Drug Repurposing Guidebook

Building Block E136

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	DARWIN-EU (data-analysis-real-world-interrogation network)
References	EMA-Website: https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-world-interrogation-network-darwin-eu
Description	DARWIN-EU is a new European initiative with the aim to give EMA and national competent authorities in EU Member States access to valid and trustworthy real-world evidence, for example on diseases, patient populations, and the use, safety and effectiveness of medicines, including vaccines, throughout the lifecycle of a medicinal product. The DARWIN-EU Coordination Center has been selected in 2022 and will be hosted by the Erasmus Medical Center in Rotterdam (the Netherlands). DARWIN-EU will also act as a pathfinder for the European Health Data Space (EHDS) and will ultimately connect to the EHDS services, enabling the use of the EHDS in the context of medicines regulation in Europe. The first DARWIN-EU pilot studies have been delivered in 2022. EMA will oversee the Coordination Centre, connect it to the work of the EMA medicines committees and monitor its performance. There are three main areas of EMA committees decision-making for which Real World Evidence from DARWIN-EU can be requested: 1) Support the planning and validity of applicant studies (e.g. design and feasibility of planned studies, representativeness and validity of completed studies), 2) Understand clinical context (e.g. disease epidemiology, clinical management and drug utilization, 3)

ITEM	DESCRIPTION
	Investigate associations and impact (e.g. effectiveness and safety studies, impact of regulatory actions).
Category	Availability of data
Type of BB	Regulatory
Geographical scope	Europe
Availability	The first studies by DARWIN-EU started from 2022. These studies will be initiated based on questions from the regulatory authorities, such as EMA (e.g. EMA Scientific Committees) and the national European competent authorities. It is expected that in the long-term also questions coming from academia will be addressed, but no timelines are yet available.
Scope of use	Currently DARWIN-EU only focuses on questions from regulators.
Stakeholders involved	Regulators including EMA and national competent authorities, Erasmus University
Enablers/ Requirements	Be part of the DARWIN-EU network
Output	Real World Data that can assist in regulatory decision making. Below a few examples are provided: • to inform recruitment in pre and post authorisation studies: - number of incident and/or prevalent patients per year (for diseases and/or drug), geographical variation of incident and/or prevalent patients. • To evaluate external validity - measure the representativeness of the clinical trial population (treatment and control arm) versus the real-world target population, e.g., similar age distribution, severity of underlying illness.

ITEM	DESCRIPTION
	• To generate evidence on the actual clinical standards of care and compare in different populations - How are patients diagnosed and treated, treatment patterns.
Best time to apply and time window	Not applicable yet.
Expert tips	Not applicable yet. The use of DARWIN-EU is currently limited to regulators.

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ITEM	DESCRIPTION
Building Block (BB) Title	**Paediatric-use marketing authorisation (PUMA)**
References	1-https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/paediatric-medicines/paediatric-use-marketing-authorisations 2 - REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL - State of Paediatric Medicines in the EU - 10 years of the EU Paediatric Regulation 3 - Toma M, Felisi M, Bonifazi D, Bonifazi F, Giannuzzi V, Reggiardo G, de Wildt S, Ceci A and TEDDY European Network of Excellence for Paediatric Research (2021) Paediatric Medicines in Europe: The Paediatric Regulation—Is It Time for Reform? Front. Med. 8:593281. doi: 10.3389/fmed.2021.593281 – https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7884470/pdf/fmed-08-593281.pdf
Description	Paediatric-use marketing authorisation (PUMA) is a dedicated marketing authorisation covering the indication(s) and appropriate formulation(s) for medicines developed **exclusively** for use in the paediatric population.
Category	Regulatory and HTA engagement
Type of BB	Regulatory
Geographical scope	Europe

ITEM	DESCRIPTION
Availability	PUMA was introduced by the Paediatric Regulation (2007) as a new type of marketing authorisation, to incentivise the development of paediatric indications for **off-patent** products
Scope of use	The PUMA was introduced by the Paediatric Regulation for medicines that are: - already authorised; - no longer covered by a supplementary protection certificate (SPC) or a patent that qualifies as a SPC; - to be exclusively developed for use in children. The development of a PUMA must follow a paediatric investigation plan (PIP), to be agreed by the Paediatric Committee (PDCO).
Stakeholders involved	Drug developers, Regulators (European Medicines Agency)
Enablers/ Requirements	**Applying for a PUMA -** PUMA applications follow existing procedures for the authorization of medicines. Before applying for a PUMA, applicants should request confirmation of eligibility by submitting a PDF icon pre-submission request form to cpeligibility@ema.europa.eu. PUMA applications should contain: - the same range of supporting documentation as other marketing-authorisation applications, with a combination of new data or existing data. Depending on the legal basis for the application, literature and cross-references to other medicines' dossiers can be used. This includes, in particular, cross-reference to data contained in the dossier of an authorised medicine, if the relevant data protection of the reference medicine has expired (in accordance with Article 14(11) of Regulation (EC) No 726/2004 or Article 10 of Directive 2001/83/EC). - results of all studies performed and details of all information collected in compliance with a PIP; - the PDCO opinion and corresponding EMA decision on compliance or the applicant's compliance report (in Module

ITEM	DESCRIPTION
	1.10). For more information on compliance, see Paediatric requirements for marketing-authorisation applications. - A risk management plan detailing measures to ensure the follow-up of efficacy and of possible adverse reactions to the paediatric use of the medicine. For more information on how to apply, see Pre-submission guidance: questions and answers.
Output	• Automatic access to the centralised procedure if the applicant chooses this route, even if the application falls outside of the mandatory scope of this procedure. • 8 plus 2 years of data and market protection • Authorisation under the same name and branding as the authorised medicine containing the same active substance, if the marketing authorisation holder is the same • Partial fee exemption under the centralised procedure for marketing authorisation and post-authorisation activities for a year. For more information, see Fees payable to EMA
Best time to apply and time window	As early as possible to allow interaction with EMA PDCO and PIP completion and before the time of Marketing Authorisation
Expert tips	PUMA, established by the Paediatric Regulation, was an attempt to generate specific interest in paediatric-only developments. It is largely considered as not having delivered fully on its expected potential. One can expect some changes with the current revision of the legislation. **From ref 2 above:** The main goal of the PUMA concept (Article 30) is to stimulate research in existing compounds that are off-patent and/or to help transform known off-label use into authorised use that is safer and better framed through the marketing authorisation. Once approved, the PUMA provides the manufacturer with a ten-year period of marketing protection during which generic copies cannot be placed on the market. In 2017 (see **ref 2** above), only three PUMAs have been granted - and only six PUMA authorised by the end of 2018 (see **ref 3** above). This is clearly below expected levels, given that ear-marked EU funding from the FP7 programme has been provided for several years for off-patent medicines. While EMA agreed more than 20 PIPs with a view to

ITEM	DESCRIPTION
	submitting a PUMA, it remains uncertain how many will ever be completed and lead to the commercialisation of a new product. In an attempt to create additional interest, the Commission and EMA clarified in 2014 that a PIP for a PUMA does not have to necessarily cover all age groups, but the impact has so far been limited. While this may allow companies to focus research on the most prevalent paediatric subsets, it risks further reducing the target population and potential revenues. The PUMA concept struggles with similar issues like any scheme meant to encourage companies to invest in additional research for known compounds that have been on the market for a long time (repurposing). Medicine developers fear that a PUMA will not necessarily prevent physicians from continuing to use competitor products with the same active ingredient but authorised for other indications off-label, at lower costs, nor substitution for cheaper forms at the level of pharmacies. Moreover, national health care payers are generally hesitant to agree a premium price for such products. Given the current limited number of granted PUMAs it is neither possible to check whether those risks are substantiated nor the economic value of the PUMA reward. While the available data shows that the products authorised through PUMAs have received positive reimbursement decisions in several Member States and represent good business cases, it may simply be the exception to the rule, partly supported by the specificities of the products rather than the PUMA concept alone. This shows that the commercial success of a PUMA is influenced by complex factors that can be hardly addressed at EU level. They concern downstream decision-making at national level, which is outside the scope of EU law. Legislative incentives cannot compensate for economic success. There have been suggestions that a PUMA might be effective where a child-specific formulation or dosage form is required, but while this hypothesis is valid in theory, experience shows that the PUMA label does not fully exclude physicians continuing to prescribe non-child-adapted products. As mentioned as well in **Ref 3**: 'data confirm that sponsors prefer to apply under the simplified procedure of Directive 2001/83/EC where an off-patent drug is concerned.' i.e. rather than through PUMA.

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ITEM	DESCRIPTION
Building Block (BB) Title	Innovative Licensing and Access Pathway (ILAP)
References	https://www.gov.uk/guidance/innovative-licensing-and-access-pathway
Description	The Innovative Licensing and Access Pathway (ILAP) is a unique initiative that connects the medicines regulator with health technology assessment bodies in the UK, creating a pathway that aims to deliver safe, effective, financially sustainable, and early patient access to innovative medicines. These medicines include new chemical entities, biological medicines, new indications and repurposed medicines. It comprises of an Innovation Passport designation, a Target Development Profile (TDP) and provides applicants with access to a toolkit to support all stages of the design, development and approvals process. ILAP offers an opportunity to align regulatory evaluation and access activities throughout the development pathway, integrating multi-stakeholder views to create medicines that are both regulatory and access ready.
Category	Regulatory and HTA engagement
Type of BB	Regulatory
Geographical scope	Europe
Availability	Available to developers of innovative medicines, including repurposing approaches

ITEM	DESCRIPTION
Scope of use	Provides opportunity for enhanced regulatory and other stakeholder input through the Target Development Profile and ILAP toolkit.
Stakeholders involved	UK Regulatory and HTA bodies, sponsors, patient groups through the ILAP patient and public reference group
Enablers/ Requirements	The first step in the ILAP is the Innovation Passport application. The Innovation Passport is the mandated entry point to the ILAP and is open to developers at the pre-clinical trial stage through to the mid-development programme point. For repurposing projects, the following criteria must be fulfilled. **Criteria 1: details of the condition, patient or public health area** • the condition is life-threatening or seriously debilitating and/or there is a significant patient or public health need **Criteria 2: the medicinal product fulfils one or more of a specific area (indicate which are applicable in your application).** b) medicines being developed in a clinically significant new indication for an approved medicine **Criteria 3: the medicinal product has the potential to offer benefits to patients** You must provide a summary of how patients are likely to benefit from the product or indication, including proposed improved efficacy or safety, contribution to patient care or quality of life, as compared to alternative therapeutic options. This should be based on evidence from the applicant with the product. The claims can be supported either by data from valid non-clinical models of the condition or if justified extrapolated from another relevant model. Depending on the stage of development of the product any available clinical data in a relevant population of patients can be provided. Applicants are strongly encouraged to include the views from patients or patient organisations around the benefits of a product in their evidence, if available.

ITEM	DESCRIPTION
Output	Develop products that are both regulatory and access ready through the use of the ILAP toolkit, particularly novel methodology and real-world data collection
Best time to apply and time window	Early to mid-stage development programmes The pathway will allow entry very early, based on non-clinical data, where all the tools described below might be options, as well as catering for products with mid-development 'global' dossiers. However, to maximise the benefits, applicants are encouraged to apply early in the development of their products. Products that are towards the end of their development programme are generally not suitable for the ILAP unless there are one or more indications still under active investigation.
Expert tips	Although ILAP is a UK initiative, the framework could produce data helpful in other jurisdictions. If you would like help with the Innovation Passport email innovationpassport@mhra.gov.uk For queries about the Target Development Profile email TDP@mhra.gov.uk

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ITEM	DESCRIPTION
Building Block (BB) Title	EMA pilot project to support academia
References	• EMA-website: https://www.ema.europa.eu/en/news/repurposing-authorised-medicines-pilot-support-not-profit-organisations-academia including the following documents: • Questions and Answers on repurposing pilot project on proposal for framework to support not-for-profit organisations and academia in repurposing authorized medicines. • Submission form – Repurposing pilot project for authorised medicines
Description	The medicines repurposing framework proposal was developed by the European Commission's STAMP Expert Group composed of representatives of EU Member States together with EMA and stakeholders from not-for-profit organisations, patients, healthcare professionals, industry, health technology assessment bodies and payers. EMA and the Heads of Medicines Agencies (HMA) launched in October 2021 a pilot project to support the repurposing of medicines as a follow-up to the European Commission's Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) discussions on a proposal for a medicine repurposing framework. The aim of the pilot is to support not-for-profit organisations and academia (only) to gather or generate sufficient evidence on the use of an established medicine in a new indication with the view to have

ITEM	DESCRIPTION
	this new use formally authorised by a regulatory authority. This project doesn't provide grants/funds, instead it meant to provide indirect support through advices on how to generate robust and reliable data packages. The innovation of the project is that in case of selection, then the project is not receiving a single scientific advice, but instead a series of advices until a marketing licensee who can bring the product to the registration/market is identified. The EMA fees for a scientific advice are free in case of orphan, otherwise are those payable to the EMA (https://www.ema.europa.eu/en/human-regulatory/overview/fees-payable-european-medicines-agency). The pilot will run until the completion of scientific advice for the selected repurposing candidate projects and optimally until the filing of an application by a pharmaceutical company for the new indication. A report will be published after the pilot. Repurposing of medicines for COVID-19 falls outside the scope of this pilot project.
Category	Regulatory and HTA engagement
Type of BB	Regulatory
Geographical scope	Europe
Availability	Only for Not-for-profit organizations and academia (institutions and individuals) who has a particular interest in repurposing an authorized medicine for a new indication in an area of public health interest, have a rationale for their repurposing program and would like to seek scientific advice from a regulatory authority.
Scope of use	EMA proposes to support the development and implementation of a repurposing framework in its Regulatory Science Strategy to 2025, which is its plan for advancing engagement with regulatory science over the next five to ten years. While marketing authorization holders may develop medicines for uses in other indications, sometimes they lack the incentives or the commercial interest to pursue the necessary research and development and complete the regulatory process needed for the authorization of a new indication for old medicines which are no

ITEM	DESCRIPTION
	longer protected by a patent or data exclusivity. This could be a wasted opportunity for public health. At the same time, academic institutions and/or patient organizations may be interested in carrying out this development for the benefit of public health. However, they may not have the necessary regulatory experience and have no intention of becoming a marketing authorization holder themselves.
Stakeholders involved	Not-for-profit organisations, academia, industry developing repurposed drugs and regulators
Enablers/ Requirements	The deadline for submission for projects was 28 February 2022. Currently, it is not possible to participate anymore in this pilot. For information, candidate medicines for the pilot should have fulfilled the following criteria: - contain a well-established active substance; - be an authorised medicine (containing the concerned active substance) out of data exclusivity and market protection periods and out of basic patent / supplementary protection certificate (SPC) protection; - target an indication in a condition distinct from the currently authorised indication(s); - target an indication in an area where important public health benefits are likely to be achieved. Conditions for which no or few medicines are currently authorised or which are associated with high morbidity and / or mortality despite available medicines, will be the focus of the pilot.
Output	A report will be published after the pilot project is completed, i.e. when all selected drug repurposing projects have received scientific advices from the EMA and/or national agencies and optimally until the filing of an application by a pharmaceutical company for a new indication.
Best time to apply and time window	Not applicable, as currently it is not possible to apply anymore for this pilot. EMA website to be checked periodically in case another pilot project is to be implemented.

ITEM	DESCRIPTION
Expert tips	Not applicable (the pilot is currently running; no experience tips to be shared right now).

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ITEM	DESCRIPTION
Building Block (BB) Title	STAMP initiative
References	1 - https://health.ec.europa.eu/medicinal-products/pharmaceutical-committee-veterinary-pharmaceutical-committee-and-expert-groups/commission-expert-group-safe-and-timely-access-medicines-patients-stamp_en 2 - Asker-Hagelberg C, Boran T, Bouygues C, Eskola SM, Helmle L, Hernández C, Houÿez F, Lee H, Lingri DD, Louette L, Meheus L, Penninckx W and Stepniewska B (2022) **Repurposing of Medicines in the EU: Launch of a Pilot Framework**. Front. Med. 8:817663. doi: 10.3389/fmed.2021.817663 - https://www.frontiersin.org/articles/10.3389/fmed.2021.817663/full
Description	The STAMP (**Safe and Timely Access to Medicines for Patients**) expert group is set up to provide advice and expertise to the Commission services in relation to the implementation of the EU Pharmaceutical legislation, as well as programmes and policies in this field. The STAMP expert members exchange views and information about the experience of Member States, examine national initiatives and identify ways to use more effectively the existing EU regulatory tools with the aim to further improve safe and timely access and availability of medicines for patients. STAMP has a work stream to support not-for-profit and academic stakeholders in Repurposing, which is the purpose of this BB
Category	Regulatory and HTA engagement

ITEM	DESCRIPTION
Type of BB	Regulatory
Geographical scope	Europe
Availability	Through EMA and the Heads of Medicines Agencies
Scope of use	Follow-up of STAMP activities in the field (think-tank) + see BB on 'EMA pilot project to support academia' for the implementation
Stakeholders involved	European Commission, Members States, Regulators (EMA and HMA), Developers of medicines (the proposed framework is dedicated to non-for-profit organisations and academia), patients.
Enablers/ Requirements	In June 2019, STAMP, with the European Medicines Agency (EMA) and stakeholders, developed a proposal for a framework to support not-for-profit organisations and academia in drug repurposing. The proposed framework will be tested through a pilot project launched by EMA and the Heads of Medicines Agencies on 28 October 2021. The aim of the pilot is to support not-for-profit organisations and academia to gather or generate sufficient evidence on the use of an established medicine in a new indication to have this new use formally authorised by a regulatory authority. This is a way of making affordable new treatment options available to patients. Further information is available in a question-and-answer document. The pilot is open to not-for-profit stakeholders and academia (institutions and individuals) who have a particular interest in repurposing an authorised medicine for a new indication in an area of public health interest, have a scientific rationale for their repurposing programme and would like to seek scientific advice with a regulatory authority. They should apply to EMA or national authorities: European Medicines Agency: Scientific advice and protocol assistance (see under 'Scientific advice on medicine repurposing') or Heads of Medicines Agencies The pilot is one of the actions highlighted in the Pharmaceutical Strategy for Europe to inform the review of the pharmaceutical legislation. For more details of the strategy see: A pharmaceutical strategy for Europe. Previous activities of the STAMP expert group: Overview of the activities of the STAMP expert Group in 2015 – 2016.

ITEM	DESCRIPTION
Output	Proposal for a framework to support not-for-profit organisations and academia (institutions and individuals) in drug repurposing - https://health.ec.europa.eu/system/files/2021-10/pharm773_repurposing_annex_en_0.pdf
Best time to apply and time window	Not applicable for STAMP – see BB on 'EMA pilot project to support academia'
Expert tips	STAMP acts as a think-tank. Please see BB on 'EMA pilot project to support academia' which is related to the implementation of the aforementioned framework.

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Building Block E141

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ITEM	DESCRIPTION
Building Block (BB) Title	Strengthening Training of Academia in Regulatory Science (STARS)
References	• STARS Common Strategy: Regulatory Support and Advice for Academia (https://www.csa-stars.eu/files/STARS_Common_Strategy.pdf) • Starokozhko et al., 2017, Strengthening Regulatory Science in academia: STARS, an EU initiative to bridge the translational gap, Drug Discov Today • Starokozhko et al., 2023, Strategic recommendations from the STARS project to foster academic drug development, NRDD. • Kallio et al., 2022 (Online Ahead of Print), Translating Academic Drug Discovery Into Clinical Development: A Survey of the Awareness of Regulatory Support and Requirements Among Stakeholders in Europe, Clin Pharmacol Ther • Website: https://www.csa-stars.eu/ • Slides are also available from the course "The Winding Road from a Brilliant Idea to Drug Approval: An Online Course in Regulatory Science for Academic Researchers". https://www.csa-stars.eu/Results-Pilot-I-Best-Practice-Transfer-1754.html.
Description	STARS was a collaboration of 21 partners from 18 countries, including the majority of the European national competent authorities (NCA), the European Medicines Agency, and the German Aerospace Center (DLR) Project Management Agency focusing on strengthening training of academia in regulatory science (STARS) in Europe. The project was supported by the European Commission's (EC) Framework Program for Research and Innovation Horizon 2020. It was running from 2019 until 2022

ITEM	DESCRIPTION
Category	Regulatory and HTA engagement
Type of BB	Regulatory
Geographical scope	Europe
Availability	The STARS initiative was targeting academic and clinical researchers, however, the material can be accessible by any developer interested in this exercise.
Scope of use	The comprehensive inventory and presentations can be used to become more familiar with regulatory requirements. The course and the material prepared was not specifically focused on drug repurposing, but on clinical trials and bringing a medicine to the market in general. It provides clear recommendations how the dialogue between regulators and academic/clinical researchers and drug developers can be enhanced.
Stakeholders involved	Regulators, funders, academic/clinical researchers
Enablers/ Requirements	Being an academic/clinical researcher/SME aiming to develop a drug
Output	If you use this tool, then you access comprehensive training material prepared by regulatory bodies on how to develop a drug, and when it is best to interact with the Regulatory Authorities to check that the plan you're envisaging, fulfills the regulatory requirements/ expectations
Best time to apply and time window	Early in the development (as soon as you think your idea can become a drug)
Expert tips	- The project has just been deployed and so a running period is needed to collect tips. - Of note, from 2022 onwards it is intended to incorporate the recommendations from STARS in the European Regulatory Network, and changes are foreseen that increase among

ITEM	DESCRIPTION
	others the dialogue between regulators and academic/clinical researchers.

