3 could be selected to take part into the pilot. The other two did not meet the selection criteria: one was a proposal for harmonisation of the product information across the EU rather than repurposing the medicine in a new indication while for the other project the proposed repurposed indication was already claimed by another applicant.

3.1.3. Characteristics of the candidate projects submitted

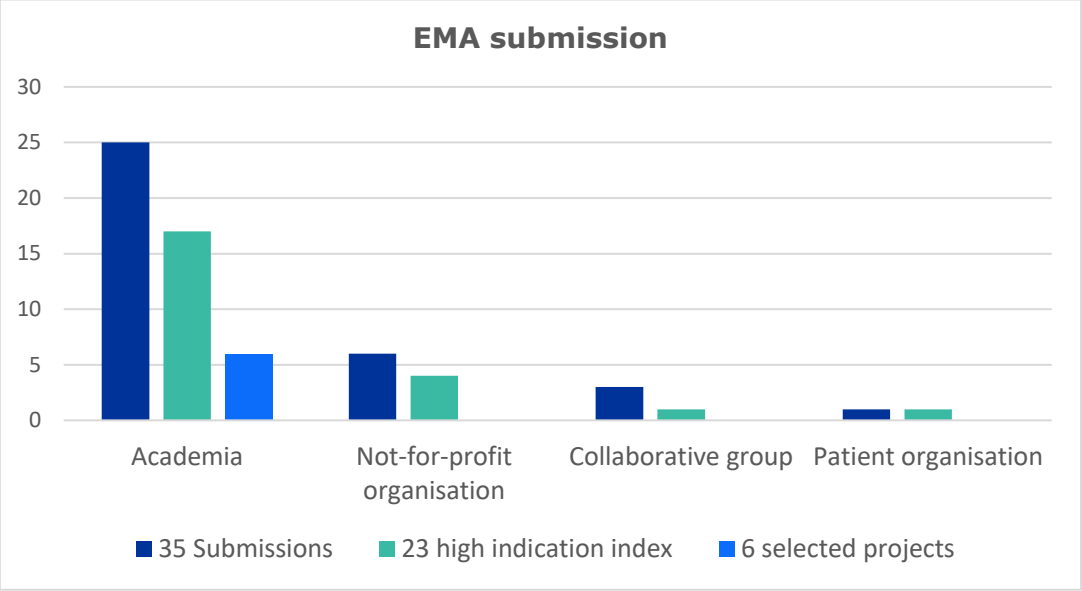
Characteristics of the candidate projects submitted to EMA and to AEMPS are provided below.

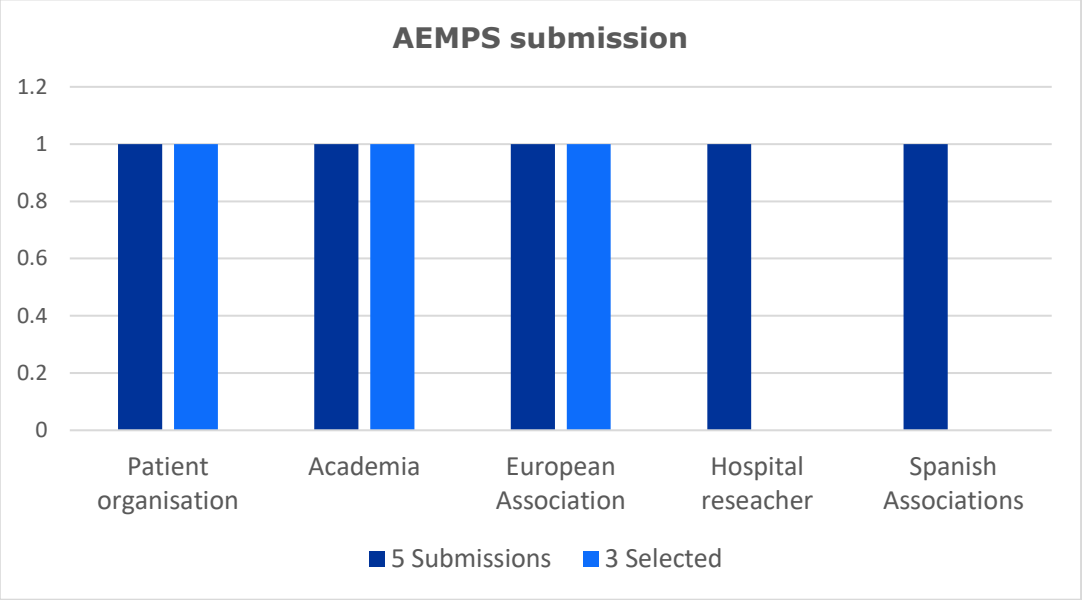
Champions' status

Champions of the 35 candidate projects submitted to EMA met the definition of not-for-profit organisation and mainly belonged to the academic sector (see Figure 5).

The champions of the 6 selected projects belonged to the academic sector. They were hospital physicians, supported by patients' organisations and/or research organisations from EU, UK or the US.

Figure 5. Champion status for repurposing projects





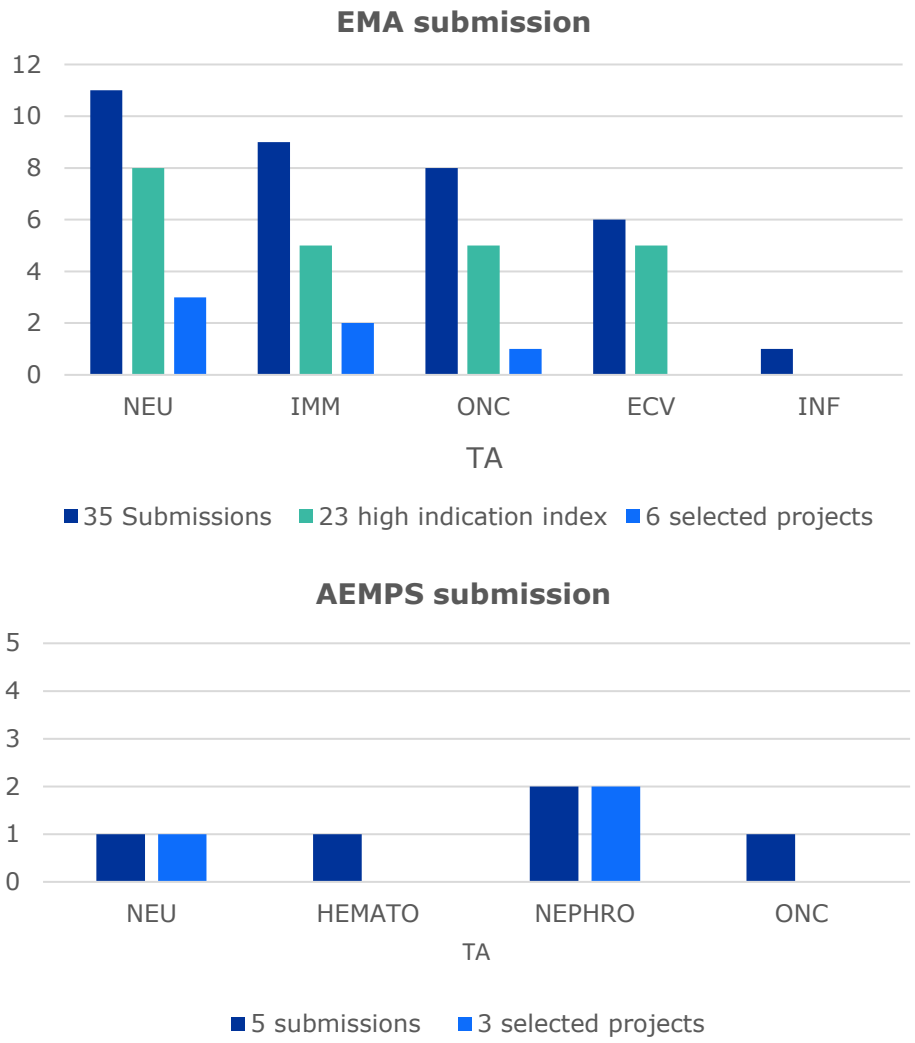
Therapeutic Areas

The 35 candidate projects covered 5 therapeutic areas (neurology; immunology; oncology; endocrinology and cardiovascular; infectious diseases, see Figure 6), with fewer projects in the infectious diseases area, for which only one project was submitted, which was considered not eligible due to the medicinal product no longer being authorised in the EU and only available through import. Of note, for EMA submissions, the therapeutic areas are broadly defined and for instance, "immune diseases" encompasses gastro-enterology / hepatology as well as dermatology diseases when related to an autoimmune disease; similarly, "endocrine-cardiovascular" also covers renal diseases.

The final 6 projects which went through EMA SA covered 3 therapeutic areas, namely neurology, immunology and oncology.

The therapeutic areas of the projects submitted to AEMPS covered: nephrology (inc. to assess renal diseases, but also for living kidney donation and renal transplantation evaluation), neurology, oncology and haematology. The selected ones were nephrology and neurodegenerative diseases. To date, in the context of this pilot, the only project that has been successfully implemented involved repurposing of Iohexol to evaluate renal function in patients in whom a reliable (accurate and precise) evaluation of GFR is needed. The target indication, for children and adults, is the measurement of the glomerular filtration rate for the evaluation of the renal function, mainly in a group of clinical conditions where a reliable evaluation of renal function is needed, i.e. patients with chronic kidney disease (CKD), living kidney donation and transplantation evaluation.

Figure 6. Therapeutic areas of the repurposed indications



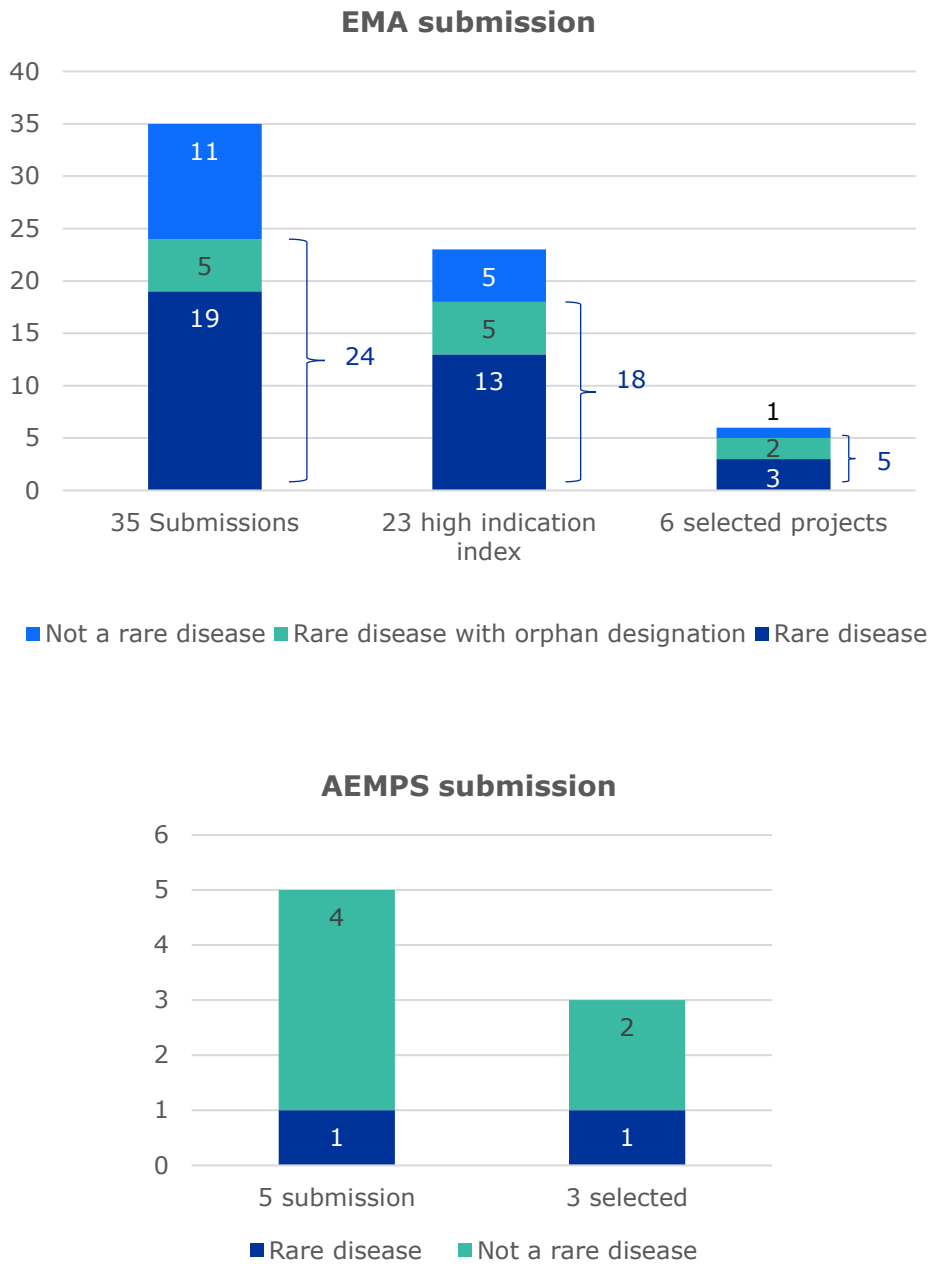
(NEU: Neurology; IMM: Immunology; ONC: Oncology; ECV: Endocrinology, cardiovascular; INF: Anti-infectious diseases; NEPHRO: Nephrology)

Rare Disease and Orphan Designation

As shown in Figure 7, 24 of the 35 submitted projects targeted a new indication in a rare disease, including 5 for which an orphan drug designation was applied for independently. Of the 6 final projects for EMA SA, 5 covered a rare disease, and for 2 projects, an orphan designation was granted in parallel to the repurposing pilot. The champions had applied for an orphan designation independently of their selection into the repurposing pilot.