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Building Block E142

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ITEM	DESCRIPTION
Building Block (BB) Title	EATRIS – European Infrastructure for Translational Medicine
References	www.eatris.eu https://doi.org/10.1038/nrd.2017.72 (European best practices and infrastructure for biomarker validation) Publications citing EATRIS - EATRIS
Description	EATRIS is the European Infrastructure for Translational Medicine. It brings together resources and services for research communities to translate scientific discoveries into benefits for patients. It offers a broad range of research services for both academia and industry across various research fields. In addition, it works with public funding agencies, charities and policy makers with tailored actions to help improve the translational research and innovation ecosystem. EATRIS coordinates the Horizon Europe project REMEDi4ALL that aims to establish an EU platform for Drug Repurposing. EATRIS has currently 127 institutions in 14 EU member states as its members.
Category	Supporting tools
Type of BB	Development resource
Geographical scope	Europe
Availability	It is available for users (researchers, charities, patient organisations, industry) that are in need of translational research capacity or expertise. A Coordination and Support office in Amsterdam serves as central point of contact to process requests and set up (tailor made) collaborations.

ITEM	DESCRIPTION
Scope of use	EATRIS can provide access to specific resources or expertise required to translate research findings to the clinic, ranging from predictive models (in vitro and in vivo), biomarker validation, drug target engagement studies, pharmaceutical development (e.g. reformulation) to clinical/disease expertise patient centric drug repurposing approaches. Non-technical services include innovation management support to RD research projects, regulatory and health technology, mentoring and education & training.
Stakeholders involved	EATRIS is a membership organization with a central office based in Netherlands (hosted by AmsterdamUMC, location VUmc). It has currently 14 EU member states with a total of 127 academic research institutions and medical centers as service providers. Its users range from academic researchers, pharma, biotech to charities and it engages with policy makers
Enablers/ Requirements	The more specific the research requests the better the matching expertise can be identified (e.g. clear drug repurposing hypothesis/rationale, gaps in research plan). If research requests need to be further defined, experts can be involved to do so. Specific drug repurposing expertise will be gathered in expert teams in REMEDi4ALL that can perform a gap analysis of the project. Users need to bring funding. Public-private collaborations can be facilitated.
Output	New research collaborations, regulatory compliant repurposing development plans, services, drug repurposing portfolio (REMDi4ALL platform), engagement with policy makers, education & training programs, international networking,
Best time to apply and time window	EATRIS – continuously. REMDi4ALL is in construction phase 2022-2023 after which it will be open to users to explore collaborative research projects and using the specific drug repurposing expertise gathered in the platform.
Expert tips	Generate a Target Product Profile describing the repurposing drug minimal requirements and opportunities compared to current standard of care. This helps the generation of a clear development plan with the end goal in mind.

ITEM	DESCRIPTION
	Consider the medical need as a driver for the project and identify opportunities where patients can be involved in project design and/or decision making. Identify gaps in the project as detailed and as early as possible. Consult drug development, IP and regulatory experts to generate an understanding of the non-technical challenges of the development path. Also check the BB on https://remedi4all.org/

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ITEM	DESCRIPTION
Building Block (BB) Title	EU openscreen
References	https://www.eu-openscreen.eu/
Description	EU-OPENSCREEN integrates high-capacity screening platforms throughout Europe. These platforms use several specially selected EU-OPENSCREEN compound collections, which are centrally stored and managed at the EU-OPENSCREEN laboratory facility on the Research-Campus Berlin-Buch (Germany). All compound structures and primary screening data will be published in the open-access European Chemical Biology Database (ECBD), where they are made available to a wide scientific audience. EU-OPENSCREEN collaboratively develops novel molecular tool compounds and early therapeutic candidate molecules together with external users from various disciplines of the life sciences.
Category	Compound and network databases and tools to use them
Type of BB	Development resource
Geographical scope	Europe
Availability	Researchers from academia and industry from countries inside and outside of the European Union Open source database

ITEM	DESCRIPTION
Scope of use	New knowledge: - To discover new targets - To optimize the compounds - To test the compounds functions and properties - For repurposed drug development
Stakeholders involved	Chemists, pharmacologists, biologists, bio-informaticians, artificial intelligence scientists
Enablers/ Requirements	Clinicians Drug developers: Start-ups, Pharmaceutical industries Compliant with national/regional regulations
Output	Pre-clinical studies
Best time to apply and time window	Drug repurposing candidate discovery
Expert tips	Interesting to have a look at in the early phases. However, you need to have a clear development plan in order to make best use of this resource.

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Building Block E144

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ITEM	DESCRIPTION
Building Block (BB) Title	REMEDi4ALL
References	https://remedi4all.org/ https://twitter.com/REMEDi4ALL?s=20&t=rT7o_iqRGYpgLZA2UXWGjw www.eatris.eu
Description	**REMEDi4ALL** is a large-scale European Commission funded infrastructure project dedicated to advancing the field of medicines repurposing, comprising 24 partners from several sectors. Coordinated by EATRIS ERIC, the European infrastructure for translational medicine, REMEDi4ALL has two primary objectives: 1. *Assembling EU's "Bricks and Brains" to support high impact projects today and tomorrow* - To bring together a complete, multi-sectoral and accessible platform comprising the innovative approaches and cutting-edge technologies and expertise necessary to advise, support and advance a large volume of high potential drug repurposing projects at any stage of development. 2. *Future-proofing the repurposing process* – by bringing together all relevant stakeholders into a think-tank like environment to openly discuss, develop and debate the policy measures required to advance and sustain the eco-system for repurposing, so that 5-10 years from now disincentives to patient-centric drug repurposing are addressed and essentially eliminated. Key policy areas include – but are not limited to - economic models for fair pricing of repurposed drugs; regulatory mechanisms and incentives for repurposing; access to data, and funding policy.
Category	Supporting tools
Type of BB	Development resource

ITEM	DESCRIPTION
Geographical scope	Europe
Availability	REMEDi4ALL is available for users (researchers, charities, patient organizations, SME, funders, and pharma industry) that need research & development capacity, expertise, or advice for their drug repurposing project. A coordination team is available to explore collaboration and help find partner specific requests to support any step along the drug repurposing development value chain.
Scope of use	REMEDi4ALL can provide access to specific resources or expertise required to support drug repurposing development activities such as in silico tools (AI), predictive models (in vitro and in vivo), drug target validation, pharmaceutical development (e.g., reformulation), prediction of drug combinations (efficacy and safety). It specifically supports patient centric drug repurposing approaches (co-creation with patient champion). REMEDi4ALL can compile the right Drug Repurposing Development Team that can create a regulatory compliant Drug Repurposing Development Plan, tailored to the project needs and development stage.
Stakeholders involved	EATRIS ERIC is Coordinator of REMEDi4ALL. Preclinical researchers and clinical investigators involved in the consortium are testing and developing the platform during its construction phase. Additional users, ranging from academic researchers, pharma industry, SME/biotech can contact REMEDi4ALL for support in their project. Charities, funders and policy makers are encouraged to engage through the platform's stakeholder forum.
Enablers/ Requirements	The REMEDi4ALL platform can provide expertise, advice, provide support in developing the repurposing development plan (e.g., clear drug repurposing hypothesis/rationale, target product profile, gap analysis and critical path in research plan) and identify the service providers to execute the plan. Regulatory experts can be brought in upon an as need basis. Specific drug repurposing expertise will be gathered in expert teams in REMEDi4ALL that can perform a gap analysis of the project. Users can contact the platform for advice and explore collaborations. Once identified, the cost of the services has to be covered by the user. Public-private collaborations can be facilitated. A funders network is established during the construction phase.

ITEM	DESCRIPTION
Output	Improved drug repurposing projects, regulatory compliant repurposing development plans, access to drug repurposing resources (preclinical and clinical), de-risked drug repurposing projects/portfolio, engagement with policy makers, education & training programs, international networking.
Best time to apply and time window	Continuously. REMEDi4ALL is in construction 2022-2023 after which it will be open to users to explore collaborative research projects and get access to specific drug repurposing expertise gathered in the platform. REMEDi4ALL can immediately be contacted to build a relationship and explore a collaboration with the platform.
Expert tips	Generate a Target Product Profile describing the repurposing drug minimal requirements and opportunities compared to current standard of care. This helps the generation of a clear development plan with the end goal in mind. Consider the medical need as a driver for the project and identify opportunities where patients can be involved in project design and/or decision making. Identify gaps in the project as detailed and as early as possible. Consult drug development, IP and regulatory experts to generate an understanding of the non-technical challenges of the development path. Consider that execution of the Repurposing Development Plan can require significant resources and can in some cases be as complex and costly as a conventional drug development project. In case pharmaceutical development activities are included (e.g., reformulation, dose adjustment or change to pediatric population), additional preclinical studies may be required that need to be considered in the funding strategy.

Drug Repurposing Guidebook

Building Block E145

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	LifeArc Repurposing Medicines Toolkit
References	LifeArc and the Medical Research Council (MRC): New toolkit launched to help repurposed medicines reach patients. 10 Oct 2022 Repurposing Medicines Toolkit - Guidance for navigating the process Repurposing medicines: the opportunity and the challenges, summary of a workshop findings.
Description	Tool is intended to stimulate thinking on the drug repurposing, including opportunities and challenges. It is not intended to be a step-by-step guide.
Category	Supporting tools
Type of BB	Development resource
Geographical scope	Europe
Availability	Charities, not-for-profit organization, including patients' organization, researchers/academic groups, and pharma companies.
Scope of use	This BB provides high level considerations for the following key activities in the drug repurposing: • Target Product Profile (TPP) • Nonclinical discovery

ITEM	DESCRIPTION
	• Nonclinical development • Clinical development • Possible paths to patent access including “on-label” or “off-label” prescribing • Funding opportunities in UK
Stakeholders involved	• Researchers • Representatives of not-for-profit organization • Patients • Contract Research Organisation (CRO) • Medicines and Healthcare products Regulatory Agency (MHRA) • National Institute for Health and Care Excellence (NICE) and Scottish Medicines Consortium (SMC). • NHS Medicines Repurposing programme and Innovation service
Enablers/ Requirements	Product is approved and marketed in UK for some “other” indication
Output	Tool provides a high-level outline of the key stages for the drug repurposing development. The tool is presented in a “Questions and Answers” format
Best time to apply and time window	No application is required. Best used at the time of the selection of the drug for repurposing, especially if UK is considered as a future market for the repurposed drug.
Expert tips	Best to be evaluated at early stage of drug development and re-evaluated during the drug development progression.

Drug Repurposing Guidebook

Building Block E146

This document defines the content of the Building Block created for each identified tool, incentives, initiative or practice introduced by public bodies or used by developers to expedite drug development in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	Engaging with HTA
References	https://health.ec.europa.eu/health-technology-assessment_en https://health.ec.europa.eu/health-technology-assessment/key-documents_en Palkmets O, Nagda N, Sear R. Early HTA Advice In European Countries: Scope And Associated Costs. Value in Health 2017; 20 (9): A695.
Description	The HTA is procedure for assessing the added value of new medicines and medical devices. In Europe, pricing and reimbursement decisions on the drugs are a national/regional responsibility, and are made based on a process of appraisal by national Health technology Agencies (HTA) that includes value assessment and economic considerations, amongst others. Regional and national HTA bodies provide recommendations on medicines and other health technologies that can be financed or reimbursed by the healthcare system in a particular Member State or region. The assessment criteria used by HTA bodies differ between Member States, in accordance with regional and national legislation. At the request of Sponsors, Regional and national HTA bodies can provide recommendations on the data to be submitted at the time of application for pricing, funding or reimbursement of medicines and other health technologies by the healthcare system in a particular Member State or region.

	National advice can be sought by sponsors during clinical development of new drugs and repurposed ones, in order to advance which will be the likely criteria for value assessment that will drive the price and reimbursement decision, and whether the data collection that has been planned by the sponsor for pivotal trials will be appropriate and sufficient to inform the process. The advice received can be used to timely implement changes to the clinical development plan to ensure that all the required information is available at the time of authorization, so that any delays in access due to lack of data can be avoided. However, the current systems fail to account to distinguish between products developed de novo and "repurposed" drugs, Development costs would typically not be accounted for when assessing value, but could be regarded by the decision-makers during the deliberative process and pricing negotiations. Early engagement with HTA bodies is then of paramount importance to set correctly the scene and inform the evidence generation. The process of National Scientific Advice with HTA bodies is applicable to any kind of product, thus not restricted to rare diseases, nor to "de novo" drugs but may be especially relevant for repurposed drugs intended for rare diseases with anticipated low market volume and high prices per treatment, because substantial differences may occur across countries in the criteria for appraisal and the need for a health economic assessment due to differences in standards of medical and social care, as well as in the affordability of high prices for new drugs.
Category	Regulatory and HTA engagement
Type of BB	HTA and reimbursement
Geographical scope	Europe
Availability	Applicants developing medicines for rare and non-rare diseases.
Scope of use	As per the traditional drug development of "de novo" products, clinical development is mainly focused on regulatory approval of marketing authorization applications, and the criteria for approval of orphan drugs in Europe is applied at an Europeanlevel (i.e., mandated centralized procedure for orphans). However, the competence for pricing and reimbursement decision in Europe relies on National authorities. While European countries share regulatory criteria, they diverge in wealth, economic systems and healthcare models, so that funding and public coverage may be substantially different. Because reimbursement is arranged at a national level, despite a common positioning may be reached from supranational consultation through coordinated procedures

	involving many HTAs, it may still be required to gather opinions on particular requirements for a given country. National advice would allow for timely planning of data collection (I ex: related to different clinical practices in a given country) and/or specific studies (I ex: comparison to different standards of care) that might be required by the HTA in order to appraise the new product. Similarly of the "de novo" drugs, the BB is to be used by sponsors in preparation of the post-authorization process of pricing and reimbursement, in order to anticipate that all the relevant data needed to support application for pricing and reimbursement is collected timely and appropriately, in order to satisfy the HTA procedures for value assessment and criteria for drug appraisal.
Stakeholders	• Sponsors of products intended for marketing authorization application and future application for pricing and funding/reimbursement. • National Health Technology Agencies receive the applications and issue opinions on the questions raised by the Sponsors.
Enablers/ Requirements	The Sponsor of a given clinical development of any kind of drug should identify the strategic need or convenience of a national scientific advice with HTA, and the best moment for consultation. This is relevant also for the repurposed drug under development. The Sponsor contacts the HTA for requirements, prepares documentation and submits application. The HTA reviews the materials and prepares answers. The format of consultation can be in writing or in the form of a face to face meeting, depending on HTA internal procedures.
Output	The HTA issues opinion in writing or in the form of a face-to-face meeting, depending on HTA internal procedures. The opinion is generally kept confidential.
Best time to apply and time window	The tool can be used starting from product discovery until market access being the optimal times to apply right before First in Human Ready, after human PoC and before market authorization.
Expert tips	A description of the European HTAs can be found here: https://health.ec.europa.eu/health-technology-assessment_en

	• The Sponsor of a given clinical development identifies the need for a national scientific advice with HTA, ideally by the end of phase II, before beginning of phase III. • The number of HTAs and the selection of which HTA to approach is a strategic decision of the sponsor, that may vary depending on the degree of uncertainty on the country procedures, clinical differences in the standards of care for the indication sought for the new treatment, and strategic considerations of the company, amongst other factors. • The name of the procedure may be different in each country (HTA Scientific Advice, pre-submission meeting, Technical consultation, amongst others). • The Sponsor contacts with the selected National HTA to request advice, and which are the requirements for the procedure and fees of the HTA, where applicable. • A product briefing document is produced that is shared with the HTA ahead of discussions. The document includes a summary of product data and a list of questions with background support and proposed sponsor positioning regarding the potential response. • The HTA reviews the briefing document and prepares answers to the Sponsor's questions. The answers include whether the sponsor positioning is endorsed or not acceptable, and if an alternative positioning is hold by the HTA. Answers may be issued in writing or verbally during a face to face meeting with the sponsor; the number of meetings may vary between HTA depending on their internal procedures. • Also depending on the HTA, a final report with recommendation may be issued, or company minutes of the face to face meeting are circulated. PROs: Generally national scientific advice with HTA is a more direct, shorter and agile procedure than a full parallel consultation process through EUnetHTA. Also, national scientific advice may be a first approach to obtain initial opinions to prepare a future parallel consultation procedure through EMA/EUnetHTA, including a preliminary selection of preferred participating/leading HTAs in the multistate procedure. When issues on lack of predictability are limited to one singular country, the direct consultation with the concerned HTA may be agile and may allow the sponsor and the HTA to define mutually agreed solutions to be implemented only at the national level, with no involvement of other territories where a more standard approach can be done. Also, if higher exigencies or more strict policies are expected, these can be handled in isolation, avoiding generalization of the worst scenario to HTAs in other countries if a

	parallel consultation with regulators and health technology assessment bodies was done involving the concerned HTA. CONs: Asking for individual advice to all concerned HTAs is time and resource consuming and inefficient. Also, risks of individual advice with no multistate coordination include divergent advice from several national HTA for a single product. Inconsistencies between recommendations may pose a difficult scenario to Sponsors, who will have to deviate from part of the advice received. Asking for advice is not binding, but any deviation from previously received recommendations will require justification and may become problematic at the time of application. Because of that, generally a parallel consultation procedure is more sensible than several national procedures. Waiting for advice before closing the designs of phase III trials may represent a delay. Outcomes of the advice may require changing key features of the clinical plan, leading to strategic discussions on clinical positioning, objectives and goals of the clinical development plan. This can be difficult to manage within the sponsor team.

Drug Repurposing Guidebook

Building Block I433

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	CURE ID
References	- https://cure.ncats.io
Description	Describes case reports where drugs have been repurposed to treat infectious diseases lacking adequate approved treatments. Cases include those contributed by clinicians around the world via the short electronic case report form, as well as those extracted from published articles, found via systematic literature reviews in Pubmed. Also includes a treatment discussion forum, newsfeed with daily journal and news articles on drug repurposing in infectious diseases and a calendar of events. Clinical trials are also pulled from clinicaltrials.gov where applicable.
Category	Availability of data
Type of BB	Development practice
Geographical scope	International
Availability	Available to anyone and anytime. Free website and mobile app including offline access for use in resource-limited settings.
Scope of use	Limited – specific to infectious diseases (currently), expansions to replicate the platform in rare diseases (including rare cancers) and diseases affecting specific populations (e.g., neonates and pregnant individuals) is underway

ITEM	DESCRIPTION
Stakeholders involved	Clinicians, patients, regulators, researchers, policymakers, drug developers, funders
Enablers/ Requirements	Access to the internet to initially download the app or view the website
Output	A treatment registry of close to 5000 cases of treatment of infectious diseases with repurposed drugs (many for rare infectious diseases). New implementation of a patient portal that allows patients to enter their own case reports, in addition to those from clinicians.
Best time to apply and time window	Any time
Expert tips	Contact Heather Stone heather.stone@fda.hhs.gov for more information or to get involved. Can download the mobile app on the App or Play Store by searching for "CURE ID" Is a joint initiative of U.S. FDA and NIH, with support from the Critical Path Institute, who have convened an associated public-private partnership – the CURE Drug Repurposing Collaboratory (CDRC) – www.c-path.org/cdrc Also in partnership with WHO, IDSA, JHU, SCCM, IDDO/Oxford, Emory A case report on use of a repurposed drug can be submitted in less than 3 minutes

Drug Repurposing Guidebook

Building Block I434

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	Off label use
References	1. https://www.nivel.nl/sites/default/files/bestanden/Report_OFF_LABEL_Nivel-RIVM-EPHA.pdf 2. https://www.braincouncil.eu/wp-content/uploads/2018/07/GOLUP_Declaration.pdf 3.https://www.ahrq.gov/patients-consumers/patient-involvement/off-label-drug-usage.html#:~:text=Off%2Dlabel%20prescribing%20is%20when,are%20for%20off%2Dlabel%20use. 4.https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label 5. https://sgp.fas.org/crs/misc/R45792.pdf 6. https://ascopubs.org/doi/full/10.1200/OP.20.00131 7. https://rdodjournal.com/article/view/4472
Description	Off-label use refers to any intentional use of an authorized product not covered by the terms of its marketing authorization and therefore not in accordance with its label. According to the study on off-label of medicinal products in the EU published by the European Commission in 2017 [reference 1], off-label use is common practice in both the hospital and outpatient setting; it is particularly high within the paediatric population and is of interest in clinical areas with unmet medical needs. It is estimated by the Agency for Healthcare Research and Quality (AHRQ) in the US that at least one in five prescriptions is off-label. Off-label use covers a broad range of therapeutic areas, especially rare diseases, infectious diseases, and cancer.

ITEM	DESCRIPTION
	Note that a medicinal product may have different approvals in different countries or regions of the world, so it could be that the same use is considered off-label in one country whereas it is on-label in another country. Generally use of a medicinal product off-label is at the discretion – and responsibility – of the prescribing physician. Good Off-Label Use Practice (GOLUP) principles aim to create a harmonised approach on how and when off-label prescription might take place in the EU [Reference 2]. The five GOLUP principles are as follows: 1. Presence of a medical therapeutic need based on a current examination of the patient by a suitably qualified health care professional. 2. Absence of authorised treatment and licensed alternatives tolerated by the patient or repeated treatment failure. 3. A documented review and critical appraisal of available scientific evidence favours off-label use to respond to the unmet medical need of the individual patient. 4. Patients (or their legal representative) must be given sufficient information about the medicines that are prescribed to allow them to make an informed decision. 5. Presence of established reporting routes for outcomes and adverse events linked to off-label use. In Japan, the 1980 notification from the Ministry of Health, Labour and Welfare has been used to address the off-label use. The 1980 notification allows a case-by-case decision to be made regarding whether off-label use should be covered by health insurance. This decision is limited to drugs approved in Japan and have passed the post-marketing reexamination period. The off-label use is approved when there is scientific evidence and known pharmacologic effects supporting the drug's use. Specifically, in Japan, the 1980 notification is often granted when stated in the clinical practice guidelines of each medical society [Reference 6]. Off-label use can be motivated and driven by various factors at different levels: # *Examples of off-label use drivers at regulatory level during the marketing authorization or the post marketing authorization process* - Limited incentives for investigating new indications - Disruption in the manufacturing of a product leading to drug shortage - Long drug development times and high costs # *Examples of off-label use drivers at healthcare system level in terms of pricing & reimbursement* - The on-label product is more expensive than the off-label one - Despite marketing authorization, a product is not available in all countries due to economic reasons

ITEM	DESCRIPTION
	# *Examples of off-label use drivers at patient and healthcare professional level* - Unmet medical need and no approved drug available - Patient pressure
Category	Availability of data
Type of BB	Development practice
Geographical scope	International
Availability	Healthcare professionals; Patients and patient associations; industry developing medicines for rare and ultra-rare diseases. Off-label use of a licensed medicinal product should be by mutual agreement between patient (or carer) and the treating physician. Responsibility of any adverse events of using the medicinal product in this way rests with the treating physician.
Scope of use	Examples of the scope of use of a medicinal product off-label include: • use in an unlicensed dose or dose frequency • use in an unlicensed route of administration • use in an unlicensed age group (e.g., children or infants) or special population (e.g., pregnant individuals) • use for an unlicensed different indication
Stakeholders involved	Healthcare professionals, pharmacists and pharmaceutical industry, patients and patient's associations, regulatory authorities, health technology assessment bodies.
Enablers/ Requirements	To be off-label, this implies an approved label exists. So a basic requirement must be that there is at least one authorisation [in the relevant country / region] for the product (at some dose, some route of administration, etc.). Off-label use can be appropriate but only in the context of specific requirements. See also the 5 GOLUP principles above.
Output	Treatment option when the available, approved products' arsenal does not meet the patient's need.
Best time to apply and	Not applicable in terms of "applying". But product must be authorised first, i.e., it must have a label, before off-label use can be considered.

ITEM	DESCRIPTION
time window	
Expert tips	Off-label use should not be confused with "compassionate use" (Regulation 726/2004/EC, article 83) which refers to an unauthorized medicinal product either subject of a marketing authorization application or under evaluation in a clinical trial. Off-label use is an unapproved use of an approved drug whereas compassionate use allows the use of an unapproved drug. PROs • Economic advantages and increased access to drugs otherwise not available. *Of note, 95% of the over 7000 known rare diseases have no approved treatment.* • Off-label use could benefit from Drug Repurposing (DR) approach. DR consists of investigating existing drugs for new therapeutic indication; it is often presented as offering various advantages over developing an entirely new drug such as fewer risks, lower costs and shorter timelines. Approved products also used off-label for a new indication could be repurposed and obtain regulatory approval for that new indication. Programs, such as CURE ID (see BB I433) try to capture healthcare provider's and patient's experiences with off-label use, in order to identify candidates for more formal drug repurposing efforts. *Marketing Authorization Holders can also apply for an orphan designation (and get incentives) for a new indication of an approved product (that might also be used off-label for that new indication).* • At national levels, countries may have put in place specific policy tools for off-label use that could be of interest for common perspectives. *Legal frameworks to issue temporary recommendations for use and permission to prescribe off-label; measures to regulate reimbursement; policy tools providing guidance for prescribers and policy tools focused on the patient.* CONs • No legal framework in Europe [References 1 and 7]. Off-label prescription is not regulated on a European Union level and therefore not harmonized in the EU Member States**.** Each MS has its own policy with regard to off-label prescribing and reimbursement. Off-label use is also not regulated in the United States (with the exception of off-label promotion which is prohibited).

ITEM	DESCRIPTION
	• The lack of information on the benefit-risk ratio of the off-label use can lead to unpredictable outcomes of the treatment. The responsibility lies with the treating physician. • Lack of clarity about the liability may be an issue in case of off-label prescribing. • Widespread off-label use can discourage Research & Development and make future clinical trials (particularly placebo-controlled trials) difficult (if the off-label use has become the standard of care). • It may be unclear how to move a drug through the development pipeline once it is approved if a new indication is sought by someone other than the original MAH or manufacturer. The pathways to updating a label can be difficult to navigate and expensive. If the drug is used off-label, there may be little incentive to pursue a labelled indication and the rigorous studies required to demonstrate safety and efficacy for the new use.

Drug Repurposing Guidebook

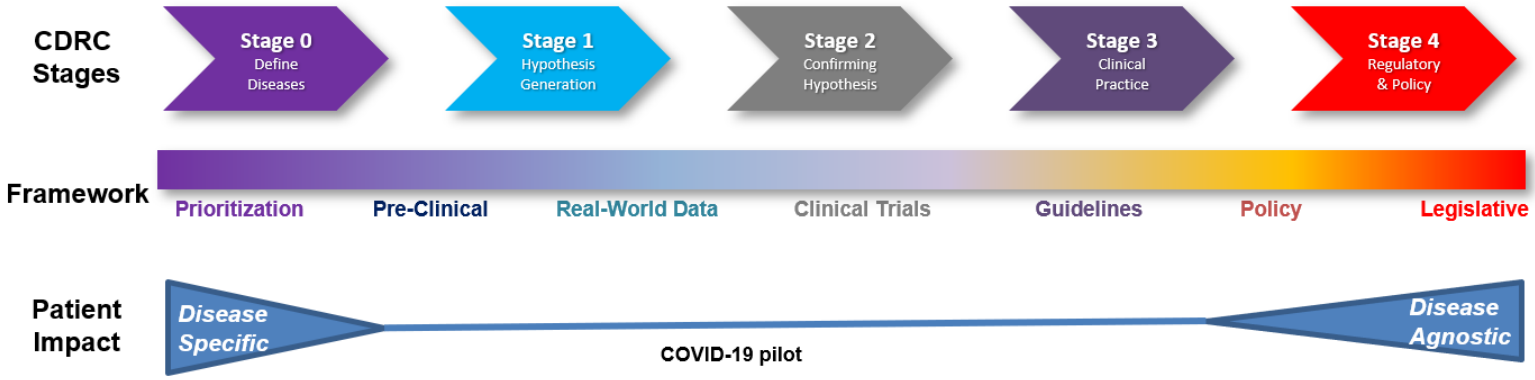
Building Block I435

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

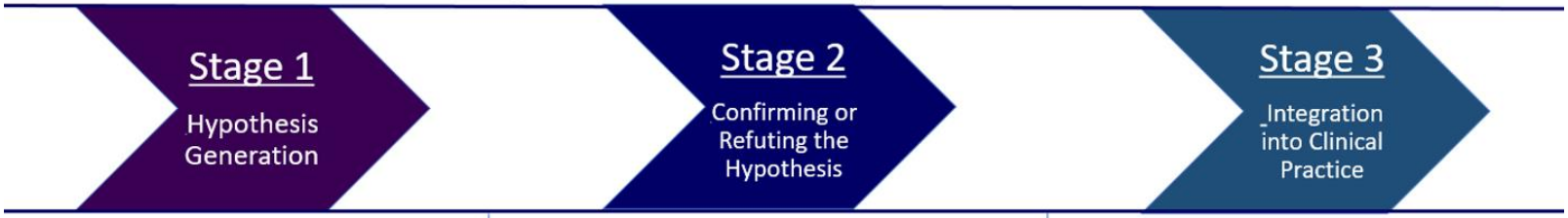
ITEM	DESCRIPTION
Building Block (BB) Title	CURE Drug Repurposing Collaboratory (CDRC)
References	https://c-path.org/programs/cdrc/
Description	CDRC, convened by the Critical Path Institute (C-Path), in partnership with the FDA-NCATS CURE ID* platform, is a dedicated initiative designed to capture real-world clinical outcome data to advance drug repurposing and inform future clinical trials for diseases of high unmet medical need.
Category	Availability of data
Type of BB	Development resource
Geographical scope	International
Availability	App Download: "Download the CURE ID app at (https://cure.ncats.io/) and begin submitting cases today. It takes a couple of minutes and every case report counts." Any interested party is welcome to join the public-private partnership by participating in the CDRC Advisory Committee, Therapeutic Area Coordinating Committees, or disease/group of disease-specific working groups. There are also groups focused on automated extraction of EHR data, conduct of pragmatic platform randomized controlled trials to test repurposed drugs, and groups focused on policy, regulatory and legislative issues.
Scope of use	Identifying new clinical efficacy of known drugs for diseases with high unmet medical need. Covers the spectrum of drug repurposing from disease prioritization, preclinical to clinical translation, real-world clinical data, randomized controlled trials, policy, and legislation.

ITEM	DESCRIPTION
Stakeholders involved	Physicians, Drug Developers, Clinical Researchers, Scientists, Regulators, Policymakers, Non-profit organizations, Patient and patient advocacy groups
Enablers/ Requirements	Participation in the public-private partnership activities. The Advisory Committee meets every 3-6 months, the Therapeutic Area Coordinating Committees (e.g., Infectious diseases, Rare diseases, Special Populations, etc.) meet once a month, and the disease-specific working groups or other specific projects typically meet every 1-4 weeks. Any qualified party is welcome to participate in these groups. To participate, they must sign a simple non-disclosure agreement (NDA) to protect the confidentiality of internal discussions, in order to participate.
Output	Movement of drug repurposing candidates from initial efficacy signal identification through the development process of real-world data collection and randomized trials or other robust study designs. Activities to try to facilitate drug repurposing, including legislative and policy initiatives to specifically facilitate repurposing of off-patent drugs.
Best time to apply and time window	Any time, no formal application, just reach out to mschito@c-path.org and heather.stone@fda.hhs.gov
Expert tips	Reach out to Marco Schito, CDRC Executive Director (mschito@c-path.org) for general information and participation in working groups on rare diseases (including rare cancers and rare non-oncologic diseases); Smitty Heavner, CDRC Scientific Director (sheavner@c-path.org) about EHR activities; Heather Stone, FDA Liaison to CDRC (heather.stone@fda.hhs.gov) about regulatory and policy topics and infectious diseases; Mili Duggal, Special Populations Coordinating Committee co-chair on pregnancy and neonates (mili.duggal@fda.hhs.gov).

Developing partnerships and infrastructure to provide sustainable resources to impact patient treatments globally



Long-term Vision for CDRC



Methods of Generating Hypotheses

a. Learning from Clinical Care Experience
- Clinical Care Data (from off-label use)
  - CURE ID – clinician case reports
  - Registries
  - EHRs and automated extraction
  - Claims Data
  - Published literature
  - Clinical trials & observational studies

b. Pre-clinical Signal Identification
- High Throughput Screening
- Biological studies of drug targets, mechanisms and disease pathways
- AI literature and record mining to identify targets or associations

Result
- Identification of a Safety or Efficacy Signal

Next Steps
- Determine the strength of the signal and whether it merits further study
- Determine if additional data (pre-clinical, animal studies, RWE, etc.) are needed prior to trial

Translating Real-world Data Hypotheses into Evidence

a. Generate a prioritized list of which drug-disease combinations look the most promising

b. Determine the Type of Study Needed to Generate Confirmatory Evidence of Safety and Efficacy
- Is randomization needed? Is it ethical and feasible?
- What patient population will be included? How large does it need to be? How will the outcome be measured?
- Is it intended for regulatory purposes (IND required) or is it exempt? Consult with FDA on study design.

c. Address the practical considerations
- Who will fund the trial? What will it cost?
- Who will conduct the trial?

Result
- Execution of clinical trial(s) or other robust research methods to provide confirmatory evidence

Next Steps
- Determine if trial or other evidence will be submitted for regulatory approval (IND required)
- Determine how the results of the trial(s) may be disseminated if regulatory approval is not an option

Result Dissemination and/or Regulatory Approval

3(a) Regulatory Approval Route
- Is there a pathway for regulatory submission?
- If a normal pathway is not available, is there a less traditional pathway that could be used (e.g. BPCA)?
- Need to determine:
  - Who will serve as the sponsor?
  - What level of evidence will be required?

3(b) Non-Regulatory Route

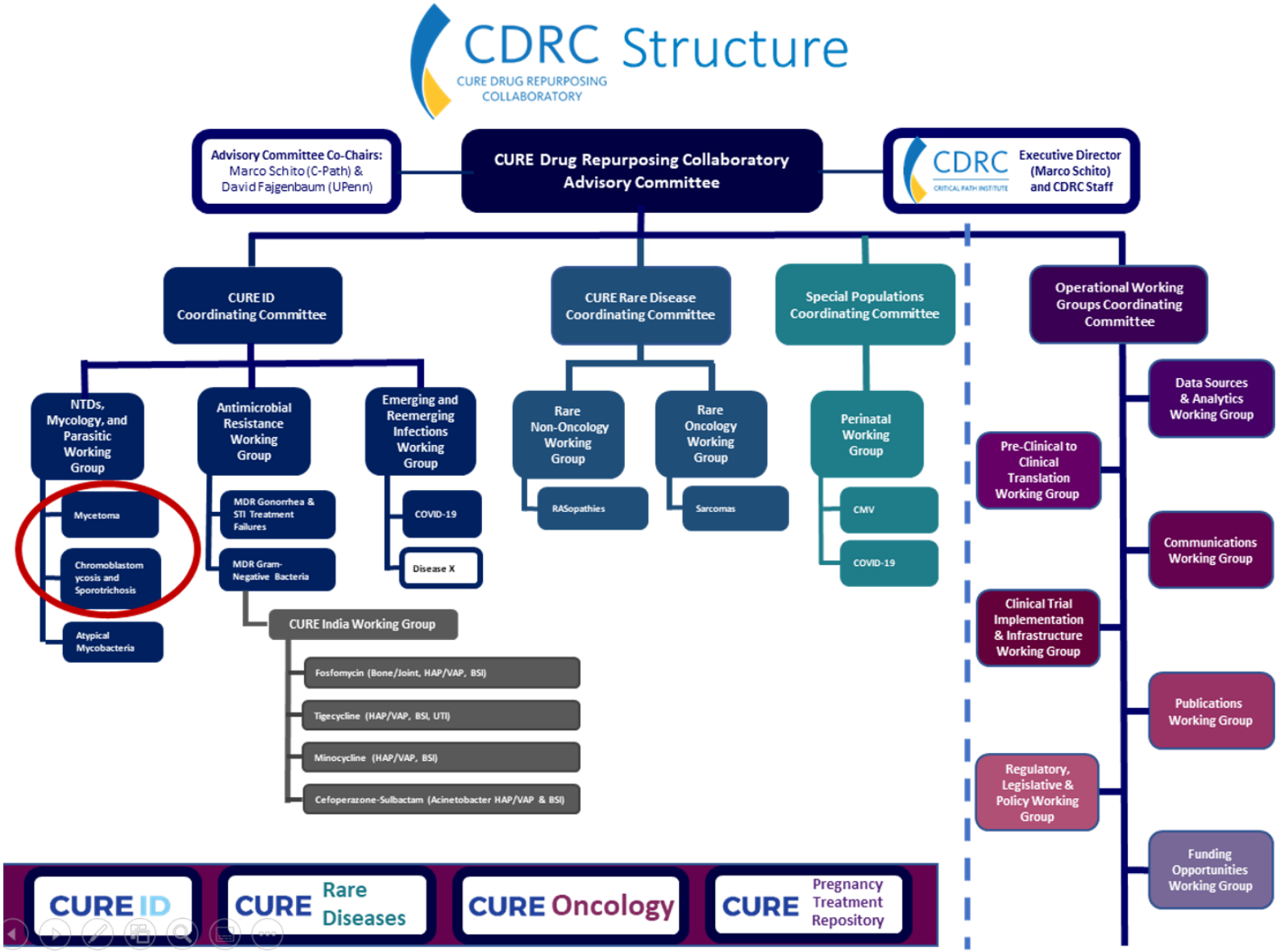
If there is no available or feasible route to US regulatory approval, consider other means of review and dissemination:
- Approval by other Stringent Regulatory Authorities/WHO
- Recommended by CDC or Professional Societies
- Publication in Peer-reviewed Literature

Result
- FDA Review/labeling change and/or other Evidence dissemination

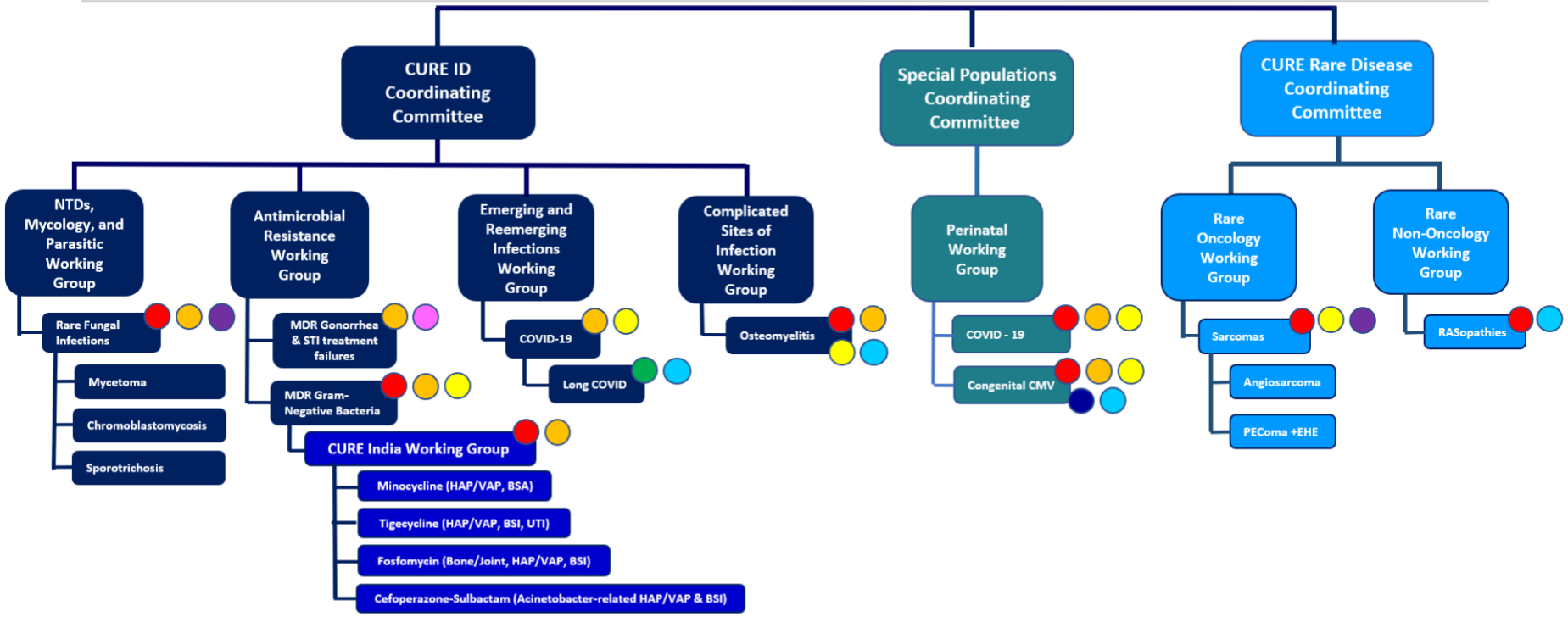
Next Steps
- Explore new legislative/policy opportunities that would create pathways for others to submit data to FDA
- Ensure patients have access to affordable treatment with sustained manufacturing of high-quality product

CDRC CURE DRUG REPURPOSING COLLABORATORY CRITICAL PATH INSTITUTE | CURE ID Challenging cases... New approaches

www.fda.gov


CDRC Structure
CURE DRUG REPURPOSING COLLABORATORY
Advisory Committee Co-Chairs: Marco Schito (C-Path) & David Fajgenbaum (UPenn)
CURE Drug Repurposing Collaboratory Advisory Committee
CDRC CRITICAL PATH INSTITUTE
Executive Director (Marco Schito) and CDRC Staff
CURE ID Coordinating Committee
CURE Rare Disease Coordinating Committee
Special Populations Coordinating Committee
Operational Working Groups Coordinating Committee
NTDs, Mycology, and Parasitic Working Group
Mycetoma
Chromoblastomycosis and Sporotrichosis
Atypical Mycobacteria
Antimicrobial Resistance Working Group
MDR Gonorrhea & STI Treatment Failures
MDR Gram-Negative Bacteria
CURE India Working Group
Fosfomycin (Bone/Joint, HAP/VAP, BSI)
Tigecycline (HAP/VAP, BSI, UTI)
Minocycline (HAP/VAP, BSI)
Cefoperazone-Sulbactam (Acinetobacter HAP/VAP & BSI)
Emerging and Reemerging Infections Working Group
COVID-19
Disease X
Rare Non-Oncology Working Group
RASopathies
Rare Oncology Working Group
Sarcomas
Perinatal Working Group
CMV
COVID-19
Data Sources & Analytics Working Group
Pre-Clinical to Clinical Translation Working Group
Communications Working Group
Clinical Trial Implementation & Infrastructure Working Group
Publications Working Group
Regulatory, Legislative & Policy Working Group
Funding Opportunities Working Group
CURE ID
CURE Rare Diseases
CURE Oncology
CURE Pregnancy Treatment Repository