Among the projects submitted to AEMPS only one covered a rare disease but the champion did not apply for an orphan designation.

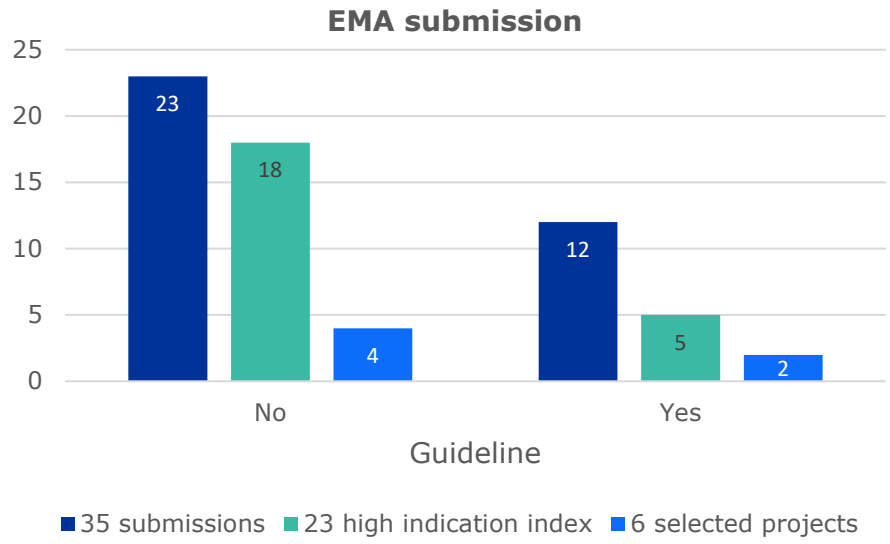
Figure 7. Repurposed indications in rare disease with/without an orphan drug designation (ODD)



Therapeutic guidelines

12 of the 35 submitted projects and 2 of the selected projects were already reflected in European therapeutic guidelines (see Figure 8) for the targeted indication.

Figure 8. Repurposed indications in EU treatment guidelines

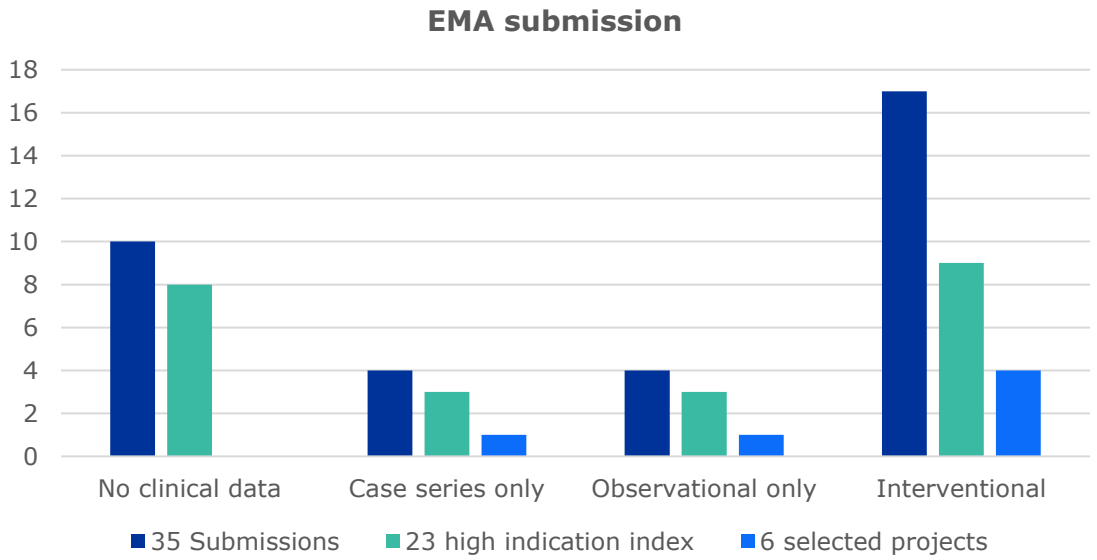


Type of available data (non-clinical, clinical)

Out of the 35 candidate projects, 10 had only non-clinical data and lacked clinical data. However, all the 6 projects selected for EMA SA included clinical data (see Figure 9) although for one project the clinical data were very limited (5 case series). Amongst the selected projects, 3 included interventional studies (one with a randomised clinical trial (phase II) and two with an open-label clinical trial (phase II)). Additionally, 1 project included non-interventional/observational studies only.

The majority of the data presented within the projects selected by AEMPS came from routine clinical practice (also known as real-world data – RWD) and from literature data.

Figure 9. Type of data submitted



Overview of the characteristics of the selected projects

This section summarises the aforementioned characteristics of the selected projects, including the evidence and scientific rationale provided by champions to EMA and AEMPS to support the repurposed indication (Table 1).

When applying to the repurposing pilot, the champions were not systematically required to make proposals for further development plans in their repurposing programme, but most champions provided proposals for data generation.

Table 1. Baseline information on the selected projects by EMA and AEMPS

Medicinal Product	Therapeutic area	Rare disease	Orphan designation	Paediatric indication#	Non-clinical data on MoA	Non-clinical data on medicine in targeted indication	Clinical data## on dose	Clinical trial data ###	Observational clinical data ###	EU therapeutic guidelines	Clinical development status	Champion's proposal for additional data generation (at pilot start)
Projects to EMA												
Case study 1	IMM	Yes	No	Yes (in addition to adults)	Yes	No	Yes	Yes	Yes	Yes	*Primary disease*: 2 uncontrolled clinical trials (literature references) + Data on registry-based study *Secondary disease*: 1 uncontrolled clinical trial + several retrospective studies	Ongoing retrospective registry-study
Case study 2	ONC	Yes	No	No	Yes	No	Yes	No	Yes	Yes	Retrospective studies based on its off-label use	Ongoing prospective registry study
Case study 3	NEU	No	Not applicable	No	Yes	Yes	Yes	No	No	No	Phase IIa, multicentre, randomised, double blind, placebo controlled (ongoing)	Toxicology study for high dosing Phase II/III clinical trial
Case study 4	NEU	Yes	OD granted	Yes (in addition to adults)	Yes	No	Yes	Yes	No	No	Phase II, randomised, open-label, blinded endpoint (literature reference)	Phase II/III clinical trial
Case study 5	IMM	Yes	No	Yes (in addition to adults)	Yes	No	Yes	Yes	Yes	No	Phase II, randomised, double-blind, placebo controlled clinical trial (ongoing)	Phase III clinical trial
Case study 6	NEU	Yes	OD granted	Yes (paediatrics only)	Yes	No	Yes	No	Yes	No	Case series	Phase II and phase III clinical trials

Projects to AEMPS												
Case study 7[8]	NEPHRO	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Non-clinical studies and clinical studies Retrospective studies based on its off-label use Retro- and ongoing prospective observational study	None
Case study 8	NEU	Yes	No	yes	yes	No	No	yes	Yes	Yes	Non-clinical studies and clinical studies Retrospective studies based on its off-label use Retro- and ongoing prospective observational study	None
Case study 9	NEPHRO	No	No	No	No	No	No	No	Yes	Yes	Retrospective studies based on its off-label use Retro and ongoing prospective observational study	That was the main question posed to the AEMPS assessors

MoA: Mechanism of action / ONC: oncology; IMM: immunology; NEU: neurology; NEPHRO: nephrology

[#] Targeted paediatric population: as intended by the champion, often mirroring whether the disease exists in the paediatric population.

[##] Clinical data on dose in targeted indication include dosing study or case series or clinical trial

[###] Clinical trial data in targeted indication this reflects the main available data at the time of the SA submission

[8] Iohexol – repurposed indication: measurement of the glomerular filtration rate for the evaluation of the renal function for children and adults, mainly in a group of clinical conditions where a reliable evaluation of renal function is needed, i.e.: patients with chronic kidney disease (CKD), living kidney donation and transplantation evaluation

3.2. Objective 2: Regulators' tailored support

Preparatory phase timeframe

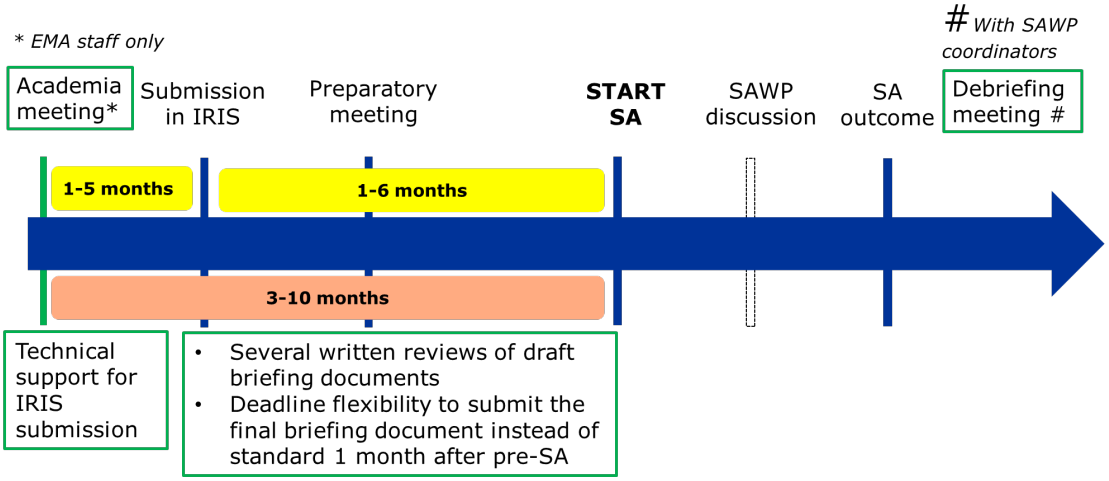
In the context of the pilot, the champions of the 9 projects selected by EMA and by the NCA had the opportunity of 2 preparatory meetings with the regulators. However, for 2 projects selected by EMA one meeting only was held (one had only the SA pre-submission meeting as submission of the briefing document was made directly in IRIS and the other had only the Academia Introductory meeting as the briefing document was finalised between the meeting and submission in IRIS).

In addition, all projects benefited from a few rounds of verbal and/or written comments to support the champions in bringing their briefing document to a mature stage for the SA procedure. There was an average of 3 rounds of review of the briefing document by the EMA staff. These occurred either before or straight after submission in IRIS. In all cases, the champions asked for extra time to address the comments and requested to postpone the SA start, sometimes more than once.

For projects submitted to EMA, all champions needed from 3 to 10 months between the Academia introductory meeting and the SA start, with an average of 6 months, to provide a mature version of their briefing document (Figure 10) as opposed to the current SA procedure which foresees only 1 month between submission of the briefing document in IRIS and the start of the SA procedure (see Figure 2, under section 2.4.3). The SA process at AEMPS is provided Figure 3.

Figure 10. Tailored EMA scientific advice procedure and timeframe of the preparatory phase

(green boxes correspond to the additional regulatory support offered to the champions)



Regulators' input during the preparatory phase

In order to reduce the administrative burden for not-for profit and academia sponsors, the Academia introductory meetings were conducted in an informal way. The champions were requested to present their project using slides and to identify their questions and topics for discussion. A preliminary draft briefing document was not requested at this stage.

During the Academia introductory meeting, champions' teams were composed of patient representatives and/or research organisations (from EU, UK or even US) as well as experts (non-clinical, statistician, clinical study design, clinician from other country, etc) as applicable. It was noted that a broad range of expertise was useful to address technical aspects such as the statistical and data analysis.

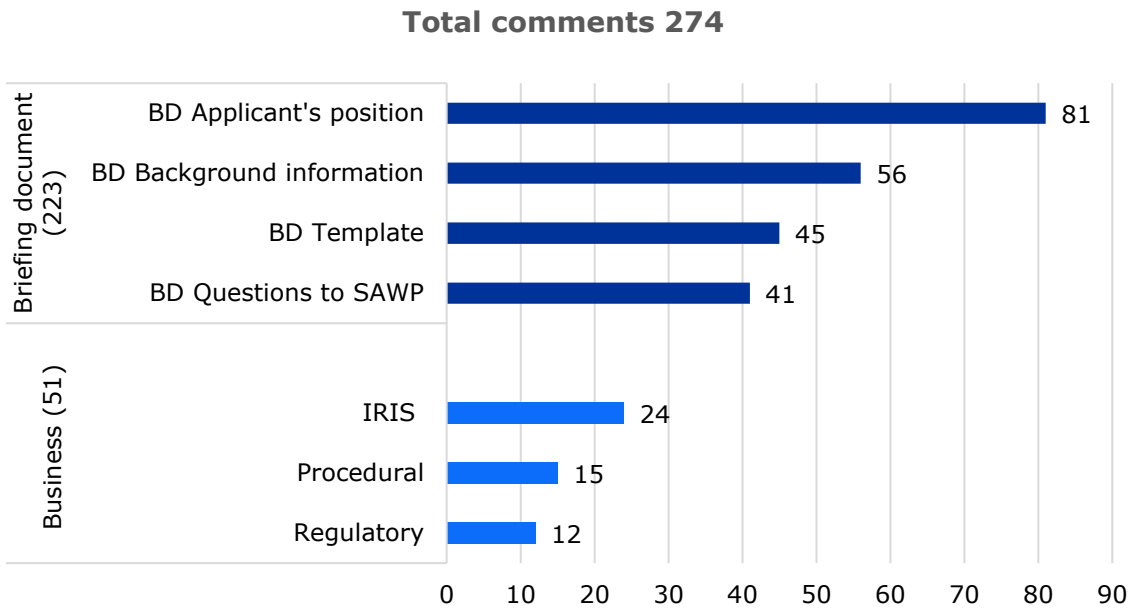
During the preparatory phase, EMA staff and the innovation office from AEMPS reviewed the draft briefing document from the champion to ensure it met the standard for seeking scientific advice from the SAWP or AEMPS, guided the champions through the procedure and addressed regulatory questions. Experience showed that providing the briefing document before the meeting allowed for a more fruitful, focused and efficient dialogue between the regulators and the champions on the proposed development program. Consequently, the input provided for the drafting of the briefing document was more concrete, and subsequent rounds of review were shortened.

To measure the value of the preparatory phase, the regulators' inputs were also compiled and categorised into 2 main groups: 1) procedural, regulatory and technical input, and 2) input on the content of the briefing document, as summarised in Figure 11. A more detailed sample of the comments made is attached to this report in Annex 1.

The input provided on procedural, regulatory and technical aspects included 51 comments, and covered for example the SA process, explanation of concept of type II variation or conditional marketing authorisation, or technical questions on IRIS (e.g. creation of a 'reference product identification', etc). The input on the content of the briefing document represented the majority of the comments, i.e. 223 in total, including:

- Comments (45/223 i.e. 20%) on the structure and format of the briefing document to improve the presentation and overview of the data;
- Comments on the formulation of the questions (41/223 i.e. 19%) (e.g. to add, group, re-formulate questions, including advice to use the right regulatory terminology or avoid redundancy);
- Suggestions to increase comprehensiveness of the briefing document (56/223 i.e. 25%) (e.g. more details on the study description such as age range of the population covered, exclusion and inclusion criteria, dosing regimen, study results, elaboration on data to support the mechanism of action, the proof of concept, pivotal versus supportive data, the dosing regimen or the regulatory application for a new indication);
- Scientific input on the project development plan and need to further elaborate champion's position / proposal (81/223 i.e. 36%) such as on study design, endpoints, methodology, etc.

Figure 11. EMA and NCA input during the preparatory phase



3.3. Objective 3: Added value of scientific advice to the projects

To analyse the added value of the SA on the development plan of the champions, the level of divergence between the development plan presented by the champions and the respective SAWP/AEMPS position was analysed. Figure 12 shows the results of this analysis, by highlighting the number of topics for which there was/were:

- "agreement", when the SAWP was overall aligned with the champion's proposal,
- "soft recommendations", when the SAWP partially agreed with the champion's position, and
- "critical recommendations", when the SAWP advised the champion to significantly change their approach on development.

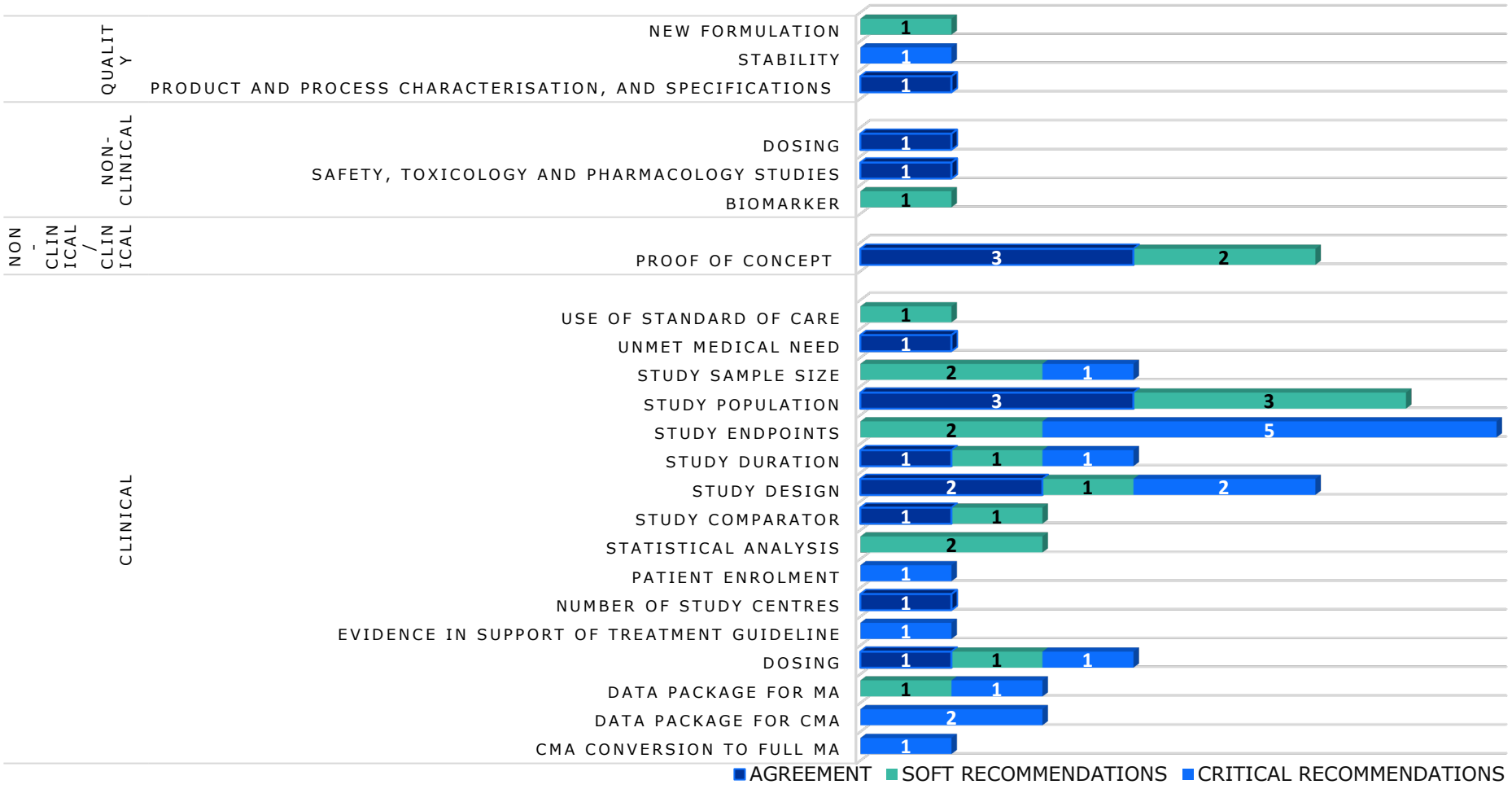
These reflect the level of convergence between the champions proposals and the regulators views on each topic. In some cases, the SAWP even made recommendations beyond the questions asked, when considered relevant to highlight additional aspects to be considered in the clinical development plan.

A narrative on each project selected by EMA and AEMPS with a summary of the SA outcome can be found in Annex 2.

A post-SA survey was sent to the champions after the SA was given for feedback on the tailored support received by regulators (see Annex 3). Champions were satisfied with the enhanced support given by EMA and AEMPS. They confirmed that the advice obtained was very important to clarify the opportunities for their repurposing project and the next steps. Some had expectations that the pilot would ensure a partnership with an MAH. Suggestions were also made to consider nomination of a dedicated EMA contact point for the champions from the start of interactions with EMA.

Figure 12. Frequency of agreement between champions' proposals and SA outcome per topics

Of note, the numbers in bars do not reflect the number of questions in SA but the topics of discussion (for instance a few questions related to the same topic were grouped).



3.4. Objective 4 (exploratory): Feasibility of using the EMA RWE initiatives

In the context of the repurposing pilot, EMA explored whether the EMA RWE generation pathways (EMA in-house, DARWIN EU® and EMA FWC (Framework contract)) could be used to support the repurposing projects during the selection phase and the SA phase.

Only the EMA in-house pathway was considered due to the short timelines of the SA process and the early establishment phase of DARWIN EU® at the time of the pilot start.

During the selection phase in June 2022, a feasibility assessment was carried out in the primary care databases accessible to EMA to quantify the extent of use of the medicines in the new indication (off-label in 2022) targeted by the 23 "high-indication index" repurposing projects. The feasibility included count of patients with the conditions of interest irrespective of treatment, patients treated with the candidate products irrespective of the indication, and the number of patients starting treatment with the candidate products after diagnosis of the off-label indication.

For 21 out of the 23 projects, sufficient exposure data to the candidate products were available in at least one database for a study (irrespective of the condition). However, the off-label indication was not explicitly recorded. One reason for that could be that most of the repurposed indications are managed in the secondary care setting. For the 6 final selected projects, no off-label use of the candidate products in the repurposed indications could be identified.

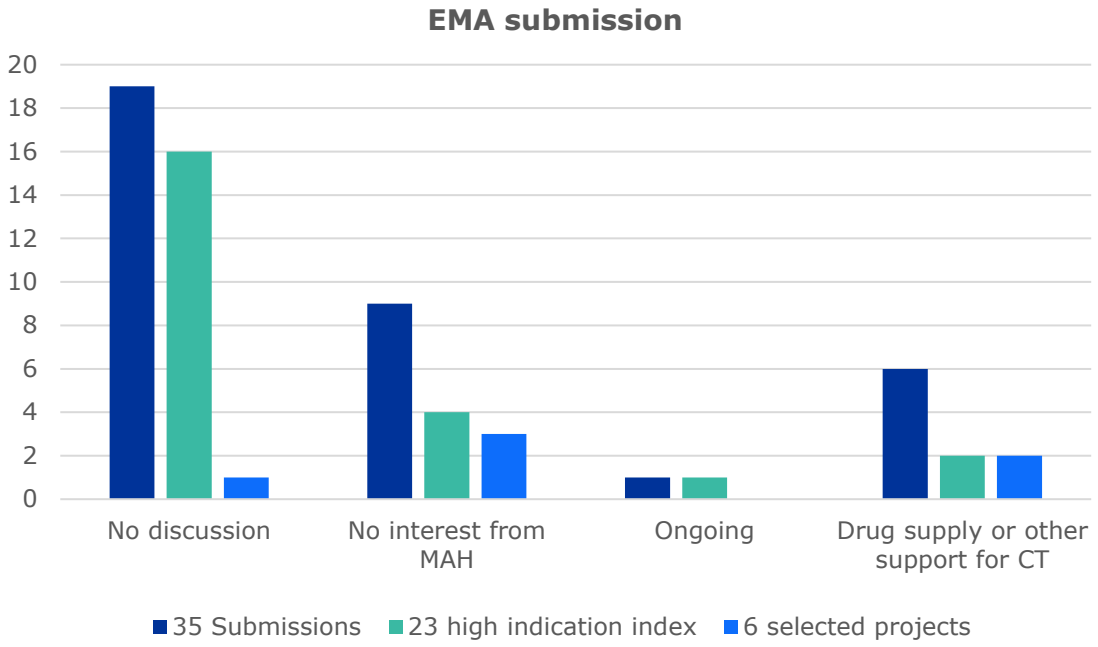
Besides the feasibility counts described above, considerations were made in preparation of scientific advice on whether any other RWD would be needed to complement the provided evidence on a specific aspect. However, no research question could be identified during the SA procedure in the pilot and therefore no feasibility assessment for a RWE study, through the EMA RWE generation pathway was carried out.