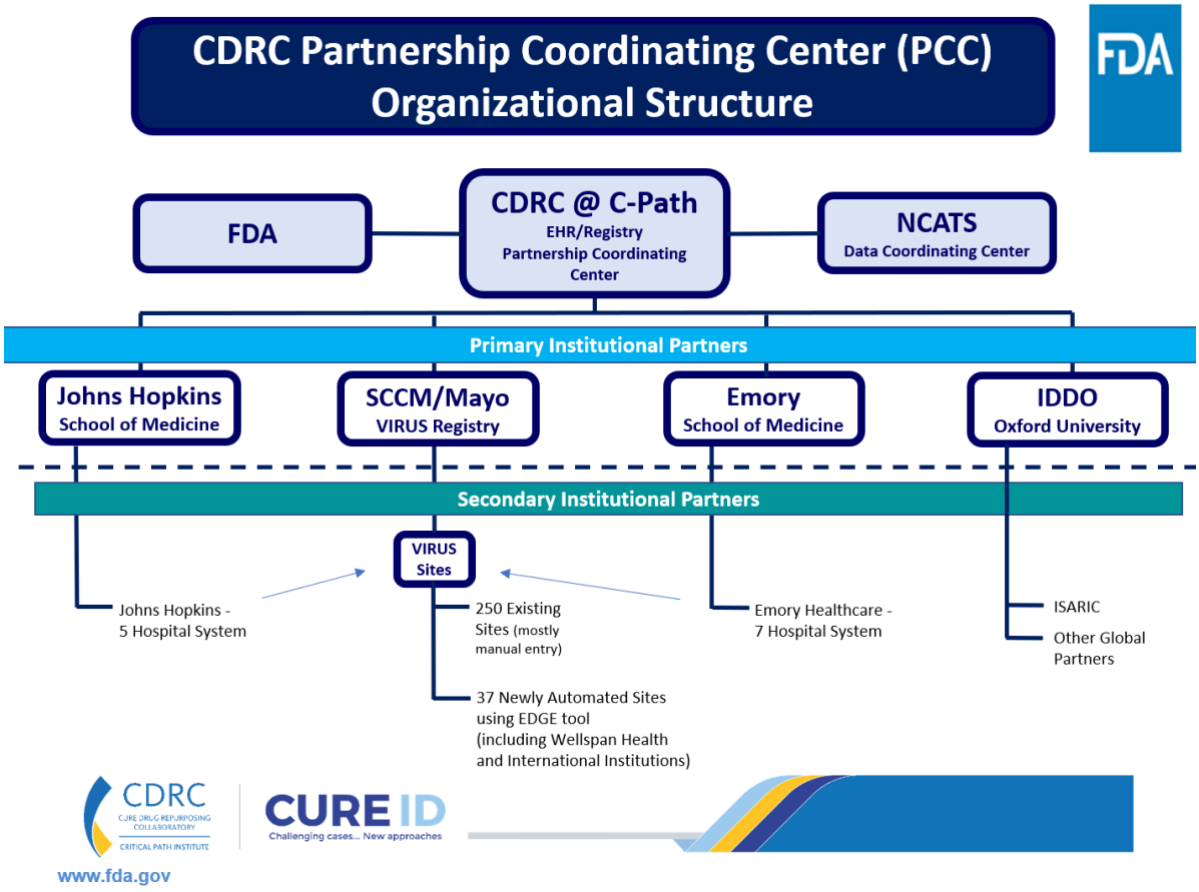
CDRC Sources of Data for Each Therapeutic Area

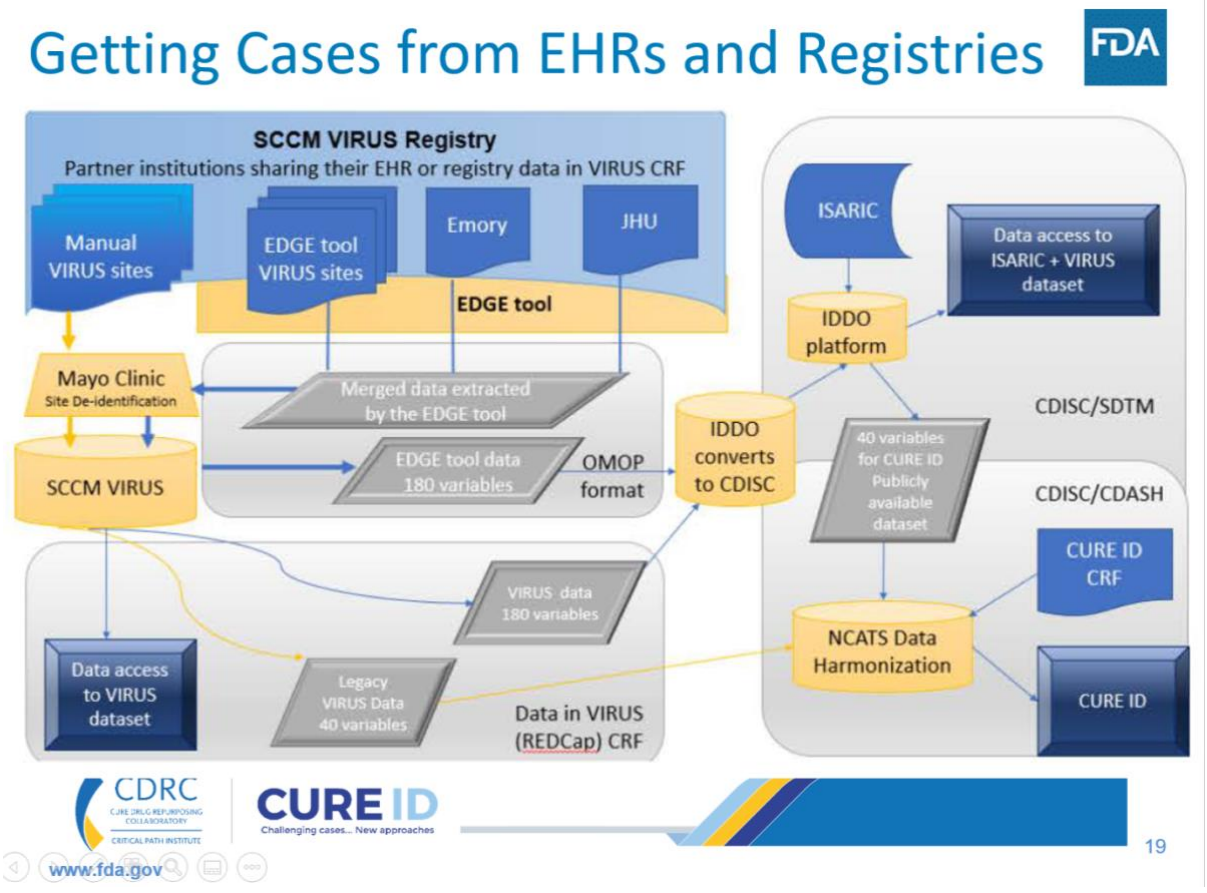


Legend:

- = Clinician-Submitted Case
- = Published Case Report
- = Case extracted from EHR "EDGE" Tool
- = Government/Health Authority Supplied Case
- = Combined Registries
- = Clinician Survey on Off-Label Use
- = Patient Treatment Survey
- = Patient Portal
- = Patient-Supplied EHRs

1


CDRC Partnership Coordinating Center (PCC)
Organizational Structure
FDA
FDA
CDRC @ C-Path
EHR/Registry
Partnership Coordinating
Center
NCATS
Data Coordinating Center
Primary Institutional Partners
Johns Hopkins
School of Medicine
SCCM/Mayo
VIRUS Registry
Emory
School of Medicine
IDDO
Oxford University
Secondary Institutional Partners
VIRUS
Sites
Johns Hopkins -
5 Hospital System
250 Existing
Sites (mostly
manual entry)
37 Newly Automated Sites
using EDGE tool
(including Wellspan Health
and International Institutions)
Emory Healthcare -
7 Hospital System
ISARIC
Other Global
Partners
CDRC
CURE ID
Challenging cases... New approaches
www.fda.gov


Getting Cases from EHRs and Registries
FDA
SCCM VIRUS Registry
Partner institutions sharing their EHR or registry data in VIRUS CRF
Manual
VIRUS sites
EDGE tool
VIRUS sites
Emory
JHU
EDGE tool
Mayo Clinic
Site De-identification
SCCM VIRUS
Merged data extracted
by the EDGE tool
EDGE tool data
180 variables
OMOP
format
IDDO
converts
to CDISC
ISARIC
Data access to
ISARIC + VIRUS
dataset
IDDO
platform
CDISC/SDTM
40 variables
for CURE ID
Publicly
available
dataset
CDISC/CDASH
CURE ID
CRF
NCATS Data
Harmonization
CURE ID
VIRUS data
180 variables
Data access
to VIRUS
dataset
Legacy
VIRUS Data
40 variables
Data in VIRUS
(REDCap) CRF
CDRC
CURE ID
Challenging cases... New approaches
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Drug Repurposing Guidebook

Building Block I436

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	Chemical Compound Databases
References	https://ecbd.eu/ https://www.ebi.ac.uk/chebi Global Substance Registration System (GSRS) | National Center for Advancing Translational Sciences (nih.gov)
Description	Several chemical compound databases exist, which include collections of small molecules. Examples are the Chemical Entities of Biological Interest (ChEBI), which is a freely available dictionary of molecular entities focused on 'small' chemical compounds. The term 'molecular entity' refers to any constitutionally or isotopically distinct atom, molecule, ion, ion pair, radical, radical ion, complex, conformer, etc., identifiable as a separately distinguishable entity. The molecular entities in question are either products of nature or synthetic products used to intervene in the processes of living organisms.
Category	Pre-clinical development
Type of BB	Development resource
Geographical scope	Accessible from all over the world
Availability	Open-source
Scope of use	The cope of use is to find a molecule that modulates the previous found drug target or signaling pathway.

ITEM	DESCRIPTION
Stakeholders involved	The experts supporting the databases: ChEBI merges data from different sources: IntEnz, KEGG COMPOUND, PDBeChem, and ChEMBL to eliminate redundancy. The repurposing developer
Enablers/ Requirements	Quick availability of known molecules with known mode of action. The signaling pathway or drug target should be identified.
Output	Shortcut to existing molecules to target a drug target or pathway. Data on the different molecular structures can be downloaded.
Best time to apply and time window	In the early phases of development, once the disease and molecular target are identified.
Expert tips	When a drug target or pathway is identified it is a “must-to-do” to check whether already known/approved drugs for the target or pathway exist.

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Drug Repurposing Guidebook

Building Block I437

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ITEM	DESCRIPTION
Building Block (BB) Title	Network databases
References	KEGG database: https://www.genome.jp/kegg/pathway.html doi: 10.1093/nar/gkp896 MSIG database: http://www.gsea-msigdb.org/gsea/msigdb/index.jsp doi: 10.1016/j.cels.2015.12.004 WikiPathways: https://www.wikipathways.org/index.php/WikiPathways doi: 10.1093/nar/gkv1024 Reactome: https://reactome.org/ doi: 10.1093/nar/gkab1028 GeneOntology: http://geneontology.org/ doi: 10.1038/75556 NDEX: https://www.ndexbio.org/#/ doi: 10.1016/j.cels.2015.10.001 LINCS database: https://lincs.hms.harvard.edu/db/ doi: 10.1039/c4mb00677a
Description	General biological pathway and network databases such as KEGG, MSigDB, WikiPathways, Reactome, GeneOntology and NDEX, contain information on molecular pathways, some of which are druggable. Unfortunately, these resources contain few pathway descriptions that reflect the molecular action of drugs. The molecular mRNA expression signatures changing after exposure to drugs have been recorded in the LINCS databases.

ITEM	DESCRIPTION
Category	Compound and network databases and tools to use them
Type of BB	Development resource
Geographical scope	International
Availability	Webversions are open. Downloads are also allowed without restrictions with the exception of KEGG
Scope of use	Drug repurposing candidate discovery or prioritization. General biological pathway and network databases such as KEGG, MSigDB, WikiPathways, Reactome, GeneOntology and NDEX, may be used to identify druggable molecular pathways with aberrant activity from molecular (omics) profiling experiments. The molecular mRNA expression signatures changing after exposure to drugs have been recorded in the LINCS databases. A way to identify drug repurposing candidates is to determine which mRNA expression disease signatures are changing in an opposite direction after drug exposure. Alternatively, molecular disease signatures are intersected with known protein targets from existing drugs, such as recorded in ChEBI (see building block 'Chemical compound databases')
Stakeholders involved	Intended audience are preclinical researchers from academia and industry
Enablers/ Requirements	All tools are equipped with a web interface but advanced use may required bioinformatics skills
Output	Druggable pathways and drug repurposing candidates
Best time to apply and time window	Drug repurposing candidate discovery

ITEM	DESCRIPTION
Expert tips	The pathway databases are generic. Not all pathways may be active in all cells or tissues. The LINCS database is limited in the cell lines included. For some rare disorders, no or limited data on relevant cell types may be present. The LINCS database is quite noisy, i.e. replicate experiments may not always correlate well. Additional manual review of drug repurposing candidates may be required.

Drug Repurposing Guidebook

Building Block I438

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ITEM	DESCRIPTION
Building Block (BB) Title	Engaging with Market Authorisation holders (MAH)
References	The Article 57 data base list product names /active substances and marketing authorisation holder's and give a contact email address and telephone number for pharmacovigilance enquiries. (QP PV) https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/public-data-article-57-database Helpful background reading: Drug repurposing from the perspective of pharmaceutical companies - PMC Drug repurposing: a systematic review on root causes, barriers and facilitators On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients Current Drug Repurposing Strategies for Rare Neurodegenerative Disorders
Description	There are two main reason to engage with a MAH • engage with the originator who owns the original license to get access to development history, data and regulatory files

	• identify the future MAH to guide the development for the repurposed indication As per the EMA definition, the Marketing Authorisation Holder (MAH) is a legal entity that has the authorization to market a medicine in a given market and will fulfill the legally binding requirements to maintain that authorisation. Marketing authorisation holders are responsible for ensuring that they and any parties working for them comply with all relevant standards set out in the research and development, marketing authorisation and post authorisation stages. To inform the regulatory strategy for a new indication with an "available" product it is most logical to first engage with the pharmaceutical company who maintains the original marketing authorisation. The originator will have a full understanding of the development history of the molecule, the IP rights and access to the regulatory master file. It is also recommended to identify early or during the process if other entities beside the originator could be the future Marketing Authorisation Holder for the repurposed indication and under which circumstances (resources, regulatory and IP status). There is no single defined process to engage with a MAH and part of the challenge will be to identify the right decision maker within a company and to convince them of the strategic importance of this new indication.
Category	Engagement with MA
Type of BB	Development practice
Geographical scope	International
Availability	This is a must to bring on label a new clinical use for any product or active substance.
Scope of use	This BB is for approved chemical entities that have reached or will soon reach the end of their IP and regulatory exclusivities. The engagement with the MAH and the level of support the MAH will demonstrate for the new indication development will impact development timelines and shape the regulatory strategy. If the original MAH doesn't intend to develop the additional indication, then you need to have access not only to the MAA modules of the regulatory dossier, but also to ALL the raw data (basis of the MAA

	dossier). To this extent the repurposing champion will have to engage multiple times with the "originator" with a solid argumentation. The case of a redevelopment of an active substance that has never obtained a marketing authorisation or the case of a medicine still well within intellectual property or regulatory data protection periods, are considered out of scope for this BB as the freedom to operate is significantly different. It is still relevant to contact the originator MAH to confirm the exclusivity rights and signal interest in a new indication.
Stakeholders involved	Principal investigator leading on the new clinical use, marketing authorisation holder and IP holders. Of note IP holders can be a different entity from the marketing authorisation holder, they will receive royalties without necessarily being involved in the development plan or carry the liability which is with the MAH. Within the context of a collaborative framework more stakeholders can be represented in the engagement: physicians, academics, hospitals and not-for-profit organizations, patient organizations, pharmaceutical industry, health technology assessment bodies, payers, and regulators
Enablers/ Requirements	Convincing pharmaceutical industry to join forces can be challenging, fulfilling requirements from the list below will increase your chances of success to find an interested MAH - Project supported by a mature and robust data set - Documented scientific advice from regional authorities (EMA, FDA,...) with scientific and regulatory guidance - Evidence generated according to GxP and meeting the regulatory standards expected from the MAH (see also definition of MAH above). - Natural history data and other data to fit an economic model supporting cost-effectiveness. - Being aware of the competitive landscape and the strategic fit for the company portfolio and pipeline - Repurposing undertaken within a multi-partner project involving collaborators who are respected, knowledgeable, and experienced in getting repurposed drugs approved for new indications.

Output	1. Access to important information like the development history, data and the regulatory master file 2. A defined regulatory strategy and path to patient access 3. Identify the future MAH that will carry the risks and meet legal obligations linked to MA.
Best time to apply and time window	At the time it is decided to bring a new clinical use on label Each time a new milestone is reached in the development process Till a MAH is identified for the repurposed indication
Expert tips	Often the original MAH will already have evaluated whether to develop the drug in that indication and has not prioritized that development program. You will have to work to reverse that decision. Understanding why the program wasn't considered in the first place can be very useful to build a convincing case (see also enablers). Be aware that beyond the costs for the MA holder to submit a regulatory dossier and to maintain the product on the market (life-cycle management), repurposing will require the MAH to dedicate skilled staff to the project. If the repurposed program doesn't have a high a strategic fit with the MA holder activities - the dossier might experience significant delays as other priorities take precedence. Consider generic companies interested in value-added medicine as MAH for out of patent products Show a good understanding of PV and adverse event reporting standards. Companies are liable for the products they commercialize. Keep in mind it is not all about efficacy. Pharmacovigilance and the risk brought by a new clinical use to an existing on label indication might be a deterrent for a company to support a label update. Persistence will be key, start with your contacts within the industry and make sure your support for the repurposed indication has a direct influence on decision-making in portfolio reviews. Multi-partner collaborations between pharmaceutical companies, academic institutions, non-profit organizations and biotechnology

	companies was the most commonly discussed facilitator for drug repurposing cited in the literature.

Drug Repurposing Guidebook

Building Block I439

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ITEM	DESCRIPTION
Building Block (BB) Title	NewFound initiative
References	https://newfoundmed.org/ https://newfoundmed.org/resources/
Description	NewFound is a global alliance that promotes collaboration in medicines repurposing, repositioning or reuse. Its partners are involved in open-science health research and development and join forces in a hub focused on repurposing medicines, believing that global collaboration is critical to achieving these objectives. It explores opportunities to collaborate and, where feasible, establish partnerships with each other to achieve these shared interests. As a result, the alliance cross-leverages resources from different institutions and countries in open and transparent model through specific data sharing agreements as needed.
Category	Supporting tools
Type of BB	Development resource
Geographical scope	International
Availability	It is available for users (researchers, charities, patient organizations, industry) that are in need of drug repurposing research capacity or expertise or are seeking for project mentoring or want to explore an international partnership. A central website is available with contact

ITEM	DESCRIPTION
	form and any of the partners involved can handle requests and/or facilitate set up of (tailor made) collaborations.
Scope of use	Networking with global organizations involved in drug repurposing (e.g. to expand network around specific project/disease indication) Access to specific resources or expertise, including pharmaceutical compound collections and screening facilities. Share data in in open preclinical, regulatory and clinical data portals and participate in rare and neglected diseases as well as rapid response to future pandemic outbreaks through repurposing Project mentoring and support (including support for funding applications) and Intellectual Property (IP) assessments. Assistance in regulatory planning and access to health technology assessment expertise. Support for funding applications (i.e., finding partners with right expertise to develop a consortium)
Stakeholders involved	NewFound is a global alliance that is composed of the Oswaldo Cruz Foundation (FioCruz, Rio de Janeiro, BR), EATRIS infrastructure for Translational Medicine (Amsterdam, NL), National Institute of Health's (NIH) National Center for Advancing Translational Sciences (NCATS) (Bethesda, US) and Open Source Pharma Foundation (OSPF) (Bangalore, IN).
Enablers/ Requirements	NewFound was established to create awareness, provide a contact point and offer research capacities and expertise for drug repurposing initiatives and collaborations on a global level. It can help researchers and patient organizations further I their project by establishing new connections and bring in experts for mentoring to identify bottlenecks and provide possible solutions in the project. Relevant medicines repurposing projects are based on confirmed unmet medical need. The alliance is opened to explore collaborations with other stakeholders, including pharma, funders, patient organizations, opensource research initiatives, regulators and policy makers to and share experience and best practice to improve the (global) drug repurposing ecosystem.

ITEM	DESCRIPTION
Output	Networking, new connections, partnerships, mentoring programs, improved design and resourcing of drug repurposing projects.
Best time to apply and time window	Continuous
Expert tips	A drug repurposing, repositioning or reuse project can be as complex as conventional drug development. If you are stuck in your project expanding your (global) network can help finding a solution, whether technical or organizational. The regulatory systems for medicines development can vary across different global regions, with different levels of attention to, experience with and incentives for drug repurposing. Contacting a global network of peers can help understand these differences better, through exchange of best practices.

Drug Repurposing Guidebook

Building Block I440

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ITEM	DESCRIPTION
Building Block (BB) Title	*In silico* models for screening for drug repurposing candidates
References	https://www.frontiersin.org/articles/10.3389/fchem.2020.00343/full https://www.frontiersin.org/articles/10.3389/fchem.2020.00093/full https://pubmed.ncbi.nlm.nih.gov/30205360/ https://www.imi.europa.eu/projects-results/project-factsheets/etox
Description	One of the developments that has shown quite some promise for drug repurposing is the development of *in silico* models. Over the last decades, the use and efficacy of computational, or *in silico,* models in drug development has significantly grown. Thanks to the availability of increasing amounts of data, and growing numbers and possibilities of data analysis strategies, in silico models have gained in usability and therefore traction in drug repurposing. There are different *in silico* models, for example, working on drug: target interactions using molecular dynamics, or in silico prediction of toxicities. These in silico approaches are demonstrating their ability to generate reliable predictions as well as new knowledge on the mode of action of drugs and the mechanisms underlying their side effects.
Category	Compound and network databases and tools to use them
Type of BB	Development practice
Geographical scope	International

ITEM	DESCRIPTION
Availability	Open Access (code and repository). For both rare and non-rare diseases. For both drug repurposing and de novo drug development.
Scope of use	To combine different types and kinds of data, and extract most available information from this.
Stakeholders involved	Preclinical researchers from academia and industry
Enablers/ Requirements	NA
Output	A list of drug repurposing candidates for a specific disorder that can be tested in further wet-lab studies. New knowledge based on existing datasets.
Best time to apply and time window	Discovery of drug repurposing candidates
Expert tips	If you do intend to use *in silico* models, make sure you have several robust data sets, including different data sources Pro: Allows you to systematically discover new correlations that you might have missed otherwise. Con: Sufficient (freely accessible) data is needed if you want to be able to find new information

Drug Repurposing Guidebook

Building Block I441

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ITEM	DESCRIPTION
Building Block (BB) Title	Machine learning & data mining
References	Bio.tools https://bio.tools/ doi: 10.1093/nar/gkv1116 Drug Repurposing Knowledge Graph https://github.com/gnn4dr/DRKG/ https://arxiv.org/pdf/2010.11367.pdf
Description	Bio.tools is a general repository for software tools, databases and services for bioinformatics and the life sciences. Relevant machine learning methods can be retrieved through this search: https://bio.tools/t?topicID=%22topic_3474%22. Bio.tools uses terms from the EDAM ontology to describe the features of the tools in the repository, to increase findability. Deep learning methods, and more specifically graph convolutional networks, constitute a novel class of machine learning methods that appears particularly useful for predicting novel drug repurposing candidates. These methods use existing information from expert-curated or non-curated (primarily obtained from text mining the scientific literature) sources about molecular defects observed in rare diseases, disease phenotypes and drugs proven to reverse disease phenotypes captured in a drug repurposing knowledge graph. The Drug Repurposing Knowledge Graph (DRKG) is one of the most extensive knowledge graphs available for drug repurposing studies. Although initially focused on identifying drug repurposing candidates for Covid-19, the graph can be used for other diseases as well. DRKG incorporates DrugBank, Global Network of Biomedical Relationships (GNBR), Hetionet, STRING, IntAct, and DGIdb.

ITEM	DESCRIPTION
Category	Compound and network databases and tools to use them
Type of BB	Development practice
Geographical scope	International
Availability	Open Access (code and repository)
Scope of use	The problem of predicting drug repurposing candidates can be defined as a machine learning problem where new links between drugs and diseases are predicted from a knowledge graph through training of a graph convolutional network algorithm on known drug:disease relationships. This is called link prediction. The algorithm is trained on true positives (drugs known to treat diseases), but also requires a set of true negatives. In practice, these are difficult to find because of the underreporting of drugs that are not effective in treating a disease, and therefore a subset of drug:disease combinations that are not yet in the knowledge graph is taken as true negatives. Workflows and service bundles that encompass different steps in the drug repurposing could be a useful step. This was successfully done for other pressing problems like the pathogenicity assessment of genetic variants.
Stakeholders involved	Preclinical researchers from academia and industry
Enablers/ Requirements	Application of this type of advanced machine learning methods requires bioinformatics and programming skills (primarily python and use of PyTorch libraries). Training in deep learning is also required.
Output	A list of drug repurposing candidates for a specific disorder that can be tested in further wet-lab studies.
Best time to apply and time window	Discovery of drug repurposing candidates

ITEM	DESCRIPTION
Expert tips	A comprehensive evaluation of the predictive performance of this type of deep learning algorithms is still lacking, in particular for rare disease, i.e., it is unknown how many of the predicted drugs can be validated in preclinical and clinical studies. Current drug repurposing knowledge graphs are mostly generic and may not contain information about the rare disease of interest or lack information on the context of the disorder (phenotypes, affected tissues, affected molecular pathways). When predicting drug repurposing candidates for a given disorder, it is wise to add information about the specific disorder to the knowledge graph and to keep only the parts of the knowledge that are relevant in the context of the disorder. Several additional resources can be included in the building of knowledge graphs, including resources specified in building blocks 131 (Drug databases), 105 (chemical compound databases), 106 (network databases)

Drug Repurposing Guidebook

Building Block I442

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ITEM	DESCRIPTION
Building Block (BB) Title	Competitive intelligence
References	**Open-source competitive intelligence software or online tools:** 1/ Governmental tools • US tools: **[1]** Pubmed https://pubmed.ncbi.nlm.nih.gov/ **[2]** NIH tool https://www.nlm.nih.gov/services/databases_subject.html **[3]** FDA tool https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases • EU tools: **[4]** Data Europe: https://data.europa.eu/en the official portal for European data **[5]** European Galaxy Server: https://usegalaxy.eu , the open, reproducible, web-based platform for data intensive research 2/ Commercial or OSINT software from non-governmental organisations: **[6]** Google analytics: https://analytics.google.com **[7]** Babel X - AI-enabled data aggregation and analysis **[8]** Maltego - Interactive datamining with rich visualization showing relationships between different data in the collection In IP, for freedom-to-operate studies: **[9]** https://clarivate.com/ **[10]** https://www.inquartik.com/ **[11]** https://www.lens.org/lens/
Description	"Competitive intelligence" software or tools consist in gathering and analysing information related to research discovery, biopharma,

ITEM	DESCRIPTION
	medtech, IP matters or real-world data intelligence in the life science field. On one side, governmental organisations developed "open-source intelligence (OSINT)" that can be used for free. On the other hand, non-governmental organisations or companies developed their own tools or software [6-8] with specific software and databases for IP matters and freedom-to-operate studies [9-11].
Category	Compound and network databases and tools to use them
Type	Development practice
Geographical scope	International
Availability	Open source or access, and; Commercial software/tool restricted to the payers
Scope of use	• Basic Research investigations • Drug development • Clinical studies • Market studies
Stakeholders involved	Researchers, bioinformaticians, data scientists, From academia or industry Consultants in IP, innovation
Enablers/ Requirements	Basic researchers in chemistry, pharmacologists, bio-informaticians, data scientists Drug developers from academia or industry
Output	New knowledge for faster drug development • Discovery of new targets for a RD • Discovery of new applications for a drug • Freedom-to-operate studies
Best time to apply and time window	At all stages of drug development.
Expert tips	PROs: Open-source competitive intelligence tools are accessible to all stakeholders

ITEM	DESCRIPTION
	CONs: commercial software are usually very expensive for academia and can be used only by companies. The competitive intelligence software must be used by specific experts (data scientists, IP expert)

Drug Repurposing Guidebook

Building Block I443

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ITEM	DESCRIPTION
Building Block (BB) Title	Drug prioritization analysis
References	Examples of software and references are: http://www.dreimt.org/ https://www.nature.com/articles/s41598-019-42806-6 https://www.scienceopen.com/hosted-document?doi=10.14293/S2199-1006.1.SOR-.PPPGCKMC.v1
Description	Databases can be used to explore possible drug-indication pairs that suggest likely therapeutic response. These pairs can then be followed up with more traditional clinical studies.
Category	Compound and network databases and tools to use them
Type of BB	Development practice
Geographical scope	International
Availability	Databases will vary in their availability. Some will have constraints based on patient confidentiality reasons, some may have constraints due to commercial and intellectual property reasons. In cases of patient confidentiality, it may be possible to anonymise some data and release a de-identified version.

ITEM	DESCRIPTION
Scope of use	To combine different types and kinds of data, and extract most available information from this, and consequently being able to prioritize candidates for repurposing.
Stakeholders involved	Owners / custodians of databases, whether commercially held or available for public access.
Enablers/ Requirements	Exitance of (and access to) suitable databases.
Output	Possible drug candidates and associate therapeutic targets. But all identified drug-indication pairs will need to be explored in more traditional clinical studies.
Best time to apply and time window	There is no best time to "apply" but large databases will need to be available to support these types of activities.
Expert tips	If you do intend to prioritization models, make sure you have several robust data sets, including different data sources Pro: Allows you to systematically discover new candidates that you might have missed otherwise. Con: Sufficient (freely accessible) data is needed if you want to be able to find new information

Drug Repurposing Guidebook

Building Block I444

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ITEM	DESCRIPTION
Building Block (BB) Title	**How to search and use IP and legal databases**
References	**[1]** Arora A et al., 2017. *Papers to patents*. Nature. 552: S10. https://www.nature.com/articles/d41586-017-07421-3 **[2]** Rotolo D el al., 2022. *Why do firms publish? A systematic literature review and a conceptual framework.* Research Policy. 51:104606. https://www.sciencedirect.com/science/article/pii/S0048733322001299 **[3]** Smith J et al., 2017. *Evidence of insufficient quality of reporting in patent landscapes in the life sciences*. Nat Biotechnol. 35:210-4. https://www.nature.com/articles/nbt.3809 **[4]** Krauß J and Kuttenkeuler D, 2021. *When to file for a patent? The scientist's perspective.* N Biotechnol. 60:124-9. https://www.sciencedirect.com/science/article/pii/S1871678420301849 **[5]** Donald K et al., 2018. *Tips for reading patents: a concise introduction for scientists*. Expert Opin Ther Pat. 28:277-280. https://www.tandfonline.com/doi/full/10.1080/13543776.2018.1438409 **[6]** Krauß J and Kuttenkeuler D, 2018. *Intellectual property rights derived from academic research and their role in the modern bioeconomy-A guide for scientists*. N Biotechnol. 40:133-9. https://www.sciencedirect.com/science/article/pii/S1871678416326450 **[7]** Dias C and Almeida R, 2013. *Scientific production and technological production: transforming a scientific paper into patent applications*. Einstein. 11:1-10. https://www.scielo.br/j/eins/a/RxYC4VQftCzNGsXcfzpW3Mj/?format=pdf&lang=en **[8]** Southan C, 2020. *Opening up connectivity between documents, structures and bioactivity*. Beilstein J Org Chem. 16:596-606. https://www.beilstein-journals.org/bjoc/articles/16/54 **[9]** Senger S, 2017. *Assessment of the significance of patent-derived information for the early identification of compound-target interaction hypotheses*. J Cheminf. 9:26. https://jcheminf.biomedcentral.com/articles/10.1186/s13321-017-0214-2

ITEM	DESCRIPTION
	[10] Krallinger M et al., 2017. *Information Retrieval and Text Mining Technologies for Chemistry*. Chem Rev. 117:7673-7761. https://core.ac.uk/download/pdf/87660278.pdf **[11]** Barbieri M, 2022. *Patent Prior Art Searches: Basic Principles and Strategies*. Preprints 2022, 2022050054. https://www.preprints.org/manuscript/202205.0054/v1 **[12]** Van Rijn T e Timmins J, 2023. *Patent landscape analysis—Contributing to the identification of technology trends and informing research and innovation funding policy*. Microbial Biotech https://ami-journals.onlinelibrary.wiley.com/doi/10.1111/1751-7915.14201 **[13]** Patentscope help page https://patentscope.wipo.int/search/en/help/help.jsf **[14]** Lens Patents Help page https://support.lens.org/article-categories/patent/ **[15]** Google Patents https://support.google.com/faqs/answer/7049475?hl=en **[16]** IPC patent classification search engine https://ipcpub.wipo.int/ **[17]** CPC patent classification search engine https://worldwide.espacenet.com/patent/cpc-browser **[18]** Pubchem Docs (help page) https://pubchemdocs.ncbi.nlm.nih.gov/about **[19]** Kim S et al., 2022. *PubChem 2023 update*. Nucleic Acids Res. gkac956. https://doi.org/10.1093/nar/gkac956 **[20]** DrugBank https://go.drugbank.com/drugs **[21]** Zhou Y et al., 2022. *Therapeutic target database update 2022: facilitating drug discovery with enriched comparative data of targeted agents*. Nucleic Acids Res. gkac95. https://academic.oup.com/nar/article/50/D1/D1398/6413598 **[22]** Avram S et al., 2022. *DrugCentral 2023 extends human clinical data and integrates veterinary drugs*. Nucleic Acids Res. gkac1085. https://doi.org/10.1093/nar/gkac1085
Description	Even a quick analysis of literature shows, on one side, the progressive growth in scientific publishing activities reporting the content of patent literature that is relevant for developing and using drugs, but, on the other side, the quite limited (if not biased) understanding of the patent system by many authors who do not evaluate correctly the actual relevance of patent-related issues for evaluating, accessing and using drugs, in particular with respect to rare diseases. Moreover, there are sparse but clear evidences that, while several companies have reduced their scientific publishing activities (preferring to disclose such information only or, early on, in own patent publications [1,2]), the quality of reports summarizing the content of patent publications in scientific literature is quite uneven [3]. Indeed, only few PubMed-indexed articles try conveying basic information about the patent system and the content of patent documents to the academic audience [4-7], while the opportunities to perform extensive analysis across patent and scientific literature are growing, in particular for medicinal chemistry topics

ITEM	DESCRIPTION
	relevant for drug repurposing [8-12]. Thus, it is important to provide investigators with a guidance about how to effectively extract and evaluate findings from patent literature, to be combined with findings from biomedical literature in order to elaborate work hypotheses for selecting candidate drugs to be repurposed in a rare disease and evaluate how testing such compound(s) in models or patients. This BB provides investigators with an overview of some basic concepts about patent documents and data (application Vs grant, priority Vs final filing, technical disclosure Vs claims, geographical Vs commercial scope, patent classification codes, patent maintenance, claims categories, etc.) and details about using most effective free databases indexing patent information (coverage, search strategies, data extraction/ archiving, programmatic access, etc.), proposing simple case studies for - Patent-only databases such as Patentscope [13], Lens Patents [14], Google Patents [15], and related Patent Classification search engines [16-17]; and - Public databases indexing patent, scientific, and regulatory information for chemical compounds [18-22].
Category	Contact with TTO and Patents
Type of BB	Development practice
Geographical scope	International
Availability	It covers information resources are freely available (unless indicated otherwise, in particular for copyright reasons or subscription-based access).
Scope of use	Support to investigators involved in Drug Repurposing & Rare Disease research by avoiding duplicated efforts and improving the process for selection & (pre)clinical validation of drug candidates by: - Increasing awareness about the (pre)clinical information that is available in patent literature; - Correcting some common opinions and practices about patent activities for pursuing (pre)clinical research activities; and - Improving the practices about the use of databases of patent literature and the extraction of information and data from patent publications.
Stakeholders involved	Investigators involved in (pre)clinical research activities and data analysis; patients' organizations; technology transfer offices (TTOs) and business development professionals within academic institutions, agencies and companies that work in the fields of drug development, regulatory affairs, and health policy.
Enablers/ Requirements	Previous experience in: - use of internet resources for scientific research and literature;

ITEM	DESCRIPTION
	- drug and/or rare disease research, clinical, Technology Transfer, or regulatory activities.
Output	Useful knowledge for a faster selection, validation, and access to new therapeutic strategies in rare diseases by: - taking full advantage of (pre)clinical evidences already available; and - better understanding patent rights and obligations that apply to commercially available drugs.
Best time to apply and time window	This BB is mainly applicable in the early phases of drug development, to gather all relevant information before/during the process for selection & (pre)clinical validation of drug candidates but it can support activities also in later steps, before taking any major commitment or decision when pursuing the regulatory proceedings and facilitating the access to the selected drug (acquisition, distribution, manufacturing, clinical use, safety, reimbursement).
Expert tips	PROs: - Growing examples in the scientific literature and extensive support can be found in the cited websites; - NO copyright issues apply to patent documents. CONs: - A regular use of the described databases and search strategies is needed to consolidate the knowledge and skills based on this BB; - Some commercial databases are more effective than those described but their access and use require more resources; - Non-English languages can be used in patent literature, thus translation tools may be needed; - Patent databases, patent classification, and some patent/legal provisions may evolve over time and guidance may become incomplete/incorrect; - The patent information that is identified using the guidance in the BB needs to be evaluated by specialists in legal proceedings at national level (since many patent rules and other legal provisions applicable to drugs may differ at the country level) and in strategic management before taking any major commitment or decisions related to intellectual property and avoiding to be over-confident in such matters.

Drug Repurposing Guidebook

Building Block I445

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	**Patent Framework of Drug Repurposing**
References	**[1]** *Study to support the evaluation of the EU Orphan Regulation*. (European Commission report; 2019) https://health.ec.europa.eu/system/files/2020-08/orphan-regulation_study_final-report_en_0.pdf **[2]** *Orphan Drugs In The United States: An Examination Of Patents and Orphan Drug Exclusivity* (NORD® Commissioned Report, 2021) available https://rarediseases.org/wp-content/uploads/2021/03/NORD-Avalere-Report-2021_FNL-1.pdf **[3]** Seki K et al., 2022. *Lifecycle management of orphan drugs approved in Japan*. Orphanet J Rare Dis. 17: 299. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9336109/ **[4]** *"Drugs and Orphan Diseases"* issue in Therapies 2020 https://www.sciencedirect.com/journal/therapies/vol/75/issue/2 **[5]** Verbaanderd C et al., 2020. *On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients* Front Pharmac. 10:1664 https://www.frontiersin.org/articles/10.3389/fphar.2019.01664 **[6]** Strohbehn G et al. 2021. *Combination therapy patents: a new front in evergreening*. Nat Biotechnol. 39: 1504-1510. https://www.nature.com/articles/s41587-021-01137-6 . **[7]** Krauß J and Kuttenkeuler D, 2021. *When to file for a patent? The scientist's perspective.* N Biotechnol. 60: 124-9. https://www.sciencedirect.com/science/article/pii/S1871678420301849 **[8]** Donald K et al., 2018. *Tips for reading patents: a concise introduction for scientists*. Expert Opin Ther Pat. 28: 277-280. https://www.tandfonline.com/doi/full/10.1080/13543776.2018.1438409 **[9]** Krauß J and Kuttenkeuler D, 2018. *Intellectual property rights from academic research and their role in bioeconomy-A guide for scientists*. N Biotechnol. 40: 133-9. https://www.sciencedirect.com/science/article/pii/S1871678416326450

ITEM	DESCRIPTION
	[10] Aboy M et al., 2022. *European patent protection for medical uses of known products and drug repurposing.* Nat Biotechnol. 40: 465–471. https://www.nature.com/articles/s41587-022-01269-3 **[11]** *Drug Prices: The Role of Patents and Regulatory Exclusivities* (Congressional Research Service, US congress 2021). https://sgp.fas.org/crs/misc/R46679.pdf **[12]** Agranat I and Marom H, 2020. *In Defense of Secondary Pharmaceutical Patents in Drug Discovery and Development.* ACS Med Chem Lett. 11: 91-98. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7106985/ . **[13]** EMA (European Medicines Agency) Medicines portal https://www.ema.europa.eu/en/medicines **[14]** FDA (U.S. Food & Drug Administration) Drug Approvals and Databases https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases **[15]** Terrot M et al., 2019 *Overview of Orange Book and Off-Patent/Off-Exclusivity List* at "WIPO conference Standing Committee on Law of Patents, 31st Session" https://www.wipo.int/edocs/mdocs/scp/en/scp_31/scp_31_h_orange.pdf **[16]** Durvasula M et al., 2022. *The NBER Orange Book Dataset: A User's Guide (No. w30628).* National Bureau of Economic Research, Cambridge, USA. https://doi.org/10.3386/w30628 **[17]** Zhou Y et al., 2022. *Therapeutic target database update 2022: facilitating drug discovery with enriched comparative data of targeted agents*. Nucleic Acids Res. gkac95. https://academic.oup.com/nar/article/50/D1/D1398/6413598 **[18]** Avram S et al., 2022. *DrugCentral 2023 extends human clinical data and integrates veterinary drugs*. Nucleic Acids Res. gkac1085. https://doi.org/10.1093/nar/gkac1085 **[19]** Li F et al., 2022. *DrugMAP: molecular atlas and pharma-information of all drugs*. Nucleic Acids Res. gkac813. https://doi.org/10.1093/nar/gkac813 **[20]** Kim S et al., 2022. *PubChem 2023 update*. Nucleic Acids Res. gkac956. https://doi.org/10.1093/nar/gkac956 **[21]** Masoudi-Sobhanzadeh Y et al., 2020. *Drug databases and their contributions to drug repurposing.* Genomics. 112: 1087-1095, https://www.sciencedirect.com/science/article/pii/S0888754319301284?
Description	Patent-related policies play a fundamental role in drug development and approval, and even more when the objective is to evaluate how giving access to drugs that are potentially available but not to target patient populations with specific needs and expectations such as those affected by a rare disease. There is a wide literature explaining the main requirements for obtaining the official authorization of a drug to be prescribed in a rare disease with respect to legislation related to Orphan Medicinal Product Designation and drug life cycle management in various geographical areas[1-4], and the identified factors acting barriers or facilitators to

ITEM	DESCRIPTION
	translate research into repurposed orphan drugs for specific indications, as in cancer-related ones [5,6]. Unfortunately, very few PubMed-indexed articles try conveying basic information about the patent system and how academic investigators may find, read, and use relevant patent documents [7-9]. Moreover, even less have explained and exemplified the relevance of secondary patent protection which is a main issue when evaluating what type of patent protection is actually covering a candidate drug for repurposing [10-12], or have explained how identifying and interpreting the patent and regulatory data in official databases, such as the Orange Book [13-16]. Thus, it is important to provide investigators with a guidance about how to effectively identify main patent-related issues related to drug authorization with respect to rare diseases and repurposing. This BB provides investigators with an overview of basic concepts about: - General patent rights and enforcement proceedings (product claims Vs. use claims, patent Vs. market exclusivity, technical contents Vs. geographic scope of claims, legal challenge to patent rights, selection inventions, patent validity and expiry date, freedom to operate, etc.); - Specific issues related to drug repurposing for evaluating patent claims and access to drugs (second medical use, secondary patents, Supplementary Patent Certificates, Patent Term Extensions/Adjustment, patent evergreening, life cycle management, parallel import, patent "thickets", "pay-for-delay" settlements, etc.); - Evaluating the potential patent issues related to each type of drug repurposing, for instance, if the drug: ○ Is marketed under patent protection, ○ Is available as a generic drug and/or without patent protection, ○ Is no more (or never) marketed, or ○ requires some kind of improvements with respect to drug substance as initially developed or marketed in order to be used as therapy for a rare disease, and the repurposing process may involve developing specific solutions for dosage, route of administration, formulation, regimen, combination with other drug, chemical modifications, and relevant criteria and biomarkers for selecting patients or evaluating drug responses; and - Databases that index relevant drug information cross-referencing biomedical data with details about patent status, availability, and official indications in main jurisdictions, as recently reviewed in *Nucleic Acid Research* [17-20] or other journals [21].
Category	Contact with TTO and Patents
Type	Development resource

ITEM	DESCRIPTION
Geographical scope	International
Availability	It covers information resources are freely available (unless indicated otherwise, in particular for copyright reasons or subscription-based access).
Scope of use	Support to investigators and developers involved in Drug Repurposing & Rare Diseases by identifying most relevant patent-related provisions that apply to access to drugs, in general or when repurposed for a rare disease by: - Making an informed decision on patent and legal feasibility for repurposing a drug; - Increasing awareness about the means to identify, use, and communicate relevant patent-related information for any legal and regulatory scope; and - Correcting some common opinions and practices about patent-related issues that apply to (pre)clinical research activities and access to drugs.
Stakeholders involved	Investigators involved in (pre)clinical research activities and data analysis; patients' organizations; technology transfer offices (TTOs) and business development professionals within academic institutions, agencies and companies that work in the fields of drug development, regulatory affairs, and health policy; patent attorneys, IP advisors, and IP managers.
Enablers/ Requirements	Previous experience in: - use of internet resources for scientific research and literature; - oppositions, litigations, due diligences, or other activities related to the evaluation of patent validity and enforcement of patent rights.
Output	Mitigation plan or alternative strategies to address any patent-related issues for a faster access to new therapeutic strategies in rare diseases by better understanding of main patent requirements that apply to the manufacturing, authorization, and use of drugs for a given indication and/or jurisdiction.
Best time to apply and time window	This BB is mainly applicable in the early phases of drug development, to gather all relevant information before/during the process for selection & (pre)clinical validation of drug candidates but it can support activities also in later steps, before taking any major commitment or decision when pursuing the regulatory proceedings and facilitating the access to the selected drug (acquisition, distribution, manufacturing, clinical use, safety, reimbursement).
Expert tips	PROs: - It helps empowering non-profit stakeholders with knowledge and skills of drug industry, building bridges and common understanding about major barriers to make repurposed drugs accessible to the patients;

ITEM	DESCRIPTION
	- The information in this BB may be supported by/ support the activities described in other BBs, for instance when defining patent searches and monitoring the patent situation for specific compounds, indications, companies, and/or jurisdictions. CONs: - Non-English languages may be used, translation tools are needed; - Patent provisions may evolve and the guidance in the BB may become incomplete/incorrect; - The patent information that is identified using the guidance in the BB needs to be evaluated by specialists in legal proceedings and in drug life cycle management at national level (since many patent rules and other legal provisions applicable to drugs may differ at the country level), before taking any major commitment or decisions related to intellectual property and avoiding to be over-confident in such matters.