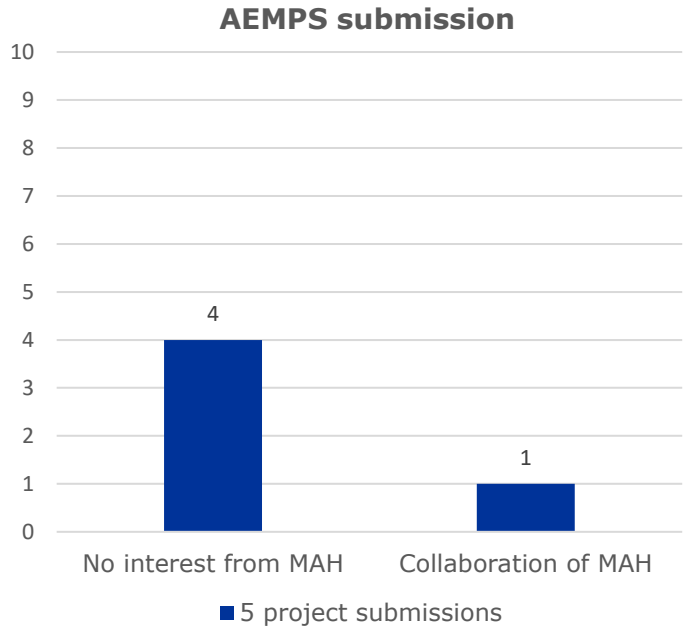
3.5. Objective 5 (exploratory): MAH's engagement

As suggested in the STAMP repurposing framework, champions were encouraged during the pilot to contact one or more of the existing MAH(s) of the authorised medicinal products containing the concerned active substance to explore their interest to partner on the data generation and/or to apply for the targeted repurposed use based on the champion's dataset.

In the submission form, candidate champions were asked to report on any interactions with MAHs in relation to the repurposed medicine before start of the pilot. In that regard, as seen in Figure 13, for 19 of the 35 submitted projects (54%), the champions indicated that they did not engage with the relevant MAHs. Out of the remaining 16 projects for which champions explored with MAHs, 9 did not receive any interest from MAHs, however of note, 6 reported support in terms of medicine supply, and for one project the interaction was ongoing. For the final 6 selected projects, 3 did not attract interest from MAHs, 2 received support with the supply of the medicinal product and for one project the champion did not engage with MAHs. At AEMPS among the 3 selected projects, 2 did not attract interest from MAHs and 1 did engage with the MAH.

Figure 13. Champions' interactions with MAHs (at time of entry into the pilot)





In addition, two surveys were also conducted with the champions of the 9 selected projects, to collect their feedback on any new/additional interactions with MAHs further to the SA outcome. Questions and outcome can be found in Annex 3. Seven of the 9 liaised with the MAHs of authorised medicinal products, but no MAHs expressed an intention to file for the repurposed indications at that stage. One champion explained that in the absence of supply from the MAH, a small manufacturing entity would

have to produce the investigational medicinal product for the clinical trial. Another champion indicated that they obtained support from a company to be able to conduct the phase II clinical trial.

Finally, the champion of one EMA project received help of a research organisation, to participate in a pilot by Medicines for Europe (Mfe) developed with the REMEDI4ALL consortium[9], whereby Mfe acted as an intermediary party to help share information with their members, those being MAHs of the concerned generic products. For use of this channel, champions had to provide a summary of the evidence for the targeted indication and of the SA outcome. This led to interactions between a champion and one MAH, owning a generic of the concerned active substance, which are still ongoing at time of this report. In order to facilitate the transmission of knowledge from the champion to the MAH regarding the SA outcome by the SAWP, the EMA offered a multiparty meeting including the national competent authority acting as RMS of the authorised generic.

Furthermore, for one project submitted to AEMPS, interactions between the champion and the relevant MAH (GE Healthcare) were facilitated by AEMPS (through the innovation office) to explore whether the MAH would consider submitting a variation to apply for the new indication. Following the meeting between the MAH and the AEMPS, the MAH acknowledged the potential benefit for the patients to include this new indication in the SmPC. Therefore, this resulted in the MAH filing including Spain and Portugal in a worksharing procedure for the new indication. In order to incentivise the MAH and according to the Article 121.5 of the Royal Decree 1/2015, which approves the consolidated text of the Law on Guarantees and Rational Use of Medicines and Medical Devices, it establishes a partial exemption from the payment of fees for marketing authorization holders of medicinal products when the AEMPS or the European Commission requests a modification for public health reasons. In such cases, the fee is reduced by 95%. Therefore the, MAH only paid the 5% of the Type II variation to fill the new indication for the Iohexol MA.

[9] REMEDI4ALL project : European platform for medicines repurposing which received funding from the European Union's Horizon Europe Research & Innovation programme

4. Discussion

4.1. Objective 1: Identification and characteristics of the projects

Champions status

The champions who applied for the scientific advice were in most cases physicians and researchers from the academic field. They were supported by patient organisations and research organisations who played an active role in the process, from bringing the pilot to their attention, supporting the preparation of the briefing document, to helping approach MAHs to seek their interest in the concerned project.

The champions were primarily hospital physicians, and researchers from academia, actively supported by patient and research organisations.

Selected repurposing projects

The number of repurposing applications submitted confirmed that there is an interest from not-for profit organisations and academia to repurpose medicines and to seek advice from regulators on the development in order to facilitate the addition of a new indication to the label of the existing medicinal products. It could be noted that number of the repurposing candidate projects were submitted upon the choice of the not-for-profit organisation to EMA. It is understood that not-for profit organisations are looking for an EU position on their repurposing development in the understanding that the targeted repurposed indication should benefit the patient population across the EU.

The pilot covered repurposing projects targeting therapeutic areas where important public health benefits / Union interests are expected. Although the focus was not specifically on rare diseases, the projects were mostly related to such conditions (24 out of 35 submitted projects - 68% and 5 out of the 6 selected projects - 83%; 1 from selected project by AEMPS). Indeed, development of medicines for rare diseases can strongly benefit from SA, considering the potential challenges linked to the limited numbers of patients available for evidence generation, or the difficulties in establishing primary endpoint in these conditions.

Of note, only a limited number of champions applied for an orphan designation (5 ODs out of the 24 projects on rare diseases - 21%, and 2 ODs out of the 6 selected projects - 33%). Whilst not knowing the reasons why there were not more requests for orphan designation, it could be speculated that academia champions were not aware of the orphan pathway, nor considering the downstream market exclusivity incentive as they have no intent to be the MAH. Nonetheless, the pilot was not aimed at stimulating orphan designation.

The selected projects varied in terms of the level of available non-clinical and clinical evidence and plans for further development. Some had no further development proposal, other were at an early development stage. In this respect, projects ranged from: 1) a completed proof of concept with a plan for phase II clinical trial, 2) phase III proposal, and 4) literature references with use recognised in scientific therapeutic guidelines. This showed an important variety in the development stages and dataset of projects selected in the pilot.

The pilot targeted repurposing projects for new indications for well-established substances in areas addressing important public health and unmet medical needs, resulting in a number of the projects targeting rare diseases. The selected projects varied in terms of the level of available non-clinical and clinical evidence and plans for further development.

4.2. Objective 2: Regulators' tailored support

Facilitating scientific advice for academia is crucial to provide an opportunity for dialogue with regulators on how to generate and/or gather data for a repurposed use in accordance with the scientific and regulatory expectations.

In that regard, the pilot aimed at providing a tailored support to address the potential shortcomings stemming from not-for-profit organisations and academia's unfamiliarity with regulatory processes.

As seen in the pilot and reported by the champions in the feedback survey, an adapted process with introductory and debriefing meetings, flexible timelines to start the SA, as well as reviews of the SA briefing document, were beneficial to:

- Enable a first interaction with regulators through a lighter administrative process (without having to submit a briefing document via IRIS) more accessible to not-for-profit organisations and academia, so they can gain confidence into the regulatory system to present their projects.
- Allow champions to familiarise themselves with the regulatory tools and expectations by obtaining detailed guidance and explanations on the different steps in an informal way. In general, academia is not fully familiar with the regulatory system and the procedural steps which can be perceived as complex. In particular it was important to clarify that SA is not a pre-assessment of data and that the answers by regulators depend on the way questions are phrased.
- Support champions in completing the briefing document in line with the required standards. In all cases, several revisions of the document were needed to allow start of the SA procedure. The main recurring issues on the briefing document were the lack of detailed description and analysis of the existing evidence, and the lack of clarity and information on the proposed study design. Significant input was also provided on phrasing the questions, to ensure that they covered the key points so that responses would be relevant.
- Accommodate the need of champions to have flexible timelines for preparing for scientific advice to ensure the maturity of the briefing document to initiate consultation with SAWP or NCAs. While flexibility is recognised, experience showed that those preparatory interactions can gain value, having a draft of the briefing document already at the time of the introductory meeting, even an early version. It helps focusing the discussion and speeding up the preparation of the briefing document to allow start of the SA within a reasonable timeframe from the initial interactions.
- Provide early insights by regulators on the data package and development plan so adjustments and refinements of the final proposal could be made before presentation to SAWP. For instance, in one case the champion considered two phase III study designs to investigate a combination of 2 medicines, and to investigate the monotherapy. The preparatory meeting helped the champion to opt for one proposed study design to seek SA on.
- Clarify and discuss the SA advice letter. The experience showed that the debriefing meeting brings value in conveying and explaining the SAWP views to the champions, especially, in cases where no

discussion meeting with the SAWP took place during the SA procedure. Such direct exchanges help champions to better understand the regulators' perspective, in particular by enabling an open discussion on points of divergence, explaining the SAWP outcome in case no definite recommendations could be given due to lack of clarity in the champion's proposals, brainstorming on any gaps flagged, and risks for applying for the indication if those gaps are not addressed as recommended by the SAWP. Regulators noted the need for clearer and simpler SA conclusions. In addition, for the regulators, this post-SA interaction helped understand the champions' intention as regards their plan to move forward the development and to consider a potential follow-up SA.

A tailored support — with "safe harbour" interactions, reduced administrative burden, flexible timelines and debriefing discussions on SA outcome — proved to be valuable for not-for profit organisations. However, challenges on capacity from both sides of the regulators and the champions, should be considered in future initiatives also considering that iterative SA is often necessary.

4.3. Objective 3: Added value of the scientific advice to the projects

The selected projects varied from having no further development proposals to being at an early development stage. In some cases, the champions considered the available data adequate for an MAA and did not present plans for conducting additional studies. In such cases, the questions pertained to the adequacy of the existing data package for a (conditional) marketing authorisation. However, in most projects, the champions presented their plans to design studies aimed at confirming the benefit of the repurposed medicine for the targeted indication. Although limited, some SA applications also included a few questions on the quality and non-clinical development.

Questions on quality aspects

Quality questions were raised in only 3 of the 9 SA selected projects. The low number of such questions can be explained by the fact that, in repurposing projects, no further quality development is typically foreseen, as medicines already authorised are used in line with the scope of the pilot. The questions raised including the following:

- A proposal to waive stability testing for the investigational product for the planned trials. This was not agreed by SAWP.
- A question on a potential change of formulation from a tablet to capsule post-licensing, aiming at improving palatability, and whether a bioequivalence study would be required for the new formulation. SAWP considered that in case the capsule contains the same excipients in the same quantity as the tablet, and if certain requirements of disintegration and dissolution time for the capsule and tablet are fulfilled, then reference to a Biopharmaceutics Classification System (BCS) class biowaiver may be acceptable and a bioequivalence study may not be necessary.
- A proposal not to conduct additional studies related to product and process characterisation or specifications for two formulations of the same authorised product formulations which are currently being studied in clinical trials for the new indication. SAWP agreed with this approach, while recommending further justification of the safety of preservatives contained in the authorised formulations, and consideration of additional studies (e.g. genotoxicity), if the product is intended for paediatric use.

Questions on non-clinical aspects

In all SA procedures, champions asked questions on non-clinical aspects. The most frequent question asked was about the adequacy of proof of concept (PoC) data for further development of candidates. Other questions pertained to use of a biomarker supporting the mode of action (MoA), dose selection, and adequacy of the non-clinical data package for MAA.

For most candidates in the pilot, the PoC data were considered adequate for further development. There were no critical recommendations by SAWP and AEMPS on any questions regarding non-clinical development. However, SAWP and NCAs recommended that ongoing trials and emergent data should also be evaluated before conducting additional studies.

For repurposed medicines with a well-known safety profile and preliminary clinical data supporting their use in the new indication, further animal studies may not be necessary to further characterise their safety and toxicity. For candidates with an uncertain MoA, more research may be needed to elucidate their MoA to minimise exposure of patients to a potentially ineffective medicine. Also, in case of further clinical development, especially in a rare disease setting where limited clinical development usually takes place due to feasibility issues, biomarkers linked to the MoA can be used as additional support for evidence of efficacy.

Dose selection for repurposed medicines can concern both, non-clinical and clinical data and, therefore, questions were asked under the respective areas of advice or as multidisciplinary non-clinical/clinical questions. In the majority of repurposing projects, there were gaps in relevant information and a need for additional support for the proposed dose/dosing regimen, especially when higher doses than authorised were proposed. In some cases, a need for investigation of dose-response relationships was identified. In that regard, SAWP highlighted that pharmacokinetic (PK) data in the target population and patients with renal/liver impairment may be needed. PopPK modelling can aid in optimising dosing regimens. The need for additional drug-drug interactions (DDI) studies also needs to be addressed, as different concomitant medications may be used in the new indication. Pragmatic approaches should be considered for determining effective and tolerable doses, potentially supported by additional in vivo studies. As part of the AEMPS SA, AEMPS also considered that in 2 of the 3 projects the dose presented was not sufficiently supported by the data provided and additional bibliographic information or further studies would be required.

Questions on clinical aspects

Clinical questions were most frequently asked and concerned the adequacy of the data package and whether it meets regulatory requirements for benefit-risk assessment. They focused on the design and key elements (study endpoints and population) of completed, ongoing and planned phase II or phase III studies.

In four repurposing projects (2 submitted to EMA and 2 submitted to AEMPS), there were no plans to conduct additional studies. Instead, the champions considered that the existing data from off-label use in retrospective studies or uncontrolled clinical trials adequate to establish the safety and efficacy for the targeted indication and sought confirmation from regulators. These were cases where either the repurposed medicines were considered standard of care (SoC) in the new indication, or the champions considered the gathered information sufficient to support the new indication. For one project received by EMA, SAWP identified some weaknesses in the existing data but acknowledged that due to the existing off-label use of the medicine, the rarity and severity of the target diseases, and the limited available therapeutic options, it would be difficult to conduct additional controlled trials. For the other

project received by EMA, SAWP discussed limitations of endpoints in completed studies, in particular time to event endpoints which are not usually suitable for uncontrolled trials. SAWP and NCAs therefore recommended generating additional data (e.g. observational study or registry-based studies) to demonstrate the benefit. Moreover, for both projects, SAWP found some uncertainties in the posology for the new indication and recommended more details to justify the proposed dose/dosing regimen. Overall, evidence synthesis is important in such cases and well-designed searches and analyses of the available data are needed, including a scientific methodology and a comprehensive discussion of the findings and limitations.

The other two projects were received by AEMPS. For Iohexol, a low osmolarity water-soluble, non-ionic non-radioactive X-rays contrast agent, used in diagnostic radiology examinations, AEMPS agreed that no additional clinical trials were required to support its use in measuring glomerular filtration rate (GFR), since there is more than 30 years of evidence on the use of iohexol as a marker of renal function. Therefore, the data presented by the Applicant, together with the RWD, were sufficient to include the new indication within the Iohexol MA. For the other project, AEMPS highlighted the need to generate data from clinical trials in order to substantiate the effect reported in the literature, which was based mainly on observational studies and only one completed clinical trial in which the most relevant endpoint for the indication was included as an exploratory endpoint.

The other five projects (four selected by EMA and one selected by AEMPS) were in the early development stage, planning for a phase II or phase III study, and questions focused on the design and key study elements, e.g. randomised vs single-arm study, choice of a comparator, population characteristics, dose, primary and secondary endpoints, study duration, and sample size/statistical analysis. After reviewing the champions' proposals, SAWP discussed possible changes to the study design with some champions during the SA procedure. This allowed the champions to suggest alternative designs before finalising the advice letter. In cases where a phase II study was ongoing during the SA process and the questions on the phase III study design were based on a preliminary study protocol, SAWP provided some initial recommendations but requested that the champions seek follow up advice once the results of the phase II study and a more mature phase III study protocol were available. In one of the projects selected by AEMPS the target population was very heterogeneous, leading to difficulties in demonstrating an effect. Moreover, the assessors stated the need to perform both Phase II and Phase III clinical trials to complete the clinical development plan.

In one case, a dose-finding phase II study was ongoing, and the champion explored the possibility of seeking a conditional marketing authorisation based on these results. Although SAWP was concerned that the doses studied, population and primary endpoint were not sufficiently justified to support a robust benefit-risk assessment, it considered that the results could be useful in designing a phase III study. Although, in a rare disease setting, a dose-finding, proof-of-concept phase II study may be used as the basis for initial marketing authorisation, the proposed design and key study elements should be appropriate to provide interpretable efficacy data, which could subsequently be confirmed in a phase III study. The majority of projects selected concerned development in rare diseases where challenges in generating evidence that meets regulatory requirements are well known and not specific to repurposed medicines. While conducting a randomised clinical trial (RCT) presents various challenges, it remains the design recommended by regulators because it minimises bias and facilitates comparative analysis. This approach increases certainty in determining the true efficacy and safety of a medicine.

If more than one medicine is to be studied, regulators’ advice should be sought to ensure that the study is designed in a way that allows the effects of the medicine to be isolated. In rare disease

settings, a single phase III study is usually considered adequate for benefit-risk assessment, provided that the study is particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency. For diseases where regulatory guidelines apply, these should be considered when designing studies and champions should discuss any deviations or uncertainties when seeking SA. Furthermore, if an application for a conditional marketing authorisation is planned, an extended follow up of patients beyond the initial data analysis should be foreseen to demonstrate long-term clinical outcomes, especially when no additional confirmatory study is planned.

The majority of critical recommendations on key study elements concerned the choice of endpoints. For some studies, SAWP considered that the proposed primary endpoints were not easy to interpret in terms of clinical benefit and asked for further justification and/or revision. In addition, some concerns related to composite endpoints were raised with the champions. In some cases, identifying a minimal clinically important difference for the primary endpoint was shown to be challenging. This depends on the targeted population and SAWP asked for further justifications due to further implications for the study design. Including secondary endpoints which reflect clinical benefit in symptoms not covered by the primary endpoint, as well as biomarkers to provide mechanistic evidence are recommended, especially in the case of rare diseases where the totality of evidence is important for benefit-risk assessment.

In all repurposing projects, SAWP agreed overall with the proposed population. In some cases, SAWP made recommendations to further improve the patient selection. SAWP suggested to carefully consider the inclusion/exclusion criteria in cases of a concomitant disease, which could have an impact on interpretability of data. In some cases, the population was very heterogenous in terms of disease severity and progression, which could decrease the chances of observing a beneficial effect within a reasonable timeframe. An enrichment approach can be useful for this purpose, as enrolling individuals with a higher chance of experiencing the event(s) being studied can speed up the development process. On the other hand, in rare diseases, it was acknowledged that all efforts should be made to include as many patients as possible. In case where a specific population is intended to be studied (e.g. paediatric patients), careful consideration of existing non-clinical and clinical data is needed, and staggered inclusion of such patients is usually recommended to ensure safety.

In most cases, the existing real-world data[10] and the planned analysis to provide real world evidence (RWE) were insufficiently described in the champions' development programmes to allow for adequate analysis by SAWP. RWE study milestones were not always clear, nor did the applications include detailed protocols describing the methodology for data collection, analysis, and the parties involved. Descriptions of data sources to evaluate the RWD were lacking, including for example, data elements to be collected, data management processes, governance aspects, data quality assurance, geographical coverage, ethical aspects (consent, ethics committee opinions) etc.

[10] Real-world data (RWD): can be defined as data collected prospectively or retrospectively from observations of routine clinical practice (outside clinical trials)

The Scientific Advice Working Party (SAWP) and National Competent Authorities (NCAs) provided extensive recommendations on many clinical aspects to help adjust development plans and generate appropriate efficacy and safety data that would best characterise the benefit-risk of candidate medicines in the targeted repurposed indication through the relevant regulatory pathway for approval. The level of input depended on the strength of the data (preclinical data and early phase clinical studies) and on the design to generate the evidence. This also highlights the importance of seeking advice early in development, as regulators can more effectively support on a prospective development plan.

While the primary focus of the SA is the development plan, the pilot also tested the value of SA for projects where the development in the targeted repurposed indication was considered complete by the champion and the champion was seeking advice on the adequacy of the data package to support the benefit risk balance. This specific situation revealed two challenges: 1) difficulties experienced by the champions in clearly describing the available data and outlining the main evidence to establish the benefit-risk balance; 2) challenges for the SAWP in addressing requests to perform an in-depth benefit-risk assessment of available data which is not within the scope of SA. However, comments were provided on the appropriateness of the study design(s) related to the available data to support efficacy and safety claims.

4.4. Objective 4 (exploratory): Feasibility of using the EMA RWE initiative in the context of the repurposing pilot

The use of the EMA RWE generation pathways (in-house, DARWIN EU® and FWC) in complement of the champion's dataset was explored during the pilot. However, some challenges were observed. Whilst the conduct of drug utilisation studies (DUS) could have been useful to understand the extent to which the repurposed medicines were already used off-label in clinical practice; these were not feasible due to the care setting covered by the databases accessible to EMA at that time. Indeed, as most of the selected projects concerned rare diseases managed in hospitals and specialised care units (secondary and tertiary care), no or only limited relevant data could be identified in the available primary care databases.

Additionally, off-label use is not systematically nor consistently captured in RWD sources, which can lead to missing and/or misclassification of information that would create various types of study biases. Moreover, RWE studies on specific topic were not requested during any SA procedure. Furthermore, for a study to be completed within the timelines of the SA, only the in-house pathway could potentially be considered. The other two pathways (DARWIN EU® and EMA FWC) were ruled out, as in view of their level of maturity at the time of the pilot (e.g. 2nd year of establishment of DARWIN EU®), a study via DARWIN EU® or the Agency's framework contract would have required more than two months.

The challenges of RWD evidence in specialised and rare disease settings were already recognised in a previous HMA/EMA review on the experience gained with regulatory-led studies using RWD.

This resulted in the recommendation to widen the access within DARWIN EU® to a larger range of data sources including secondary care databases (ideally with linkage to primary care data), and (networks of) registries amongst other. Progress has been made to date, especially through the expansion of the DARWIN EU® data partner network, the development of standard analyses and phenotype libraries, the increased awareness of the EU regulatory Network in formulating research questions and requesting studies to EMA to support regulatory assessment. All these improvements have been described in a RWE follow-up report published in July 2024.

Identification of gaps and needs as well as a potential research question whereby EMA RWE initiatives can be used would require iterative and closer interactions in a structured and consolidated manner with regulators.

4.5. Objective 5 (exploratory): MAH's engagement

At the time of this report, a limited uptake of the selected repurposing projects has been observed: only one project selected by AEMPS was successful in bringing on label the new indication, and for one project selected by EMA, the uptake by a MAH is under consideration. However, for most of the cases, no interest by pharmaceutical companies was reported. However, it should be noted that most of the projects (7 out of 9) are still under development and the situation may evolve as the data generation is progressing. Academia reported difficulties in identifying the relevant contact point/ function to reach out within a company. Despites the STAMP repurposing framework encouraged MAHs to advertise a dedicated e-mail address for repurposing enquiries on their websites, Medicines for Europe (Mfe) and European Federation of Pharmaceutical Industries Associations (EFPIA) indicated that establishing a fixed contact point was not feasible for various reasons such as own company's organisation, change in its organisation and turnover of staff, for instance several years after obtaining a MA for a product, MAHs do not necessarily maintain an R&D team for the product. Instead, Mfe tested a form, developed with the REMEDI4ALL consortium[11], to help academia reaching out to their members to introduce their repurposing project. While Mfe indicated that for the time being there was only limited use cases, the form showed to be useful. Mfe also reported that champions had difficulties in translating the outcome of SA procedures to companies through the form.

It could be noted that the support of AEMPS in facilitating the interactions between the champion and the MAH was key in bringing this repurposing project to the attention of the MAH and seeking their interest to apply for the repurposed indication. Likewise, the EMA support to offer a platform of discussion between the champion, the regulators and the potential MAH was considered useful to help the champion and MAH progressing a potential filing of the repurposed indication.

[11] REMEDI4ALL project : European platform for medicines repurposing which received funding from the European Union's Horizon Europe Research & Innovation programme

In the dedicated surveys, champions highlighted issues with engagement from MAHs as one of the biggest challenges they faced in repurposing medicines: lack of pharma interest, no support to get an MAH on board, lack of funding to complete the trial in a rare disease, unavailability of the drug to conduct a prospective clinical trial.