Drug Repurposing Guidebook

Building Block I446

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	**Regulatory Framework of Drug Repurposing**
References	**[1]** *Study to support the evaluation of the EU Orphan Regulation*. (European Commission report; 2019) https://health.ec.europa.eu/system/files/2020-08/orphan-regulation_study_final-report_en_0.pdf **[2]** *Orphan Drugs In The United States: An Examination Of Patents and Orphan Drug Exclusivity* (NORD® Commissioned Report, 2021) available https://rarediseases.org/wp-content/uploads/2021/03/NORD-Avalere-Report-2021_FNL-1.pdf **[3]** Seki K et al., 2022. *Lifecycle management of orphan drugs approved in Japan*. Orphanet J Rare Dis. 17: 299. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9336109/ **[4]** *"Drugs and Orphan Diseases"* issue in Therapies 2020 https://www.sciencedirect.com/journal/therapies/vol/75/issue/2 **[5]** Miler K et al., 2021. *"Using four decades of FDA orphan drug designations to describe trends in rare disease drug development"* Orphanet J Rare Dis. 16: 265. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8191002/ . **[6]** Chan AYL et al., 2020.*Access and Unmet Needs of Orphan Drugs in 194 Countries and 6 Areas: A Global Policy Review with Content Analysis*. Value Health. 23:1580-1591. https://www.sciencedirect.com/science/article/pii/S1098301520344132 **[7]** van den Berg S et al., 2021. *Drug Repurposing for Rare Diseases: A Role for Academia*. Front. Pharmacol. 12: 746987. https://www.frontiersin.org/articles/10.3389/fphar.2021.746987 **[8]** Krishnamurthy N et al., 2022. *Drug repurposing: a systematic review on root causes, barriers and facilitators.* BMC Health Serv Res. 22: 970. https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-022-08272-z **[9]** Tambuyzer E et al., 2020. *Therapies for rare diseases: therapeutic modalities, progress and challenges ahead*. Nat Rev Drug Discov. 19: 93-111. https://www.researchgate.net/publication/337930085_Therapies_for_rare_diseases_therapeutic_modalities_progress_and_challenges_ahead

ITEM	DESCRIPTION
	[10] Verbaanderd C et al., 2020. *On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients* Front Pharmac. 10: 1664 https://www.frontiersin.org/articles/10.3389/fphar.2019.01664 **[11]** Del Alamo M et al., 2022. *Identifying obstacles hindering the conduct of academic-sponsored trials for drug repurposing on rare-diseases: an analysis of six use cases*. Trials. 23: 783. https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-022-06713-y. **[12]** Monge A et al., 2022. *Use of US Food and Drug Administration Expedited Drug Development and Review Programs by Orphan and Nonorphan Novel Drugs Approved From 2008 to 2021*. JAMA Netw Open. 5: e2239336. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2798005 **[13]** Tan G et al., 2023. *Drug repurposing using real-world data*. Drug Discovery Today. 28: 103422. https://www.sciencedirect.com/science/article/abs/pii/S1359644622004159 **[14]** *Drug Prices: The Role of Patents and Regulatory Exclusivities* (Congressional Research Service, US congress 2021). https://sgp.fas.org/crs/misc/R46679.pdf **[15]** EMA (European Medicines Agency) Medicines portal https://www.ema.europa.eu/en/medicines **[16]** FDA (U.S. Food & Drug Administration) Drug Approvals and Databases https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases **[17]** Terrot M et al., 2019 *Overview of the Orange Book and the Off-Patent/Off-Exclusivity List* at WIPO conference "Standing Committee on Law of Patents, 31st Session" https://www.wipo.int/edocs/mdocs/scp/en/scp_31/scp_31_h_orange.pdf **[18]** Durvasula M et al., 2022. *The NBER Orange Book Dataset: A User's Guide (No. w30628).* National Bureau of Economic Research, Cambridge, USA. https://doi.org/10.3386/w30628
Description	Regulatory and patent-related policies play a fundamental role in drug development and approval, and even more when the objective is to evaluate how giving access to drugs that are potentially available but not to target patient populations with specific needs and expectations such as those affected by a rare disease. There is a wide literature explaining the main requirements for obtaining the official authorization of a drug to be prescribed in a rare disease with respect to legislation related to Orphan Medicinal Product Designation and drug life cycle management in various geographical areas [1-6], and the identified factors acting as barriers or facilitators to translate research into repurposed orphan drugs, in general [7-9] or for specific indications, as in rare diseases or cancers [10-14]. Even though some articles have explained how identifying and interpreting the patent and regulatory data in official databases, such as the Orange Book [15-18], it

ITEM	DESCRIPTION
	remains important to provide investigators with a guidance about how to effectively identify main issues related to drug authorization and regulatory approval process with respect to rare diseases and repurposing. This BB provides investigators with an overview of some basic concepts about: - General regulatory policies that apply to marketed, approved, experimental drugs that have been authorized for use in humans, drug access and reimbursement, and related proceedings in selected countries, comparing patent Vs. market exclusivity and any applicable exemptions and obligations in official patent or regulatory policies with respect to rare diseases; and - Evaluating the potential regulatory issues related to each type of drug repurposing, for instance, if the drug: ○ Is marketed under any regulatory exclusivity, ○ Is available as a generic drug and/or without regulatory protection, ○ Is no more (or never) marketed, or ○ requires some kind of improvements with respect to drug substance as initially developed or marketed in order to be used as therapy for a rare disease, and the repurposing process may involve developing specific solutions for dosage, route of administration, formulation, regimen, combination with other drug, chemical modifications, and relevant criteria and biomarkers for selecting patients or evaluating drug response.
Category	Contact with TTO and Patents
Type of BB	Development practice
Geographical scope	International
Availability	It covers information resources are freely available (unless indicated otherwise, in particular for copyright reasons or subscription-based access).
Scope of use	Support to investigators and developers involved in Drug Repurposing & Rare Diseases by identifying most relevant obligations and provisions that apply to the regulatory approval and access to drugs, in general or when repurposed for a rare disease by: - Making an informed decision on regulatory, manufacturing, and legal feasibility for repurposing a drug; and - Increasing awareness about the means to identify, use, and communicate relevant information for any legal and regulatory scope.
Stakeholders involved	Investigators involved in (pre)clinical research activities and data analysis; patients' organizations; professionals within academic institutions, agencies and companies that work in the fields of drug development, regulatory affairs, and health policy.

ITEM	DESCRIPTION
Enablers/ Requirements	Previous experience in: - use of internet resources for scientific research and literature; - drug and/or rare disease research, clinical, or regulatory activities. - Oppositions, litigations, due diligences, or other activities related to legal evaluation of patent validity
Output	Mitigation plan or alternative strategies to address any patent-related issues for a faster access to new therapeutic strategies in rare diseases by better understanding of main regulatory requirements that apply to the manufacturing, authorization, and use of drugs for a given indication and/or jurisdiction.
Best time to apply and time window	This BB is mainly applicable in the early phases of drug development, to gather all relevant information before/during the process for selection & (pre)clinical validation of drug candidates but it can support activities also in later steps, before taking any major commitment or decision when pursuing the regulatory proceedings and facilitating the access to the selected drug (acquisition, distribution, manufacturing, clinical use, safety, reimbursement).
Expert tips	PROs: - It helps empowering non-profit stakeholders with knowledge and skills of drug industry, building bridges and common understanding about major barriers to make repurposed drugs accessible to the patients; - The information in this BB may be supported by/ support the activities described in other BBs, for instance when defining strategies for drug access and reimbursement, and assessment for specific compounds, indications, companies, and/or jurisdictions. CONs: - Non-English languages may be used, translation tools are needed; - Legal and regulatory provisions may evolve and the guidance in the BB may become incomplete/incorrect; - The legal and regulatory information that is identified using the guidance in the BB needs to be evaluated by specialists in legal proceedings at national level (since many regulatory and other legal provisions applicable to drugs may differ at the country level) and in drug life cycle management, before taking any major commitment or decisions related to the manufacturing, reimbursement, or access to drugs and avoiding to be over-confident in such matters.

Drug Repurposing Guidebook

Building Block I447

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	**How to maintain a literature archive**
References	**[1]** Shourick J et al., 2021. *Assessing rare diseases prevalence using literature quantification.* Orphanet J Rare Dis. 16:139. https://doi.org/10.1186/s13023-020-01639-7 **[2]** Frederiksen S et al., 2022. *Rare disorders have many faces: in silico characterization of rare disorder spectrum*. Orphanet J Rare Dis. 17:76. https://doi.org/10.1186/s13023-022-02217-9 **[3]** Ehrhart F et al., 2021. *A resource to explore the discovery of rare diseases and their causative genes.* Sci Data. 8:124. https://doi.org/10.1038/s41597-021-00905-y **[4]** Smith C et al., 2022. *Estimating the number of diseases – the concept of rare, ultra-rare, and hyper-rare*. iScience. 25:104698. https://doi.org/10.1016/j.isci.2022.104698 **[5]** Nguengang Wakap S et al., 2020. *Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database.* Eur J Hum Genet. 28:165-173. https://doi.org/10.1038/s41431-019-0508-0 **[6]** Masoudi-Sobhanzadeh Y et al., 2020. *Drug databases and their contributions to drug repurposing.* Genomics. 112: 1087-1095, https://doi.org/10.1016/j.ygeno.2019.06.021 **[7]** PubMed Help page https://pubmed.ncbi.nlm.nih.gov/help/ **[8]** Google Scholar Help page https://scholar.google.com/intl/en/scholar/help.html **[9]** Lens Scholar Help page https://support.lens.org/article-categories/scholar/ **[10]** Clinicaltrials.gov Help page https://www.clinicaltrials.gov/ct2/help/how-find/index **[11]** EU Clinical Trials Register https://www.clinicaltrialsregister.eu/ctr-search/search **[12]** The 5-part article *"Searching the literature for studies for a systematic review"* in Am J Orthod Dentofacial Orthop. (A Littlewood and D. Kloukos; 2019) https://pubmed.ncbi.nlm.nih.gov/31153512,31053291,30935616,30712702,30826048 **[13]** Massonnaud C et al., 2020. *Identification of the Best Semantic Expansion to Query PubMed Through Automatic Performance Assessment of Four Search Strategies on All Medical Subject Heading Descriptors: Comparative Study*. JMIR Med Inform. 8:e12799. https://doi.org/10.2196/12799

ITEM	DESCRIPTION
	[14] Lacey P, 2022. *Google is goodish: An information literacy course designed to teach users why Google may not always be the best place to search for evidence.* Health Info Libr J. 39:91-95. https://onlinelibrary.wiley.com/doi/10.1111/hir.12401 **[15]** Saxena R and Kaushik J, 2022. *Referencing Made Easy: Reference Management Software.* Indian Pediatr. 59:245-9 https://www.indianpediatrics.net/mar2022/245.pdf **[16]** Wikipedia page comparing main features of reference management software https://en.wikipedia.org/wiki/Comparison_of_reference_management_software **[17]** Dos Santos Vieira B et al., 2022. *Towards FAIRification of sensitive and fragmented rare disease patient data: challenges and solutions in European reference network registries.* Orphanet J Rare Dis. 17:436. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9749345 **[18]** Abaza H et al., 2022. *Domain-Specific Common Data Elements for Rare Disease Registration:Conceptual Approach of a European Joint Initiative Toward Semantic Interoperability in Rare Disease Research.* Indian Pediatr. 59:245-9 JMIR Med Inform. 10:e32158. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9166638/
Description	Even a quick analysis of literature shows the progressive growth in scientific publishing activities disclosing properties of commercially available drugs as well as the medical management and the pathobiological mechanisms of rare diseases. Indeed, the correct identification and categorization of literature disclosing biological, epidemiological and clinical data for a given rare disease is challenging and with evolving definitions and criteria [1-6]. Thus, it is important to provide investigators with a guidance about how to effectively extract, archive, and compare the findings from biomedical literature in order to elaborate new work hypotheses for selecting candidate drugs to be repurposed in a rare disease and evaluate risks/opportunities in testing such compound(s) in models or patients. This BB provides investigators with an overview of most representative databases, search strategies, and means to archive and distribute a literature archive dedicated to a drug repurposing, proposing simple case studies and guidance about: - using four, freely available sources for biomedical publications and information being PubMed and related NCBI/EBI resources [7], Google Scholar [8], Lens Scholar [9], Clinicaltrials.gov [10], and EU Clinical Trials Register [11], comparing their specificities and (dis)advantages when searching, extracting and archiving drug repurposing & rare disease information; - How expanding search strategies for retrieving relevant literature [12-14]; - How using reference management software for archiving literature, in particular free tools such as Mendeley and Zotero [15, 16].
Category	Contact with TTO and Patents

ITEM	DESCRIPTION
Type of BB	Development practice
Geographical scope	International
Availability	It covers information resources are freely available (unless indicated otherwise, in particular for copyright reasons or subscription-based access)
Scope of use	Support to investigators involved in Drug Repurposing & Rare Disease research by avoiding duplicated efforts and improving the process for selection & (pre)clinical validation of drug candidates by: - Increasing awareness about the means to identify, use, and share relevant (pre)clinical information that is actually available in scientific literature; and - Improving the practices about the use of databases of scientific literature, the management of literature archives, and the extraction of medical hypotheses and evidences from (pre)clinical publications.
Stakeholders involved	Investigators involved in (pre)clinical research activities and data analysis; patients' organizations; professionals within academic institutions, agencies and companies that work in the fields of drug development, regulatory affairs and health policy.
Enablers/ Requirements	Previous experience in - use of internet resources for scientific research and literature; - drug and/or rare disease research, clinical, or regulatory activities.
Output	Useful knowledge for faster selection, validation, and access to new therapeutic opportunities in rare diseases taking advantage of available (pre)clinical evidences.
Best time to apply and time window	This BB is mainly applicable in the early phases of drug development, to gather all relevant information before/during the process for selection & (pre)clinical validation of drug candidates but it can support activities also in later steps, before taking any major commitment or decision when pursuing the regulatory proceedings and facilitating the access to the selected drug (acquisition, distribution, manufacturing, clinical use, safety, reimbursement).
Expert tips	PROs: - Several examples, documentation, and support for quickly applying the guidance can be found in the internet; - Compliance with open access, interoperable data and resources for promoting exchanges among investigators and European Networks (FAIRification [17, 18]). CONs: - A regular use of the described databases, search strategies, and software is needed to consolidate the knowledge and skills based on this BB;

ITEM	DESCRIPTION
	- The databases and software may quickly evolve over time and some details in the BB may become incomplete/incorrect over time.

Drug Repurposing Guidebook

Building Block I448

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	Funding Sources for Drug Repurposing
References	https://www.cureswithinreach.org/programs/funding-opportunities-rfps/ https://www.bmbf.de/bmbf/shareddocs/bekanntmachungen/de/2022/07/2022-07-15-Bekanntmachung-Biomedizin.html https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/horizon-hlth-2021-disease-04-02 https://grants.nih.gov/grants/guide/pa-files/PAR-20-301.html https://grants.nih.gov/grants/guide/pa-files/PAR-20-161.html https://www.zonmw.nl/nl/onderzoek-resultaten/geneesmiddelen/drug-rediscovery/
Description	Different forms of public and private funding are available from national and international funding organizations, such as the European Commission, the National Institutes of Health, which are either specific to drug repurposing for rare diseases or have this as a priority. This research, innovation and implementation funding is available for (multi-)national collaboration projects as well as for individual researchers and supports SMEs.
Category	Funding
Type of BB	Development resource
Geographical scope	International

ITEM	DESCRIPTION
Availability	Applicants identifying, testing and implementing drug repurposing candidates
Scope of use	To provide funding for researchers from academia and industry for different phases of drug repurposing
Stakeholders involved	Researchers from academia and industry Public and philanthropic funders, for example the European Commission, National Insitute of Health, LifeArc EMA, FDA, PMDA
Enablers/ Requirements	To meet the requisites established in the funding competitive call.
Output	A successful funding application results both in a research proposal and the means to conduct the research through a potential public-public or public-private partnership.
Best time to apply and time window	The tool has the best perspectives / results in the very early phases of drug repurposing.
Expert tips	Start applying for funding well in advance, and also consider alternative funding options. Different partners together can apply to a combination of funding sources. PROs: – Allows a substantial amount of funding, when obtained, especially for early phases of drug development. Start planning for additional funding for each phase of development. – Anticipate IP issues in the funding agreement CONs: – High commitment is required from participants, while only a part of proposals gets granted.

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ITEM	DESCRIPTION
Building Block (BB) Title	Platforms
References	REPO4EU https://repo4.eu https://cordis.europa.eu/project/id/101057619
Description	The Euro-Global Platform for Mechanism-based Drug Repurposing provides support in bioinformatics, target identification, disease agnostic development, IP strategies, regulatory advice from low precision drug therapy to high precision curative therapy through real-world data, Artificial Intelligence and a platform offering every step from lab to phase II clinical. The support is performed by experienced experts from diverse backgrounds such as data scientists, CEO of biotech companies, researchers, clinicians, policy officers, drug developers, health economists etc...
Category	Supporting tools
Type of BB	Development resource
Geographical scope	Europe
Availability	Researchers from academia and industry from countries inside and outside of the European Union
Scope of use	Offer services and develop tools for repurposed drug development - bioinformatics support for an unmet medical need, a registered compound; - search a mechanism of action; - explore your freedom to operate, need a patenting strategy or regulatory advice; - need a business partner;

ITEM	DESCRIPTION
	- a clinical trial test site for phase I-III, or - support with a business plan
Stakeholders involved	Chemists, Pharmacologists, Biologists, bio-informaticians, AI scientists, regulators, ethics experts, policy makers and drug developers, experts in translational medicine and IP
Enablers/ Requirements	Clinicians Drug developers: Start-ups, Pharmaceutical industries Experts in translational medicine and IP Policy makers, regulatory affairs experts
Output	Develop a generic framework that can be used by anybody who wishes to start a drug repurposing project according to current best practices. Clinical trial, market access for a repurposed drug
Best time to apply and time window	During the drug development process.
Expert tips	The ambition of the platform is to cover the whole development chain from identification of a molecule for a given target to providing scientific and HTA advice, IP services or business support

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Building Block I450

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ITEM	DESCRIPTION
Building Block (BB) Title	Drug Discovery Platform
References	https://www.perlara.com https://www.genfit.com/ https://www.scilifelab.se/units/ddd-platform/ https://www.nature.com/articles/s41586-020-2117-z
Description	Platform technologies, such as drug discovery platforms, are considered a valuable tool to improve efficiency and quality in drug product development. The fundamental objectives of such platforms are to support discoveries of drug molecules and provide bioanalytical support to the scientific community. A drug discovery platform brings together knowledge and expertise in the first steps of the repurposing and drug discovery process (target identification and validation, hit finding and lead optimization), as such shortening time in the repurposing process. It also can bring about new knowledge in biological research by providing access to cutting edge drug screening and evaluation resources with a particular emphasis on developing novel drugs to improve human health. The basic idea is that such a platform, in combination with a risk-based approach, is the most systematic method to leverage prior knowledge for a given new molecule. Furthermore, such a platform enables a continuous improvement by adding data for every new molecule developed by this approach, increasing the robustness of the platform.