Although no direct Industry feedback to explain this lack of engagement was collected, it can only be assumed that there are multiple factors such as evidence coming from a third-party, liability issues, expertise of the company in the therapeutic area, pharmacovigilance and potential post-authorisation requirements, HTA and payer challenges ('cross-label' use and pricing and reimbursement hurdles for such new indication), manufacturing and supply chain constraints, as reported in a recent EFPIA position paper on drug repurposing (March 2024). In a separate report from Medicines for Europe on Advancing Medicines Repurposing in the EU (March 2022) it is also highlighted that regulatory costs can be significant, especially in the absence of dedicated regulatory and market access pathways.

5. Learnings and recommendations

The pilot of the proposed STAMP repurposing framework aimed to provide support to nine selected projects (6 by EMA and 3 by AEMPS) from not-for-profit organisations and academia (termed 'Champions') in seeking regulators' advice on generating and gathering the adequate scientific evidence for a new indication for well-established, authorised medicines, with the goal of facilitating bringing on-label the new indication by the respective MAHs or any other interested applicant. The proposed framework utilises the existing scientific advice (SA) regulatory services at national and European level, with the view to facilitate ultimately the regulatory recognition of the new indication targeted by the champion.

Learnings

The pilot with the nine projects provided information on the following points:

- **Identification and characteristics of repurposing projects developed by not-for-profit organisation in the pilot**
  - The **champions** who applied for the scientific advice are mostly hospital physicians and researchers from the academic field. All were supported by patient organisations and research organisations who played an active role. These champions met the definition of not-for-profit organisation which also includes academia, as described in the Framework of collaboration between the EMA and academia on non-product related activities.
  - *As per* the pilot eligibility criteria, the pilot included repurposing projects targeting a new indication for **a well-established substance** in an area **where important public health and unmet medical needs are likely to be addressed**. On this basis and taking into account the level of available evidence and any proposed development plan, it resulted that the selected projects were mostly related to rare diseases, which could be expected as this is an area of high public health need. Development of medicines targeting rare diseases can benefit most from SA as evidence generation is often challenging due to, the limited number of patients and efforts needed for establishing an appropriate primary efficacy endpoint. However, scientific advice support to repurposing projects is not restricted to those elements.
- **Regulators' tailored support and added value of SA to the repurposing projects in the pilot**
  - Irrespective of whether the projects' clinical development was ongoing or were based on existing evidence, the **SA process provided useful scientific-regulatory interactions and guidance to help champions** understand the strengths and limitations of the evidence already generated and/or the planned studies, in light of regulatory requirements.
  - Although the number of projects selected in the pilot was limited to nine and each project had its own specificities linked to the disease characteristics and the quality of the existing data, certain **scientific issues were frequently encountered**. These included, for instance, issues with inclusion/exclusion criteria of the patient population in studies, with the isolation of the effect of the investigational medicinal product when used in combination therapy or when

investigated in a trial without an internal control, with the choice of the primary endpoint and with the amount of evidence for the proposed dosing regimen.

- While the primary focus of the SA is the development plan, the pilot also tested the value of SA for repurposing projects for which the champion sought regulators' advice on the **adequacy of available data**. This specific situation revealed especially the following challenges:
    - shortcomings in the champions' **descriptions of the available data and synthesis of the main data to establish the benefit-risk balance** such as isolating the effect of the repurposed medicine, determining the dose, defining the targeted indication *as per* the scientific and regulatory expectations (SmPC guideline), providing a clear overview of the dataset so the regulators could get a clear understanding on the adequacy of the data package, i.e. whether the concerned data can support the assessment of the benefit-risk balance;
    - although advice was provided, the remit of the SAWP **could not allow to perform an in-depth assessment** on whether the existing evidence is sufficient to carry out a **benefit-risk evaluation and whether any additional studies will be definitely needed for a comprehensive data package**.
- The **preparatory and debriefing meetings with regulators helped not-for-profit applicants** to introduce their repurposed project, to benefit from regulators' explanation on the regulatory services and what could be expected, to benefit from regulators' support and guidance for the preparation of the briefing document and proposed development plan for the scientific advice. Also, debriefing meetings on the SA outcome and follow-up regulatory interactions proved helpful to explain to academic applicants the SAWP position, rationale and options, and to discuss expectations from the regulators' perspective on how the champion should move forward.
- The pilot showed that **engaging with regulators is key for not-for-profit organisations and academia** to put together a development plan and data package which meet regulatory requirements for establishing new indications of authorised medicines. It also showed that iterative scientific advice for the repurposing project is often needed throughout the development stages.
- While it is recognised that a **tailored process** with "safe harbour" interactions with regulators, fewer administrative steps to initiate regulators' interactions and more flexible timelines is **useful** to support academia/not-for profit organisations in the SA process, it was **a resource-intensive process both for regulators and for the champion.** This needs to be taken into consideration in future repurposing activities.

- **EMA RWE generation pathways (in-house, DARWIN EU® and framework contract)**
    - The potential for using the EMA RWE generation pathways (in-house, DARWIN EU® and FWC) to support the SAWP review was explored during the pilot. **The challenges in researching specialised and rare disease settings in the primary care databases accessible to EMA** were the same as those **previously recognised in a** HMA/EMA review on the experience gained with regulatory-led studies using RWD.
    - Moreover, relevant **research questions** could not be formulated, nor **RWE studies** could be carried out during the timelines of the SA procedures. **This would require iterative and closer interactions in a structured and consolidated manner with regulators.**

- **MAH's engagement**
  - During the pilot, the champions were asked to seek interactions and explore the interest of MAHs to submit a regulatory procedure to request a new indication. However, **in most cases, pharmaceutical companies have shown so far little to no interest** as reported by champions through the surveys conducted. **One project selected by AEMPS successfully achieved on-label approval** for the new indication, in this case **the interaction between the champion and MAH was facilitated by the AEMPS** through their Innovation Office. For **one EMA-selected project**, **uptake by a Marketing Authorisation Holder (MAH)** is currently **under consideration**.
  - The pilot confirmed, as reported in the STAMP proposed framework document, that identifying and reaching out effectively to MAH is challenging for the champion. To facilitate the interface with potential MAHs, Industry Associations tested a channel for champions to bring their project, potentially ready for filing, to the attention of the concerned MAHs. This was considered helpful by champions. However, despite Academia's effort to reach out to MAHs of existing originators or generics and Industry Associations' support to test a dedicated channel to help champions present their projects to their concerned members, a survey to champions flagged that they continue to face obstacles in engaging MAHs and the lack of interactions / platforms to present their projects to MAH(s) is an issue.

Recommendations

As a result of the pilot the following recommendations have been identified:

- **Projects selected within the pilot:**
  - **continued regulators' support:** EMA and the EU Medicines Regulatory Network remain available to provide further support to the selected projects. For the time being it is unknown at which pace champions will be able to progress their projects, as this will depend on various factors such as funding, availability of the concerned medicinal product, feasibility of appropriate clinical studies, and uptake for the filing by an applicant/marketing authorisation holder.
  - **Follow-up scientific advice** is strongly encouraged after the champions made changes to their development plans, which ranged from designing a new prospective or retrospective study based on a registry or re-designing a phase III clinical trial or changing development strategy (e.g. omitting a phase II and conducting directly a phase III trial) or updating development plans and/or study protocols.
- **Future repurposing projects**

Based on the findings observed, **considerations for future repurposing projects to support data gathering and generation** include:

  - **Scientific advice:** Not-for-profit organisations and academia are encouraged **to seek scientific advice** and to engage dialogue with regulators **early in their development project through EMA and/or national competent authorities.** Not-for profit organisations can consider to have initial interactions and scientific advice with the national competent authorities, often primarily delivered by their Innovation Office, before seeking advice at EU level. Regulators' support is foreseen to be more beneficial and effective on a prospective research plan.

- Since January 2025, the new Fee regulation provides that for certain not-for-profit organisations certain requests for EMA **scientific advice can be free of charge** subject to the criteria set out in the new fee regulation working arrangements[12]. Some NCAs, including AEMPS, offer free national scientific advice for academic researchers[13].
- In their support to researchers and developers from the academic sector, EMA will continue to offer a **suite of measures as appropriate to each specific case.** While taking into account both regulators and academia capacity and the project at stake, these may include *ad hoc* interactions; proactive regulatory strategy development, regulatory and scientific input; revising documentation and briefing materials; holding debriefings and facilitating meetings with coordinators and rapporteurs, as appropriate.
- **To increase RWE footprint into repurposing activities when needed**, it can be key to consider early and closer regulators' interactions, involving relevant functions of the EU Medicines Regulatory Network with various expertise e.g. RWE, statistics (including from SAWP, EMA and other groups such as methodological working party). This would help identifying gaps and needs in a consolidated manner.
- **Widening the EMA and network access to a larger and more diverse range of complementary data sources including secondary care databases,** patient registries and specialised data sources, amongst other. Future repurposing projects may benefit from these achievements, as already identified in a previous HMA/EMA review on the experience gained with regulatory-led studies using RWD, and *as per* improvements described in a RWE follow-up report published in July 2024.
- It seems also relevant for **repurposing projects to be able to solicit services** such as in the domains of statistics, pharmacology, regulatory science and regulatory affairs. Impact on financial resources for **intramural or contracted services** should be taken into account when establishing the repurposing project, notably as part of funding discussions.

As regards the **uptake by applicant / MAHs**, the following aspects can be considered:

- **Industry Associations are encouraged to develop ways to support not-for profit organisations to reach out to their member companies** regarding a particular repurposing project and ensure that appropriate channel of interactions to explore partnership are accessible to champions for repurposing projects.
- **EMA and NCAs can explore multi-stakeholder interactions[14], as appropriate**, to facilitate the interactions and/or joint discussion between the champion, MAH or applicant, and regulators on the dataset and its potential leverage to bring the concerned use on-label, in particular where the interest of an MAH/applicant has been identified.
- **The proposed reform of the EU pharmaceutical legislation** (currently in inter-institutional negotiations) introduces **new legal measures aimed at supporting repurposing**. This entails a regulatory pathway to evaluate evidence submitted by not-for-profit champions, as well as dedicated incentives for MAHs that develop repurposed use of medicinal products.

[12] Fee regulation working arrangements

[13] https://accelerating-clinical-trials.europa.eu/our-work/support-non-commercial-sponsors/national-initiatives-non-commercial-sponsors_en

[14] For example, EMA and EORTC multi-stakeholder workshop on soft tissue and bone sarcoma

- **Other barriers** beyond level of evidence such as funding, MAHs partnership, preparation of data package, HTA, pricing & reimbursement **would benefit from initiatives led by other actors involved in the overall repurposing ecosystem.**

Glossary

AEMPS	Spanish Agency of Medicines and Medical Devices
B/R	Benefit-risk
CHMP	Committee for Medicinal Products for Human Use
CKD	Chronic kidney disease
DDI	Drug-drug interactions
DUS	Drug utilisation study
EC	European Commission
ECV	Endocrinology, cardiovascular
EFPIA	European Federation of Pharmaceutical Industries Associations
EMA	European Medicines Agency
ERN	European Reference Network
EU	European Union
FWC	Framework contract
GFR	Glomerular Filtration Rate
HMA	Heads of Medicines Agencies
HTA	Health Technologies Authorities
INF	Anti-infectious diseases
MAA	Marketing Authorisation Application
Mfe	Medicines for Europe
MAH	Marketing Authorisation Holder
MoA	Mode of Action
NCA	National Competent Authority
NEPHRO	Nephrology
NEU	Neurology
ODD	Orphan Drug Designation
ONC	Oncology
PEI	Paul-Ehrlich-Institut (German Federal Institute for Vaccines and Biomedicines)
PK	Pharmacokinetic
PoC	Proof of concept
PPO	Private Profit Organisation

RCT	Randomised Clinical Trial
R&D	Research and Development
RepOG	Repurposing Observatory Group
RWD	Real World Data
RWE	Real World Evidence
SA	Scientific Advice
SAWP	Scientific Advice Working Party
SmPC	Summary of product characteristics
SoC	Standard of Care
SPC	Supplementary protection certificate
STAMP	(EC Expert Group) Safe and Timely Access to Medicines for Patients
UK	United Kingdom
US	United States

Annexes

Annex 1: Overview summary of regulators' input during the preparatory phase

Business	Input description
IRIS	IRIS navigation and use
	Customer account number
	Research product identifier
	Technical limitations
Procedural advice	BD content guidance
	SA timelines and flexibility
Regulatory	CMA requirements
	Data and market protection
	ODD requirements
	Patent exploration
	PIP requirements
	Regulatory pathway guidance