ITEM	DESCRIPTION
Category	Supporting tools
Type of BB	Development resource
Geographical scope	International
Availability	A number of drug discovery platforms are proposed as industrial platforms, where others are academically driven platforms. Overall, costs for the use of the platform, and the expertise of the platform's managers need to be paid.
Scope of use	To screen efficiently large number of drugs for the right genetic background.
Stakeholders involved	Preclinical researchers from academia and industry
Enablers/ Requirements	NA
Output	A list of drug repurposing candidates for a specific disorder that can be tested in further wet-lab studies. New knowledge based on existing datasets.
Best time to apply and time window	Discovery of drug candidates useable for repurposing
Expert tips	If you do intend to use drug discovery platforms, be sure you have the right genetic background for the disease for which you are looking for a drug candidate. PROs: Allows you to systematically discover new candidates that you might have missed otherwise. CONs: The drug identified via the platform might not be available for use in repurposing

Drug Repurposing Guidebook

Building Block I451

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ITEM	DESCRIPTION
Building Block (BB) Title	Remedi
References	• https://drugrepurposing.org/remedi/ • https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02 • VUMC_Remedi_Jan2020_4444-1.pdf • https://drugrepurposing.org/enrolling/ • https://www.youtube.com/watch?v=MuuACS2hgX8 • https://www.jclinepi.com/article/S0895-4356(22)00325-0/fulltext
Description	**Repurposing Essential Medicines Internationally** (Remedi) represents an initiative to identify new therapeutic uses for the medications included in the list of WHO's Essential Medicines List. Safe and affordable medications are included in that list and selection is based on data about disease prevalence and public health relevance, previous evidence of efficacy and safety, as well as cost-effectiveness data. The afore-mentioned list is updated every 2 years (last update in 2021) and offers flexibility to regional authorities to use as per local priorities. Remedi is an interactive tool generated by international internship and collaboration among institutions and centres.

ITEM	DESCRIPTION
	Remedi provides an overview of the established use(s) of agents in the essential medications list, as well as an overview of their additional suggested uses. The rationale is to expand the utility of existing medications and reveal new uses to benefit populations, especially in low- and middle-income countries and for rare and serious diseases. This can also enhance and facilitate drug research but also permit safe clinical decisions and treatment choices in exceptional situations.
Category	Supporting tools
Geographical scope	International
Availability	Availability to all clinicians working with patients with rare or serious diseases, especially in settings with limited resources Availability to applicants and stakeholders involved in the process of drug repurposing, especially in the early stages.
Scope of use	This is an already existing resource. The scope with this building block is: • To increase its accessibility and promote its wider application. • To make drug developers and healthcare professionals aware of this tool • To familiarize drug developers and healthcare professionals with its use and format.
Stakeholders involved	Both from clinical and research field: • Basic scientists • Bioinformaticians • Clinical researchers (investigators)

ITEM	DESCRIPTION
	• Healthcare workers • Rare diseases experts • Research pharmacists • Clinical pharmacologists • Pharmacovigilance officers • Regional/local regulatory authorities
Enablers/ Requirements	• A basic understanding of the underlying biology, pathophysiology of and disease mechanisms • Training of all the involved stakeholders about its use
Output	The output of this block will be of both research and clinical utility. • To produce a tool which will allow drug developers (stakeholders) to have easy access to safe and sound information about medications currently in use and to identify agents which could be re-purposed. • To produce a tool which can be used by healthcare professionals in order to guide their decisions when dealing with patients with rare or serious diseases.
Best time to apply and time window	Clinical use: In all stages of clinical care, especially in areas with inadequate resources or in cases of patients with complex conditions. Research use: By definition, being familiar with the list of all available medications is applied in the early stages of the process of drug-repurposing, as the already available medications represent the "source" of repurposed drugs.
Expert tips	• To bear in mind that this list is not exhaustive and resources from additional organizations can also be considered. • To consider the special circumstances (e.g. regulatory issues) in each geographic area.

Drug Repurposing Guidebook

Building Block I452

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ITEM	DESCRIPTION
Building Block (BB) Title	Generics
References	**[1]** US FDA: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-generic-drugs https://www.fda.gov/drugs/buying-using-medicine-safely/generic-drugs **[2]** US database https://purplebooksearch.fda.gov/ https://www.fda.gov/drugs/drug-and-biologic-approval-and-ind-activity-reports/first-generic-drug-approvals **[3]** EMA https://health.ec.europa.eu/medicinal-products/pharmaceutical-committee-veterinary-pharmaceutical-committee-and-expert-groups/commission-expert-group-safe-and-timely-access-medicines-patients-stamp_en https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/generic-hybrid-medicines **[4]** EMA database: https://www.ema.europa.eu/en/medicines/download-medicine-data **[5]** Australia database https://www.pbs.gov.au/browse/medicine-listing **[6]** Latin America https://gabionline.net/ **[8]** Publications *https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cmdc.201200552* **[9]** Worldwide consortium:

ITEM	DESCRIPTION
	https://www.iprp.global/home **[10]** Worldwide database: https://www.drugs.com/availability/ https://druginfo.nlm.nih.gov/drugportal/jsp/drugportal/DrugNameGenericStems.jsp
Description	Generic drugs are medicinal products that can be manufactured and marketed by others than the innovator company after the original patents have expired. Bioequivalence is the main regulatory principle for generic drug approval in European Union and the United States. For two drugs to be bioequivalent, they must contain identical amounts of the same active ingredient in the same strength and dosage form and their bioavailabilities must be similar in such a degree that their effects can be expected to be essentially the same. Repurposing generic drugs could offer a cheaper and faster way to develop new treatments. Since patents allow drug suppliers to have a monopoly over sales for a span of time, there is less opportunity for profit with generics than with new drugs. Researchers have been collecting these "failed" compounds for further testing, trawling through research papers, patents and clinical trial databases to find repurposing candidates. Some labs have used artificial intelligence to automate this process.
Category	Availability of data
Type of BB	Development resource
Geographical scope	International
Availability	Most generics are manufactured in developing countries where production costs are cheaper- e.g. China, India, Brazil
Scope of use	• Basic Research investigations • Drug development • Clinical studies • Market studies
Stakeholders involved	• Researchers, bioinformaticians, data scientists, AI scientists, chemists • From academia to industry • Policy makers • Manufactured companies (India and China for most of them) • Distributors

ITEM	DESCRIPTION
Enablers/ Requirements	To be considered as generic: the drug must contain identical amounts of the same active ingredient in the same strength and dosage form and their bioavailabilities must be similar in such a degree that their effects can be expected to be essentially the same as the brand name. Regulators, Generic manufacturers, policy makers
Output	New knowledge to faster drug development • Discovery of new treatment for a RD • Discovery of new applications for a drug
Best time to apply and time window	From the beginning of the project since it is a strategic approach to define early on
Expert tips	PROs: in cancer, it was shown that a drug development took 10 years for a novel drug and only 5 for a generic one since the pre-clinical studies and first stage of the clinical trials could be skipped CONs: if the initiator of the project is looking for a return on investment, this strategy cannot be chosen, and it cannot be a back-up plan as it is better to go for it from the start and decide not to make any money in the patients' best interest.

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Building Block I453

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ITEM	DESCRIPTION
Building Block (BB) Title	Drug databases
References	The Drug Repurposing Hub: https://clue.io/repurposing DrugBank: https://go.drugbank.com/ DrugRepurposing Online: https://drugrepurposing.info PROMISCUOUS 2.0 from Charité: Promiscuous 2.0 (charite.de); PROMISCUOUS: a database for network-based drug-repositioning - PMC (nih.gov) OpenTargets: https://platform.opentargets.org/ doi: 10.1093/nar/gkaa1027 Pubmed Yosef Masoudi-Sobhanzadeh, et al. Drug databases and their contributions to drug repurposing, Genomics, Vol 112, Issue 2, 2020, p. 1087-1095, https://doi.org/10.1016/j.ygeno.2019.06.021
Description	**The Drug Repurposing Hub** is a curated and annotated collection of FDA-approved drugs, clinical trial drugs, and pre-clinical tool compounds with a companion information resource. Together with the website, the platform offers a drug repurposing library available as assay-ready plates at single concentration per compound or with 4-point dilution format for each compound. The screening of this library plates might be performed yourself or in collaboration with the Broad Institute's Center for the Development of Therapeutics; https://www.broadinstitute.org/center-development-therapeutics-cdot.

ITEM	DESCRIPTION
	DrugBank is a free-to-access, online database containing information on drugs and drug targets. It combines detailed drug data (i.e. chemical, pharmacological and pharmaceutical) with comprehensive drug target (i.e. sequence, structure, and pathway) information. The latest release of this database (version 5.1.9, released 2022-01-03) contains 14,747 drug entries including 2,721 approved small molecule drugs, 1,535 approved biologics (proteins, peptides, vaccines, and allergenics), 132 nutraceuticals and over 6,696 experimental (discovery-phase) drugs. PROMISCUOUS 2.0 database provides a uniform data-set for drug repositioning where the search can be performed from drug or target side. Drug repurposing online is a proprietary database, created by Numedicus. The article from Pubmed lists many databases related to drug repurposing.
Category	Supporting tools
Type of BB	Development resource
Geographical scope	International
Availability	Open access for the web versions. Use and re-distribution of the content requires a license. For all stakeholders involved in the search for new indications or uses for existing drugs. Some databases such as Drug repurposing online have various levels of access, free (restricted) and premium; the latter is available either by paying or by contributing.
Scope of use	To perform drug prioritization analysis and explore novel druggable targets for developed drugs
Stakeholders involved	Preclinical researchers from academia and industry

ITEM	DESCRIPTION
	Chemists to re-design new drugs
Enablers/ Requirements	Internet access to resources and information. Expertise in bioinformatics for advanced resources
Output	A tool to explore new indications for approved drugs or compounds in early stage research and clinical trials, susceptible to be re-purposed New knowledge for new target for a drug or for new treatment for a disease
Best time to apply and time window	In the early stages of the drug repurposing process
Expert tips	**PROS:** • Web interfaces of the tools are open access • Datasets can be download or access through an API. • Datasets cover drugs in early stage research, clinical trials and approval. **CONS:** • Use of the datasets to advanced functions (e.g. repurposing, build predictive machine learning model) may require expertise in bioinformatics skills. • A paid license is required for non-academic users

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Building Block I454

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ITEM	DESCRIPTION
Building Block (BB) Title	Combinations of drugs
References	• Drug combination and repurposing for cancer therapy: the example of breast cancer: DOI: 10.1016/j.heliyon.2021.e05948 • Drug Combinations: A New Strategy to Extend Drug Repurposing and Epithelial-Mesenchymal Transition in Breast and Colon Cancer Cells; DOI: 10.3390/biom12020190 • Evaluation of synergism in drug combinations and reference models for future orientations in oncology; DOI: 10.1016/j.crphar.2022.100110 • Combinational Drug Repurposing from Genetic Networks Applied to Alzheimer's Disease; DOI: 10.3233/JAD-220120 • The repositioned drugs disulfiram/diethyldithiocarbamate combined to benznidazole: Searching for Chagas disease selective therapy, preventing toxicity and drug resistance; DOI: 10.3389/fcimb.2022.926699 • Synergistic drug combination effectively blocks Ebola virus infection; DOI: 10.1016/j.antiviral.2016.11.017 • Rapid antimicrobial susceptibility test for identification of new therapeutics and drug combinations against multidrug-resistant bacteria; DOI: 10.1038/emi.2016.123 • Combining biomedical knowledge graphs and text to improve predictions for drug-target interactions and drug-indications; DOI: 10.1142/9789811215636_0041 • Therapies for rare diseases: therapeutic modalities, progress and challenges ahead; DOI: 10.1038/s41573-019-0049-9 • Drug Repurposing for Glioblastoma and Current Advances in Drug Delivery-A Comprehensive Review of the Literature; DOI: 10.3390/biom11121870 • Drug Repositioning in Glioblastoma: A Pathway Perspective; DOI: 10.3389/fphar.2018.00218

ITEM	DESCRIPTION
Description	Drug combination is a strategy consisting of the administration of two or more drugs. It may allow for enhanced therapeutic activity by targeting multiple pathways in the condition of interest. Additive or synergistic drug combinations using approved drugs identified from drug repurposing screens might be more effective overcoming the problem of limited activity of individual drugs or the emergence of resistance. Examples of scientific literature on drug combination is provided, illustrating different approaches.
Category	Clinical development, including extrapolation of efficacy and safety data
Type of BB	Development resource
Geographical scope	International
Availability	Applicants interested in drug repurposing in areas where there is a strong scientific rationale for combine two or more medicines
Scope of use	This BB provides examples to explore drug combination as a new strategy to extend drug repurposing
Stakeholders involved	• Drug developers including pharmaceutical companies • Academic researchers • Clinical researchers
Enablers/ Requirements	Understanding of drug interactions, understanding the pathology of the condition which allows for scientific rationale for combination therapy
Output	A tool to explore drug combination as a new strategy to extend drug repurposing opportunities
Best time to apply and time window	At the beginning of the clinical development
Expert tips	**PROS:**

ITEM	DESCRIPTION
	• Drug combination may be more effective than monotherapy, providing additional patient benefits. **CONS:** • Tolerability and adverse events may be an issue • Clinical trials may be required to test combinations of potential repurposed agents to demonstrate efficacy and determine the risks / side effects, need to understand potential drug-drug interactions and to find new optimal dosing and formulation. • Could be a higher economic burden associated with combination therapy in the rare disease context • Strategy increasingly evaluated in anti-tumor and anti-viral therapies but less explored in the rare disease field.

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Building Block I455

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ITEM	DESCRIPTION
Building Block (BB) Title	Clinical trial databases
References	https://clinicaltrials.gov/ , https://www.clinicaltrialsregister.eu
Description	The registration and posting of clinical trials (CT) in public databases is a widespread requirement in international standards, federal, national and European regulations. CT databases contain information submitted by sponsors and inform users about ongoing clinical trials. • **ClinicalTrials.gov** is commonly referred to as a "registry and results database" of privately and publicly funded clinical studies conducted around the world. It is a US government web-based resource maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH). The ClinicalTrials.gov study registry was launched in February 2000 in response to US federal law requiring the NIH to “establish, maintain, and operate a data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions . . . in a form that can be readily understood by members of the public”. The US Food and Drug Administration Amendments Act of 2007 (FDAAA) further extended the scope and legal requirements of the ClinicalTrials.gov registry, and mandated the creation of a results database, which became operational in September 2008. ClinicalTrials.gov currently includes 426,776 research studies in all 50 US states and in 221 countries. • **EudraCT** (European Union Drug Regulating Authorities Clinical Trials Database) is the EU’s electronic database of clinical studies conducted in the European Union (EU) and European Economic Area (EEA). Studies that are conducted entirely outside of the EU are also required to have

ITEM	DESCRIPTION
	results posted if they are part of a Paediatric Investigation Plan (PIP). EudraCT is confidential and accessible only to the national competent authorities (NCA) of the different Member States. The **EU Clinical Trials Register** (EUCTR) website was launched to provide the public with information held in the EudraCT database. The content and level of detail of this information is set out in the European Commission guideline and in its technical guidance. As of July 2014, it became mandatory for sponsors to post clinical trial results in the European Clinical trials Database. EudraCT is managed by the European Medicines Agency (EMA). The EU Clinical Trials Register currently displays 42663 clinical trials, of which 7022 are clinical trials conducted with subjects less than 18 years old.
Category	Clinical development, including extrapolation of efficacy and safety data
Type of BB	Development resource
Geographical scope	International
Availability	Users include study sponsors and data providers, researchers, patients, general public.
Scope of use	Clinical Trials databases are very useful tools with different objectives: - For researchers: they help them stay up to date on developments in their fields, find collaborators and identify unmet needs - For patients: they allow them to identify recruiting studies dealing with their conditions and learn about new treatments, as well as potentially identify results from trials that may inform their treatment - For sponsors and study record managers: they allow the registration of clinical studies and the submission of results after study completion
Stakeholders involved	Industry, EMA, National Competent Authorities in EU Member States, FDA, NIH, governments

ITEM	DESCRIPTION
Enablers/ Requirements	To protect public health and foster innovation, sponsors are obliged to register their trials and submit summary results in CT databases. The mandatory submission of the results is the direct responsibility of the sponsors. Result-related information has to be posted within one year after the end of a clinical trial (6 months for paediatric trials) according to the European Commission Guideline 2012/302 03/EC1. The maximum time a clinical trial result can be delayed is two years from the date the Certificate of Delay (COD) is submitted, for a total of three years in ClinicalTrials.gov.
Output	CT databases are regularly updated at different points in the drug lifecycle; study records indicate the trial protocol and provide results where available. CT can be searched by status (initiated, ongoing, completed), disease, country or by other terms. ClinicalTrials.gov includes different types of CT (interventional; observational; expanded access) while all trials registered on EU CTR are interventional CT. Phase 1 trials conducted solely in adults and which are not part of a PIP are not public in the EU CTR. Phase I trials are not required to have results posted on Clinical Trials.gov.
Best time to apply and time window	Studies are registered at the start of the study, then updated as the study is conducted. Once a study is completed, summary results can be entered. Earlier versions of study records remain accessible.
Expert tips	The CT databases do not currently provide a way to identify **Drug Repurposing studies** systematically, with the exception of searches of specific drugs which are known to be repurposed. DR consists of investigating existing drugs for new therapeutic indications and is often presented as offering various advantages over traditional development of a new drug such as fewer risks, lower costs, and shorter timelines. For many reasons, the introduction of such an item could be relevant in CT databases. PROs • CT databases are a **key source of information** for clinicians, researchers, patients, the general public and industry; they help - assist patients in finding clinical trials that might be relevant to their medical condition - facilitate enrollment

ITEM	DESCRIPTION
	- allow for tracking of the progress of trials • CT databases have been developed to **address structural problems** including non-publication of trial results, selective reporting of results in trial publications and duplication of research. • CT databases lead to increased **clinical trial transparency** by providing a free and accurate search of clinical trials CONs • **No guarantee for scientific accuracy:** study sponsors and data providers are responsible for ensuring that their submitted information is accurate and complete. • Not all listed studies are **regulated and/or reviewed** by the U.S. Food and Drug Administration, EMA or other governmental entities. There is limited quality control review for apparent errors, deficiencies, or inconsistencies. • Posted records **may contain incomplete information** In 2018, ClinicalTrials.gov contained registration information for nearly 270 000 studies in over 200 countries and had posted summary results information for only 30 000 registered studies. https://doi.org/10.1136/bmj.k1452 Efforts to increase timely reporting of results in ClinicalTrials.gov have not been very successful. • **Specificities of EudraCT/EUCTR** Sponsors needs to liaise with each and every relevant National Competent Authorities in EU Member States directly and on EUCTR each trial is broken down into separate 'protocols' specific to each Member State. For example, if a trial is run in France, Belgium and Germany then the registry holds three protocols, each with its own completion status. There is no headline completion status that covers the entire trial. • **Discrepancies between registries**. According to a cross-sectional study of 10,492 trials registered on both ClinicalTrials.gov and the European Union Clinical Trials Register (EUCTR) published in 2018 https://www.medrxiv.org/content/10.1101/2021.06.29.21259627v1.full trial completion status on registries was partially inaccurate. "33.9% of dual-registered trials listed as 'ongoing' on EUCTR were listed as 'completed' on ClinicalTrials.gov".

Drug Repurposing Guidebook

Building Block I456

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	PKPD (Pharmacokinetic and Pharmacodynamic) Modelling in children
References	https://www.certara.com/the-simcyp-consortium/ https://www.certara.com/software/simcyp-pediatric/ https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-efficacy-safety-clinical-pharmacology-pharmacokinetics
Description	Pharmacodynamics (PD) refers to the action of a drug to the body, involving receptor binding, post-receptor effects, and chemical interactions. Pharmacokinetics (PK) determines the onset, duration, and intensity of drug action. Successful drug discovery relies on the selection of drug candidates with good in vivo PK properties, as well as appropriate preclinical efficacy and safety. In vivo PK profiling is often a bottleneck in the discovery process. In order to prove effective, a drug delivered to the patient must reach the necessary concentration in the plasma and in relevant tissues (as measured by PK). This is necessary to effectively modulate the activity of the target protein (as measured by PD) in the body. To minimize the exposure of children to new drug in development and to reduce the development timelines, the developers are offered with a set of PKPD platforms, softwares and tools for modelling and simulation which describe the drug concentration in different organs, behavior across different body tissues, and thus help to inform clinical trial design, first-in-human dosing, formulation design, dose differentiation for special populations, and predictions related to potential drug-drug interactions (DDI).