BD Template	Input description
BD format	Guidance on need to provide applicant's position
	Data references to be provided
	Procedure number allocation
	Questions to reclassify (e.g non-clinical to multidisciplinary)
	Question numbering to update
	Studies to provide in tabular overview
	Template version and instructions
Out of BD and SA scope	CT application
	Regulatory questions
	Advice on study design on ongoing study
	Pre-assessment of available data
	Indications not in the scope of the advice
	Rare disease prevalence advice
	Scope of a follow-up SA procedure (e.g once a proposed study design is available)
BD Introduction	**Input description**
Disease background	Disease management information to be provided

	Existing study design mentioned to be provided
Product background	Information and rationale for using a product in combination
	Existing products indication and dose information to be provided
Regulatory background	Existing MA information to be provided
	Potential regulatory strategy to be clarified
	Indication authorised and off-label use information to be provided
	clinical trial funding information to be provided
	MAH engagement exploration
Rationale for seeking advice	Other clinical trials learnings to be provided
	History of interactions with regulators to be provided
	Applicant's position compared to the EMA position paper to be clarified

BD Product development	**Input description**
Quality background	Quality of the finished product to be provided
Non-clinical background	Non-clinical data justifying the dose
	Non-clinical data supporting the mechanism of action
	Pharmacokinetics information to provide
	Proof-of-principle data supporting the new indication
	Toxicology data justifying the dose
Explain Clinical background	Biomarker development intention
	Existing studies description To provide information on the study design e.g. phase / randomisation / blinding / multi-centre or not and to summarize clearly the supportive studies in a table.
	To provide details on the key literature references listed (e.g. number of patients treated, duration and different regimens) and to summarize it in a table format.
	Prospective observational study, outline how many pts are enrolled/treated.
	To further describe and discuss the results of the retrospective study performed based on the Registry, as these are only very briefly mentioned in the documents, although they constitute the most recent pieces of evidence coming from real world setting
	To clarify which dose was used in the clinical trial
	Pharmacodynamics data to provide
	Pharmacokinetics data to provide
	RWE studies description
	Study design description

BD Questions to SAWP		
Area	**Keywords**	**Descriptive examples**
Non-clinical	Proof-of-principle	To add a question whether the non-clinical data support the claimed new indication i.e. proof-of-principle.
	Level of NC evidence	To rephrase the question on non-clinical evidence available to be more comprehensible for the SAWP.
Clinical	Study design	To rephrase the question on the study design proposal and need to reconsider the proposed phase IIb study as it would be rather considered as a phase IIa study, instead recommendation to propose a phase III study. For the proposal on the phase III study design, consider efficacy endpoint, a bigger patient population group to avoid statistical issue to show effect with such a small group. Justify choice of a single-arm trial. Discuss possible alternatives study design (example of proposed alternatives study design provided).
		To present only one CT design instead of 2 options i.e. for the sponsor to put forward the chosen study design (either parallel trial or factorial trial) and to consider adding a back-up question with only one alternative study if not supported by SAWP.
		Registry based study instead of clinical trial-based approach to be justified.
	Dose	To consider adding question on dosing and safety, and if so to describe the authorised dose and dosing regimen for the authorised indication(s) and explain the rationale for the proposed dose/regimen in the new indication.
	Duration	To add a question on the study duration and to provide the reasoning behind in the applicant's position.
	Endpoints	To add a stand-alone question on the primary endpoint and to complement by the statistical methods which would be used to analyse the data. The QoL measure component could be a further sub-bullet, where also the scale used would be explained, and justified in its choice (as for the primary endpoint).
	Study population	To rephrase the question to study paediatric population in the planned phase IIb (emphasise the differences between adults and children).
	Safety	To add a question on the appropriateness of the safety monitoring.
Methodology	Statistical analysis	To reformulate the question considering the estimand framework.
	Data analysis	To consider adding a question and to discuss the strategy to deal with inherent intra-patient variability.
Development strategy	Level of evidence	To consider adding a question on whether further study need to be performed; if so, need to discuss the pros and cons of existing data set, acceptability of the clinical endpoints and what type of study could complement.

BD Applicant's position		
Area	**Keywords**	**Descriptive examples**
Quality	Finished product	To provide more background information on which products were used in clinical trials (e.g. usage of different form and salt/base of the active substance and related interchangeability, different products/MAH used and related traceability, any differences in administration routes (oral vs IV)).
Non-clinical	Mechanism of action	To provide information on the completed animal study to support the scientific rationale and mechanism of action.
	Toxicology	To provide under the applicant's position specific justification for not performing juvenile studies, otherwise long-term survival (e.g. genotoxic effects) could be a concern.
Clinical	Claimed indication	To clarify in which setting(s) the medicinal product is targeted to be used and present the supporting studies grouped by the setting(s) in a table format.
	Study design	To discuss under the applicant's position the rationale for e.g. the selected population, comparator, sample size, primary/secondary endpoints and associated statistical analysis, study duration, concomitant medication, safety monitoring etc.

BD Applicant's position		
		To include the study protocol and a schematic diagram of the CT.
		To justify in the applicant's position why the plan study is suitable. This implies listing the major design criteria of such a trial that will allow to make such claims.
		To reconsider proposal for generating more data: it is not possible to re-enrol patients due to introduction of bias, to explore further options to continue gather data on patients after study or long-term follow-up, outside of the primary analysis.
		To discuss options to explore the effect of the combinations of product as different components or to further justify the current position.
	Comparator	To better justify the chosen comparator.
	Dose	To further discuss on the safety profile of the medicine in the authorised indication in the high dose range (e.g. frequencies of serious adverse effect, mortality, any data linking the dose to tissue concentration).
		To further elaborate on the choice of the dosing regimen (i.e. scientific rationale information on the authorised dose, non-clinical study related to the proposed dose (e.g. data from a non-clinical model)).
		To consider providing data linking the dose to tissue concentration to support the applicant proposed dose escalation scheme from starting medium to high dose regimen.
	Duration	To include a discussion on the anticipated occurrence of endpoints with a 2-year duration.
	Endpoints	To reconsider the proposed composite primary endpoint of three separate, binary endpoints that is not aligned with the EMA guidance document.
	Study population	To add details on the study plan and population (i.e. age groups).
	Safety	To repeat the information related to the frequency of adverse effects.
	Off-label use	To discuss potential issue of off-label use that could prevent a longer study duration (e.g. provide any data on current off label use).
	RWE	To clarify if a literature review of non-interventional studies looking at other uses of the medicinal product could provide evidence on effectiveness and safety has been performed
	Mechanism of action	To discuss on the mechanism of action of the medicinal product in the claimed indication and to add literature.
	Standard of care	To describe the current standard of care.
Methodology	Statistical analysis	To reconsider proposal for generating more data: it is not possible to re-enrol patients due to introduction of bias, to explore further options to continue gather data on patients after study or long-term follow-up, outside of the primary analysis.
		To align the Bayesian credible intervals and frequentist decision-making which are mixed in the study protocol.
	Data analysis	Confirmation on the suitability of the randomisation design for an assessment of the treatment effect
		Elaborate further on the rationale for proposing a low patient number (e.g. number of patient available) and any plan for stratification per age group.
Development strategy	Unmet medical need	To integrate in the applicant's position how the product addresses an unmet medical need compared to products indicated for broader indication.
	Level of evidence	To further describe all relevant non-clinical and clinical data in tabulated view including references that support the position on further clinical development and the justification that there is no need for additional non-clinical studies given the proposed higher dose over a longer period.

Annex 2: Overview of champion's proposal and SAWP outcome

TA	Rare disease	Paediatric indication	Clinical development status	Champion's proposal for additional data generation (at pilot start)	Narratives of champion's proposal and SA outcome
Projects to EMA					
CASE STUDY 1					
IMM	Yes	Yes (in addition to adults)	*Primary disease*: 2 uncontrolled clinical trials (literature references) + Data on registry-based study *Secondary disease*: 1 uncontrolled clinical trial + several retrospective studies *(Recognised in EU therapeutic guideline)*	Ongoing retrospective registry-study	This case concerned repurposing of a medicine in two types of a rare hyperinflammatory disorder. CHMP overall agreed that no additional studies related to product and process characterization and specifications are required for the proposed indication. Moreover, CHMP agreed that no additional non-clinical studies are needed. The champion outlined that the efficacy of the medicine (in a combination regimen) in the first type of the disease was established in two single-arm clinical trials in children and is supported by retrospective studies. However, the planned indication is also intended for adults and, therefore, CHMP recommended to present adequate data to support the proposed treatment scheme and dosing in adults. Moreover, a modelling approach was recommended to further support the dosing. Given the rarity of the disease and that treatment guidelines recommend the use of the repurposed medicine in combination with other medicines, CHMP acknowledged that it is difficult to conduct a properly powered randomised trial in first line treatment, but it may be feasible to plan for a randomised controlled trial (RCT) in second line treatment. CHMP recommended that a retrospective registry-based study, could be considered to address certain uncertainties. CHMP suggested that a MAA mainly based on literature data, due to well established use, could be a possibility. It was recommended to prepare a well-structured presentation of the literature data with the main and supportive studies for each type of disease separately, including study design, treatment setting and duration, number of patients, age groups, formulation, dose/regimen, endpoints etc.
CASE STUDY 2					
ONC	Yes	No	Retrospective studies based on its off-label use (*Recognised in therapeutic guideline)*	Ongoing prospective registry study	This case concerned repurposing of a medicine in a rare (oncology) disease. CHMP agreed that the non-clinical and translational data are encouraging despite some limitations of the model used. Regarding clinical evidence, the champion proposed that data from uncontrolled retrospective studies and a time-to-event primary endpoint could be adequate for benefit-risk (B/R) assessment. CHMP disagreed that submission based on solely retrospective data is sufficient for either a conditional or full MA, because the retrospective, uncontrolled nature of the data, high variability of the patient population and the unpredictable nature of disease (in terms of manifestation, progression, and response to treatment) precludes any conclusions on B/R of

TA	Rare disease	Paediatric indication	Clinical development status	Champion's proposal for additional data generation (at pilot start)	Narratives of champion's proposal and SA outcome
					the medicine. CHMP suggested a) to consider alternative endpoints which would be more appropriate to assess efficacy in an uncontrolled setting, b) the need to generate prospective data for a MAA, ideally in a clinical trial, but data from observational studies could be accepted if prospectively planned and described in study protocols.
CASE STUDY 3					
NEU	No	No	Phase IIa, multicentre, randomised, double blind, placebo controlled (ongoing)	Toxicology study for high dosing Phase II/III clinical trial	This case concerned repurposing of a medicine in a neurological disease. CHMP disagreed that there is no need to conduct stability tests of the investigational product to be used in the planned pivotal trial. CHMP suggested that a flexible approach could be applied regarding the need to conduct dissolution or bioequivalence studies for a new formulation and pointed to existing guidance to be considered during development. CHMP supported further clinical development based on existing proof of concept data. Given the existing clinical evidence, no additional non-clinical studies were considered necessary to justify the higher dose used in the proposed indication, but additional recommendations were made to further justify the dose in planned trials. The champion described an ongoing phase IIb trial in the proposed indication and the plan for a pivotal trial where advice was sought on key design elements. CHMP overall agreed with the proposed population and comparator but suggested that the study duration should be informed by results of the phase IIb trial. CHMP proposed a different primary endpoint due to higher sensitivity to detect symptom improvements. Moreover, the sample size should be revised depending on the chosen primary endpoint and a minimum clinically important difference should be justified. CHMP recommended that the champion requests a follow-up advice once the results of their phase IIb trial are available and the protocol of the pivotal trial is refined and more detailed based on these data.
CASE STUDY 4					
NEU	Yes	Yes (in addition to adults)	Phase II, randomised, open-label, blinded endpoint (literature reference)	Phase II/III clinical trial	This case concerned repurposing of a medicine in a rare neurological disease. CHMP partially agreed with the proposed limitations of non-clinical models and suggested that data from such models could support the mode of action. However, CHMP considered that no further animal studies are needed due to existing clinical data. The dosing approach was overall accepted despite some evidence gaps. Initially, the champion described two different proposals for the clinical development: one with the medicine of interest to be tested in combination with a second medicine and one with testing only the medicine of interest. The champion was invited for a discussion meeting where they clarified that the focus would be developing only the medicine of interest and proposed a new study design. CHMP supported the overall design of the pivotal trial

TA	Rare disease	Paediatric indication	Clinical development status	Champion's proposal for additional data generation (at pilot start)	Narratives of champion's proposal and SA outcome
					and endorsed the study population and duration. CHMP made several recommendations for defining the primary endpoint, sample size, statistical analysis and implementing a randomised double-blind design.
CASE STUDY 5					
IMM	Yes	Yes (in addition to adults)	Phase II, randomised, double-blind, placebo controlled clinical trial (ongoing)	Phase III clinical trial	This case concerned repurposing of a medicine in a rare chronic immune-mediated liver disease. CHMP considered the scientific rationale sufficient for further investigating the medicine in the proposed indication despite some uncertainties in the mode of action. CHMP disagreed that the ongoing dose-finding study, intended to be used as pivotal, could be the basis for a conditional marketing authorisation due to limitations mainly in the selected population, dose and endpoints. The proposal for a phase III pivotal trial was welcomed by the CHMP but, as the study protocol was not available, only preliminary advice could be provided. The inclusion criteria were considered overall acceptable, but CHMP disagreed with some of the components of the primary endpoint and asked for further justification on the choices made. Moreover, CHMP provided advice on several key design elements of the phase III trial (e.g. comparator, randomisation, stratification, duration) not specifically part of the questions asked.
CASE STUDY 6					
NEU	Yes	Yes (paediatrics only)	Case series	Proposed phase II and phase III clinical trial	This case concerned repurposing of a medicine in a rare neuromuscular (mitochondrial) disease. CHMP considered that available non-clinical and clinical proof of concept data are sufficient for further investigating the medicine in the proposed indication, despite some uncertainties in the mode of action. The champion proposed a phase II trial with the main objective to demonstrate safety using different doses and a phase III trial to demonstrate both efficacy and safety. CHMP overall agreed with the characteristics of patients to be included in the phase II trial but did not agree with some elements of the study design and the dosing approach. Moreover, key design elements of a phase III trial were not supported. The champion was invited for a discussion meeting where they proposed an alternative design of a seamless phase II/III trial which was still not considered optimal for dose selection and demonstration of efficacy and safety. However, the revised efficacy primary endpoint was agreed. CHMP proposed two alternative study designs and made recommendations on the choice of endpoints and study duration.

Projects to AEMPS					
CASE STUDY 7[15]					
NEP HRO	No	No	Non clinical studies and clinical studies Retrospective studies based on its off-label use Retro- and ongoing prospective observational study	Nothing	This case concerned repurposing to evaluate the renal function by measuring glomerular filtration rate (GFR). Iohexol is an excellent marker of renal function and so has been used as such in the last 30 years. The researchers' aim was to add this indication to the former one (X-ray iodinated contrast agent) to spread the use and facilitate also its use in clinical practice. On the first meeting the AEMPS informed the Applicant about the information they should submit to endorse the new indication and after reviewing the information provided by the Applicant in the context of the SA, the AEMPS agreed with the Applicant that the information provided was enough to include the new indication into the MA of the already authorised medicinal product. The information provided were non-clinical studies and clinical studies, retrospective studies based on its off-label use, retro- and ongoing prospective observational study and no additional clinical trials were requested since there is more than 30 years evidence on the use of iohexol as a marker of renal function, more than 200 studies involving thousands of patients. Information (involving thousands of patients) in which iohexol has been used in clinical research in trials designed to evaluate the effect of medications in renal function, or in prospective studies in which GFR changes over time.
CASE STUDY 8					
NEU	Yes	Yes	Non clinical studies and clinical studies Retrospective studies based on its off-label use Retro- and ongoing prospective observational study	Nothing	This case concerned repurposing of a medicine in a rare (neurodegenerative) disease. AEMPS agreed that the non-clinical and translational data were needed. Regarding clinical evidence, the champion proposed that taking into account the rare condition data from uncontrolled retrospective studies could be adequate for B/R assessment. AEMPS assessors disagreed that submission based on solely retrospective data is sufficient for including this new indication into the authorised MA, because the retrospective, uncontrolled nature of the data, high variability of the patient population preclude any conclusions on B/R. AEMPS suggested to gather more information to endorse the mechanism of action on the new indication which can consist of a) more information endorsing the plausibility of the medicinal product on the new indication proposed as well as b) information about the plausibility of the medicinal product on other diseases with the same mechanism of action.

[15] Iohexol

Projects to AEMPS					
CASE STUDY 9					
NEP HRO	No	No	Retrospective studies based on its off-label use Retro- and ongoing prospective observational study	Champion asked what studies would need to be done.	This case concerned repurposing of a medicine in a renal disease. AEMPS considered that the information provided by the applicant do not justify the proposed dose. The AEMPS recommended the need to carry out a Phase II clinical trial to guarantee an optimal clinical development and also to serve as basis to the proof of concept. From a scientific point of view this clinical study to find the right dose will also serve to estimate the sample size for a Phase III clinical trial which will substantiate the efficacy of the product on the new indication.

Annex 3: Summary of feedback surveys to champions

First survey

Questions	Report version
Q4. Do you consider the context of the repurposing pilot/scientific advice useful to support your project development? Please indicate in the box what you found most useful.	• Concrete feedback on planning a pivotal trial on formulation, design including comparator, study length and outcome measures and a dose finding study • Appreciated meetings and interactions with EMA • A significant obstacle to achieving the final goal is the lack of interest from pharmaceutical companies and/or alternative to compel pharma participation or allow clinicians/patients to file independently • It helped to have a guide on how to prepare the dossier • Information obtained by AEMPS was very important and clarified the possibilities for our repurposing project • Held meetings with the AEMPS prior to starting the process to evaluate its appropriateness
Q5. Please provide any feedback and suggestions on the different phases of the repurposing pilot (introductory meeting, preparatory meeting, briefing document preparation, IRIS registration, scientific advice procedure, clarification teleconference) based on your experience?	• We understand that we are getting help to get one of the repurposed drug manufacturers on board, not sure how to approach • Very complicated to complete the briefing document, in particular the many preclinical questions, not adapted to academia with numerous other duties. Need a more focused questionnaire on i.e. focusing on the important issues for each repurposing drug and label. Not ask questions as if it was not a repurposing project but rather a novel drug. Moreover, it would have been valuable and fair for EMA to already upfront clarify that EMA requires collaboration with a pharmaceutical company, and all other requirements (such as eternal follow-up of all patients treated). • The whole procedure for scientific advice was rather difficult at the beginning, in particular due to technical issues with IRIS platform. • It would be great to have EMA contact from the start of the SA process to solve different challenges accessing web portals and understand new terminology and requirements for an academic sponsor • If the repurposing pilot project has a 100% fee reduction, would be possible not to ask for the EMA Customer Account Number • Further specific advice on where to seek EU-funding and collaborators like a pharmacological company for a pivotal trial would be very much appreciated • Met our expectations • To clearly state from the beginning that all the responsibility for demonstrating the benefits of the change of indication falls solely on the requester (including conducting clinical trials)
Q6. What are your planned next steps for the project?	• Opening more centres in a MS to complete recruitment faster in the ongoing phase II trial and started to look for funding for a pivotal trial in EU • Conduct of clinical trial with the repurposed drug • Clarify with EMA what to do if there is no commercial interest • Applying for funding a phase III study after getting grant from a MS government to conduct a cohort study

Questions	Report version
	• Submit for a follow-up Scientific Advice • Finalising a phase II study and reconsidering the phase 3 design based on SA outcome. • Despite the scientific evidence and the common off-label use of the medicinal product for the repurposed indication, as a small patient organization, we are unable to meet the requirements requested for drug repurposing (clinical trials, etc.) • Depending on ability to find financing (private investors), our approach to the pharmaceutical industry has been unsuccessful.
Q7. Did you have any interactions with Health Technology Authorities and/or payers? Please describe.	• No – 5 answers
Q8. Did you have any interactions with MAHs regarding your repurposing project, in particular, since your selection in the repurposing pilot? Please describe.	• No MAHs have been so far interested in supporting our repurposing project • Contacted few MAHs but none interested in a collaboration or giving access to their product. So realised we would have to produce our own IMP for our trial. • Several MAHs have been contacted, so far, none have reported an interest. • Yes, but they refused to be involved • Pharma company providing material support for Phase II clinical trial • No interactions with MAHs • Contacted at the beginning of the project but not interested. • AEMPS helped to liaise with the MAH of the repurposed medicinal product
Q9. What is / has been your plan regarding the funding of your project (e.g. funding of additional clinical studies, obtaining medicine for clinical trial, administrative/regulatory support)?	• Administrative and regulatory support for establishing a clinical trial • National program for clinical trials funded by health authorities across MS. Need to seek several fundings • Searching for funding from national calls • Research for additional fundings to conduct Phase III • Defined based on the outcome of the SA and following discussion with MAH and patient advocates • Not possibility to conduct clinical trials if required. • Finding private investors (if it is possible). • Not possible to conduct clinical trials
Q10. What is the biggest challenge that you face? What sort of support is needed most for your	• Patient heterogeneity and the lack of pharma support. Support to get an MAH would be needed. • Lack of funding to complete the trial and then the pivotal study • Need to have a commercial pharmaceutical company involved for a drug that is very inexpensive. How to solve that? • Funding a clinical trial in a rare disease for a well-established substance where no interest from Industry to sponsor the trial.

Questions	Report version
repurposing project to be successful?	• Lack of MAH's interest and, as a consequence, firstly, the unavailability of the drug for conducting a prospective study, and secondly, the absence of any future plans for repurposing unless Article 48 of new pharma legislation is adopted. All the work required to produce the documentation necessary for discussions with the EMA during this process has been the result of efforts from academia, which lacks the same expertise and resources as pharmaceutical companies. • Process should be streamlined and supported (SA process resource and expertise intensive for academia) • Designing correctly the trial to provide evidence of efficacy of our testing drug in a disease with no reliable biomarkers, not easily achievable hard endpoints. • very small organization, so we cannot conduct research studies. • Determine the potential incentives. When generic is marketed, no interest is observed."

Second Survey (only 3 replies received from champions of selected projects by EMA)

Questions	Report version
1. Please provide information on the number of MAHs you have contacted?	• 5-10 MAHs x 3
2. What were the challenges that you encountered in approaching a MAH?	• Getting a response from the company • Identifying the right person in the company to contact • Getting a response from the company • Others (describe): "Difficult to set up a meeting after very long time required to sign CDAs. Receiving feedback from the company after first contacts. Repurposing projects are of less interest since it cannot be distinguished regarding reimbursement, other competitors and an additional indication does not change reimbursement (mostly), even if indication is novel and does not have any other therapy. So, it is difficult to raise financial interest although interest on the indication and project is there. Further development needs to be "
3. Please describe whether it was originator or generic companies or both.	• Originator x 1 • Generic x 1 • Both x 2
4. Please describe what channels did you use to reach out to MAHs?	• With support from other organisations: a non-for profit organisation • Email - Using a specific contact of the MAH • Email - Using general email address of the company (2 replies) • Social media channels (e.g. LinkedIn) • With support from other organisations - patient organisations • With support from other organisations - others (describe)- Personal contacts, Exploitation service partner
5. When did you reach out to MAHs?	• After the SA outcome letter • When applying the repurposing pilot • After selection into the pilot (before SA) • Others (describe): After ODD was granted • Others (describe): Before starting to apply for funding in 2019
6. Did you explicitly ask for their engagement on any of the following?	• Filing for a new indication in their marketing authorisation - We only ask for filing for a new indication in their marketing authorisation • Funding • Supply of investigational product x 2 • Filing for a new indication in their marketing authorisation • Others (describe): "Developing a product for an oral administration more useful and attractive for children/babies, Developing a combinational product"

Questions	Report version
7. With whom within the MAH did you discuss the repurposing project?	• Business development staff : Developers, Scientists, clinical team • Senior medical staff • Senior medical staff and business development staff but mainly with regulatory experts. *Comment reported by a champion :* *In a repurposing project, the idea is to provide a new purpose for an existing drug. It is likely that such a repurposing will not be commercially viable since if it would be commercially viable, the MAH would likely have invested in that new indication already. Therefore, the current approach is asking a commercial company to engage in a project that is not commercially viable, and in addition asking the MAH to pay for the filing of the variation is an issue.*
8. What were the outcomes of the outreach? If you received a response, what were the reasons provided by the MAH for not engaging?	• The outcome was further contacts and positive discussions, but no decision has yet been made on whether the MAH will engage or not. • Do not want to go into repurposing, the indication is not their field of interest, Generics are on the market; no other product development seen • Product improvements identified would require a new formulation, which would significantly delay the start of clinical trials. The development costs would not be covered by the marketing of the drug (the price would have to be aligned with that of the generic)." • Original MAH did not want to support the champion, neither did the generic producers.
9. From your perspective, what would have been helpful in your interaction with the MAH? • Joint call with Competent Authorities explaining the project/SA outcome/expected next steps • Others (describe)	• Joint call with Competent Authorities explaining the project/SA outcome/expected next steps x 3 • Others (describe): Action and contact the MAH to encourage them to support the team with the IB. It makes more of an effect when the EMA addresses the MAH.

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