ITEM	DESCRIPTION
	While currently these tools are only private PK-PD tools, some of them are knowledgeable by the major regulatory bodies for their contribution to the success data package preparation of some approved drug. The Simcyp™ division for example was founded in 2001 as a spin-out company from the University of Sheffield, UK. Simcyp was acquired by Certara in 2012. The SIMCYP Consortium is a pre-competitive group dedicated to teaching, using and progressing PBPK (physiologically based pharmacokinetics) in drug development. The members of the Simcyp Consortium collaborate with Simcyp scientists to guide the scientific development of the Simcyp Simulator, determining annual software development priorities, thus ensuring that the software continues to meet and exceed industry needs. Leading regulators, including the USA, European, Canadian and Japan Health Agencies, use Simcyp for research and drug review.
Category	Clinical development, including extrapolation of efficacy and safety data
Type of BB	Development practice
Geographical scope	International
Availability	For all stakeholders involved in drug development
Scope of use	Simcyp Pediatric provides insight into drug mechanisms while minimizing the exposure of children to experimental therapies. It is a module within the Simcyp Simulator that allows for the modeling of pharmacokinetic behavior in neonates, infants and children. This provides valuable information relevant to dosing decisions, analysis of drug-drug interactions and other safety issues, design and formulation of drugs for children, and the design of pediatric clinical studies to minimize the number of required subjects.
Stakeholders involved	35 of the world's leading biopharmaceutical companies are members of the Simcyp Consortium.
Enablers/ Requirements	The Simcyp Simulator includes a full PBPK model together with extensive libraries on demographics, developmental physiology and the ontogeny of drug elimination pathways. It links in vitro data to in

ITEM	DESCRIPTION
	vivo ADME and PK/PD outcomes to help explore potential clinical scenarios and support decision-making in drug development.
Output	- Determine and optimize dose selection for children, from neonates to age 2, 2-6 years, 6-12 years and adolescents; - Predict pharmacokinetics based on *in vitro* drug data or from adult *in vivo* data by retrograde modeling; - Quantify potential drug-drug interactions (DDIs) for any age range; - Simulate pharmacokinetic variability over any pediatric age range. - Inform clinical trial design for pediatrics.
Best time to apply and time window	Early in the development: Incorporating in vivo PK/PD efficacy studies at the early stages of drug development program can significantly accelerate the selection of the most promising compounds.
Expert tips	**Pros:** - In-depth knowledge in peadiatric and orphan drug development: https://www.certara.com/software/simcyp-pbpk/simcyp-success-story/ - This tool is known by some regulatory authorities (i.e., EMA and FDA) which are aware that some developers may use it as a supporting tool of PBPK modeling for investigations in pediatric populations during drug development. - This tool predicts what should actually happen into the human body and therefore provides information relevant to dosing decisions, analysis of DDI and other safety issues, design and formulation of drugs for children, and the design of pediatric clinical studies to minimize the number of required subjects. **Cons**: - Consultancy/private services – not PPP (Public-Private Partnership) initiative

ITEM	DESCRIPTION
	- As its implementation in the clinical development plan could be subject of interpretation, it is advisable to seek advice from the relevant Regulatory Authorities before using this tool into the drug development plan.

Drug Repurposing Guidebook

Building Block I457

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ITEM	DESCRIPTION
Building Block (BB) Title	Dose finding
References	General: ICH: E4 Guideline Dose-response Information to Support Drug Registration. Also ICH M3(R2); S3; S6(R1), S9. EMA: Guideline Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products, 2017 FDA: Guidance Estimating the Maximum SafeStarting Dose in Initial Clinical Trialsfor Therapeutics in Adult HealthyVolunteers, 2005 FDA: Guidance Human Gene Therapy for RareDiseases, 2020 FDA: Guidance Rare Diseases:Common Issues inDrug Development, 2019 Orphanet Journal of Rare Disease: Wang L, Wang J at al. Dose-finding studies in drug development for rare genetic diseases. 17;156(2022) FDA: https://www.fda.gov/media/71279/download EMA: https://www.ema.europa.eu/en/documents/presentation/presentation-dose-response-assessments-guidance-experience-expectations-vikram-sinha_en.pdf Disease/Project/Group Specific: EMA: A strategic collaborative approach from EMA and FDA - Paediatric

ITEM	DESCRIPTION
	Gaucher disease FDA: Project Optimus For children: https://europepmc.org/article/med/22521954
Description	An activity resulting in a document describing the data (animal, previous human experience etc.) and the scientific approach (publications, previous experience, modeling, statistics etc.) used for dose finding
Category	Clinical development, including extrapolation of efficacy and safety data
Type of BB	Development practice
Geographical scope	International
Availability	Applicants re-purposing medicines for rare diseases
Scope of use	This BB provides guidance on the approach for dose finding for rare diseases drug repurposing. It is designed to address gaps between dose used in the approved indication and dose intended for a rare disease treatment.
Stakeholders involved	• Drug developers • Researchers (e.g. basic researchers, clinical researchers) • Healthcare professionals involved in treatment of rare disease • Experts in pharmacokinetic/pharmacodynamic and dose findings • Regulatory agencies
Enablers/ Requirements	Established biomarker Natural history study and in-depth understanding of the disease
Output	A method to incorporate dose finding into the clinical trial design, particularly in the Clinical Study Protocol
Best time to apply and time window	Dose-finding should be used through the development: • In the early stages of development from nonclinical development to First in Human (FIH) trial it is used to select a starting clinical dose

ITEM	DESCRIPTION
	and dose-escalation plan. • In the later stages of clinical development, it is used to confirm a dosing regiment It is important to have a meeting with Regulatory Agencies to seek advice and reach an agreement.
Expert tips	Best to be established at early stage of drug development and optimized with the drug development progression. Not exhaustive (to be included as limitation which needs to be taken into account)

Drug Repurposing Guidebook

Building Block I458

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	New formulation of drugs
References	http://www.eupfi.org/about-eupfi/
Description	European Paediatric Formulation Initiative (EuPFI) is a consortium working in a pre-competitive way on paediatric drug formulations. It aims to expedite the development of better and safer medicines for children by identifying and scoping issues and challenges in paediatric formulation development. It brings together the voluntary, academic, pharmaceutical industry, hospitals and regulatory agency in order to tackle the development of age-appropriate formulation for paediatrics
Category	Clinical development, including extrapolation of efficacy and safety data
Geographical scope	International
Availability	All stakeholders involved in pediatric formulation development
Scope of use	- Sharing expertise and interactive discussion between industry, academia, clinical and regulatory professionals. - Information dissemination and raising awareness (publications, conferences, etc.), linking and networking. - Identify the issues and challenges associated with development of pediatric formulation and consider ways

ITEM	DESCRIPTION
	towards better medications and clinically relevant dosage forms for children. - Promote early pharmaceutical consideration for the development of pediatric medicines. - Identify potential information, knowledge, know-how gaps in the paediatric formulation development. - Improve the availability of information of paediatric formulations.
Stakeholders involved	Members are from academia, hospital pharmacies, pharmaceutical industry (Innovators, Generics, Contract Research Organizations (CRO), Specials and Excipient Manufacturers) with European Medicine Agency (EMA) as an observer.
Enablers/ Requirements	Resources/expertise available to contribute to EUPFI and it workstreams.
Output	It provides funding, expertise and resources to support the solutions to the problems and new technologies emerging from academic research on age-appropriate formulation for paediatrics.
Best time to apply and time window	Membership is open to anyone interested in paediatric formulation development. Organizations/Institutions must apply for membership or sponsorship by filling the membership application form available on the website.
Expert tips	Some of their work could be related to the challenges of the RD patients as 70% of the RD have a pediatric onset. **Pros**: - work on the challenges in availability of and development of delivery devices for consistent administration of pediatric formulations. - age appropriateness of formulations.

ITEM	DESCRIPTION
	- provide guidance to industry and regulators on the use of Extemporaneous Preparations (EPs) and Industry Verified Preparations (IVPs) in the clinic. - focus on the limitations and technology gaps (in formulation platforms suitable for different age ranges) and identify opportunities more effective age-appropriate taste masking technologies. - pharmaceutical Excipients database project, known as STEP (Safety and Toxicity of Excipients for Pediatrics), designed to provide information for the risk assessment of use of excipients in children. - International collaboration with USA: EuPFI and USPFI are working together on the common project to build a database gathering safety data on excipients used in pediatric formulations. **Cons**: pediatric formulations only - IP situation of new formulations is unclear.

Drug Repurposing Guidebook

Building Block I459

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	Safety data across indications
References	A general comprehensive reference on pharmacovigilance and pharmaco-epidemiology (pharm-epi) is: Strom BL, Kimmel SE, Hennessy S (editors). *Pharmacoepidemiology,* 6th edition. Chichester, Wiley, 2019. https://www.wiley.com/en-us/Pharmacoepidemiology%2C+6th+Edition-p-9781119413417 There are many other references, including whole journals and dedicated journal articles.
Description	For marketed medicines, data on safety (or harms) will have been collected in non-clinical research, clinical trials, and post-marketing studies (and/or spontaneous reports). Safety data from some non-clinical work and clinical uses might be relevant to a repurposed therapy being used in new indications or in new ways, helping to define for example the correct dosing strategy and the design of future clinical studies.
Category	Clinical development, including extrapolation of efficacy and safety data
Type of BB	Development resource
Geographical scope	International
Availability	Data should be available from original regulatory assessments (e.g., from FDA or EMA), product information (e.g., summary of product

ITEM	DESCRIPTION
	characteristics) prescribing guides (e.g., national formularies) and from publications.
Scope of use	Will vary depending on the relationship between already authorised indications, and new uses. Dose and dose scheduling, route of administration, etc., might make prior data more, or less relevant to the new situation. In general, it seems appropriate to start with the known side effect profile and assume it has relevance to the new situation, then consider what might or might not be relevant, i.e., take a "top-down" approach (rather than assume none is relevant and include data only from a "bottom up" approach).
Stakeholders involved	Patients, carers, treating physicians, regulators.
Enablers/ Requirements	Availability of, and access to, data from publications or from regulatory submissions in other indications.
Output	A first basis for considering potential safety issues of a therapy in a new setting.
Best time to apply and time window	Not applicable in terms of "applying". But data would be relevant for the design of the non-clinical and clinical programmes and ethics and regulatory approvals to start new studies in new therapeutic areas / licensing decisions.
Expert tips	Consider the totality of the data available and determine relevance for extrapolation to the new use to avoid unnecessary duplication and replication. Consider patient *exposure* to medication (e.g., half-life, C_{max}, etc.) rather than just dose and dose frequency. Be cautious of selective reporting and publication of safety data from other sources (e.g., spontaneous reporting typically will under-report events, but high profile/publicly reported safety concerns may result in subsequent over-reporting.

Drug Repurposing Guidebook

Building Block I460

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ITEM	DESCRIPTION
Building Block (BB) Title	Data outside the public domain
References	https://www.ema.europa.eu/en/about-us/how-we-work/access-documents https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/output-european-medicines-agency-policy-access-documents-related-medicinal-products-human-veterinary_en.pdf https://www.fda.gov/regulatory-information/freedom-information https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7318194/
Description	An advantage of drug repurposing is that the medicine under investigation has been studied in previous indication(s). Aside from information in the published literature and from documents provided by regulatory authorities such as assessment reports, EMA Clinical Data Publication, and clinical trials registries, there may be substantial data that is held elsewhere that is not readily available in the public domain but may be requested (including voluntary initiatives for data access by pharmaceutical companies). This BB provides a starting point to investigate and source that data.
Category	Availability of data
Type of BB	Development resource

ITEM	DESCRIPTION
Geographical scope	International
Availability	Different jurisdictions have different rules on the release of information held by public bodies. Some private bodies – notably pharmaceutical companies – may be willing to sharing information following formal requests and have processes to allow external groups to access information
Scope of use	Every repurposing project should run a gap analysis to determine what information might be held by different organisations that could be helpful for the future development programme
Stakeholders involved	Industry, academia, public bodies
Enablers/ Requirements	Helps reduce duplication and replication of experiments / and or clinical studies if relevant data has already been robustly generated elsewhere
Output	Adds to the portfolio of information around the medicine in the claimed indication, providing additional knowledge for shaping the development programme
Best time to apply and time window	Before embarking on any new work such as non-clinical experimentation or clinical trials consider if someone else might have already done it!
Expert tips	Consider all potential sources of information and draw up a strategy for requesting access to information held by different organisations, understand your rights in the different regions, contact individual companies with requests, check whether the provided information is suitable (e.g., quality and date the data was generated) before concluding on its relevance

Drug Repurposing Guidebook

Building Block I461

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	How to develop pricing models for repurposing
References	EU: EUnetHTA; EC - Public Health – Health Technology Assessment; HTA Regulation; MoCA (Mechanism of Coordinated Access to Orphan Medicinal Products) UK: NICE USA: ICER International: HTAi
Description	Plan for collecting evidence to support calculation and negotiation of the price for the re-purposed product
Category	Regulatory and HTA engagement
Type of BB	HTA and reimbursement
Geographical scope	International
Availability	Applicants re-purposing medicines for rare diseases, HTA bodies and payers
Scope of use	This BB is used to evaluate market landscape, calculate cost of drug development, incorporate risk-benefit assessment and develop the

ITEM	DESCRIPTION
	general pricing model that could be adjusted to fit for a specific market
Stakeholders involved	• Drug developers • Health Technology Assessment (HTA) organizations • Payers • Investment funds • Patients' organisations • Regulatory agencies • Healthcare professionals
Enablers/ Requirements	Risk-benefit assessment based on the evidence of drug efficacy and confirmation of drug safety Cost of drug development Price of competitive product(s) Price of originator product
Output	Pricing
Best time to apply and time window	The tool should be used through the clinical development: • At the Phase 1/ 2 studies it is used to identify value of the product. • At the Phase 3 study it is used to create value of the product through evidence of its efficacy. It is important to have meeting(s) with HTA organizations and with national authorities for pricing and reimbursement to seek advice and reach an agreement.
Expert tips	The pricing model development should start together with the clinical development and it should be re-adjusted based on the value of the approved drug and the patients' needs. Developers should request early advice to HTA experts on what data is needed, to have this trajectory as smooth as possible.

Drug Repurposing Guidebook

Building Block I462

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ITEM	DESCRIPTION
Building Block (BB) Title	**Public-private partnerships** **"Shaping the collaboration between academia and pharmaceutical industry"**
References	1) https://eipg.eu/tag/pharmaceutical-policy-2/ 2) Public-Private Partnerships: Compound and Data Sharing in Drug Discovery and Development - PubMed (nih.gov) 3) Translat Regulat Sci. 2(2): 47–50, 2020; doi: 10.33611/trs.2020-008 4)https://investors.exscientia.ai/press-releases/press-release-details/2020/europes-largest-initiative-launches-to-accelerate-therapy-development-for-covid-19-and-future-coronavirus-threats/Default.aspx 5) European pharmaceutical research and development: Could public infrastructure overcome market failures? | Panel for the Future of Science and Technology (STOA) | European Parliament (europa.eu) 6) https://www.imi.europa 7) CORBEL project - https://eatris.eu/projects/corbel-coordinated-research-infrastructures-building-enduring-life-sciences-services/.eu/ 8) Academia-Industry collaboration best practice guide - https://eatris.eu/wp-content/uploads/2019/12/CORBEL_Academia_Industry_Collaboration_Best_Practices_Guide.pdf 9) BIO Europe partnering event - https://informaconnect.com/bioeurope/
Description	The collaboration between academia, pharma and funders (private-public partnerships) is critical in enhancing the success of drug repurposing by translating new repurposing ideas from research to practice. Building a partnership with aligned needs of public and private partners will enable funding to initiate these projects and provide a model framework to help streamline all the key processes right from the initial development to the final target of having a licensed repurposed product for the patient.

<table>
<tr><th>ITEM</th><th>DESCRIPTION</th></tr>
<tr><td></td><td>Academics could benefit from the experience of Pharma companies on their knowledge of the clinical development, manufacturing, commercialization, quality, regulatory, project management resources, technical know-how and funding aspects to progress with drug repurposing opportunities

Industry could benefit from added value of academia due to their scientific experience, expertise in rare, orphan diseases, understanding of unmet treatment gaps, clinical outcomes and treatment patterns. The technology transfer office (TTOs) responsible for technology transfer or collaboration of R&D projects, protection and management of the intellectual property rights, clinical trials, increase research institute/university's visibility among for-profit players in the field (including pharma and biotech companies as well as venture capital firms) and actively advertise the most advanced projects.</td></tr>
<tr><td>Category</td><td>Engagement with MA</td></tr>
<tr><td>Type of BB</td><td>Development practice</td></tr>
<tr><td>Geographical scope</td><td>International</td></tr>
<tr><td>Availability</td><td>Many repurposing ideas originate from research conducted by pharmaceutical companies and/or from academic institutions.

Experienced organisations like IMI, EATRIS, Biocat and BIO Europe augment such collaborations through advocacy, funding, connecting SME and big pharma via networking, focussed partnering events fostering sustainable dedicated public-private partnerships.</td></tr>
<tr><td>Scope of use[1]</td><td>Block on Public-private relationship, focuses on shaping the collaboration between academia and companies

Issues and respective solutions to improve Drug- repurposing

<table>
<tr><th></th><th>Issue</th><th>Solution</th></tr>
<tr><td>Finding partners for Academia to partner with</td><td>Academia have limited resources to help successfully complete and facilitate drug repurposing projects</td><td>A group created with a wide range of different stakeholders (Academics and Pharma) to encourage collaboration and data sharing to help facilitate and accelerate drug-repurposing ideas.</td></tr>
<tr><td>Improving Stakeholder</td><td>Coordination between EU institutions and organisations</td><td>An EU one-stop shop for non-commercial repurposing.
A European network of experts.</td></tr>
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</td></tr>
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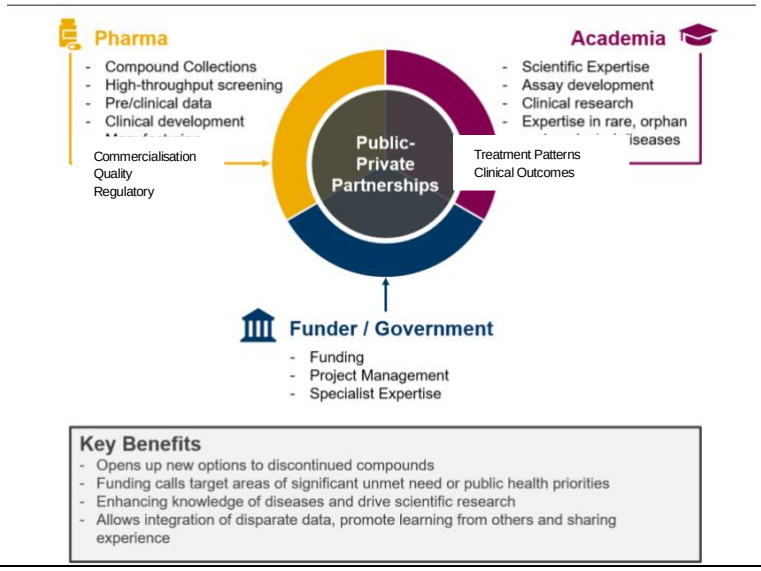
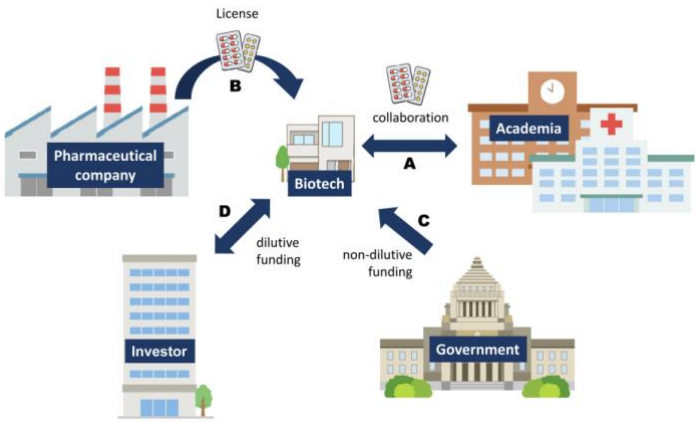
ITEM	DESCRIPTION		
	collaboration and coordination	Poor cooperation between industry and non-commercial champions	Encouraging working together to obtain regulatory approval and sharing of data on shelved products not protected by patents.
	Ensuring Funding	No Prioritisation mechanism	A European list of priority indications.
		Poor availability of funding	More funding from public sources. Exploring the viability of novel funding mechanisms. Public-private partnership to combine skills and resources for both public and private sectors.
Stakeholders involved[2]		
Enablers/ Requirements	Public-Private collaboration model for drug repurposing (Reference 3) 		

ITEM	DESCRIPTION
	Dilutive Funding: Funding that requires company to give equity/ ownership rights to the funder **Non-Dilutive Funding:** Funding that does not require company to give equity/ ownership rights to the funder Experienced business developers, legal and regulatory experts, technology transfer offices are vital to construct a complementary/synergistic partnership based on aligned needs of public and private partner and considering viable business models.
Examples	Connecting Academia and Industry for successful drug repurposing in rare diseases **1. The Alpelisib Repurposing Case study** • A first contact with industry (Novartis) initiated by French academia exploring the therapeutic potential of alpelisib, an investigational anticancer drug (phase III) in PIK3CA*-related overgrowth spectrum (PROS), a group of rare genetic disorders without treatment. The Paris team discovered that PIK3CA-related cancers and PROS shared the same pathogenetic mechanism leading to abnormal dysregulated cell growth and that activating PIK3CA mutations were found in both cancer and overgrowth syndromes. This was the basis for alpelisib, a specific inhibitor of the PI3KCA developed by Novartis in cancer, being repurposed in PROS. • After achieving impressive outcomes first on PROS mouse models and then on 2 patients suffering from severe and life-threatening PROS, the group was authorized to administer alpelisib to additional patients. The study supporting PIK3CA inhibition as a promising therapeutic strategy in patients with PROS was published in 2018. • In 2019, US FDA granted alpelisib, "Breakthrough Therapy Designation" based on real world data. In 2021, Alpelisib received an Orphan Drug Designation from the EMA. This was followed by a conditional approval from the FDA under the brand name Vijoice® in 2022. • The approval of Vijoice® marks a turning point for PROS patients. Novartis is conducting additional clinical trials to further understand the long-term efficacy and safety of alpelisib in PROS. **PIK3CA: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha* **2. COVID-19- Urgent need for accelerated therapy developments to market novel (Vaccines) and repurposed therapies (i.e. Dexamethasone) for COVID-19 (4)** • CARE (Corona Accelerated R&D in Europe), a new group supported by the Innovative Medicines Initiative (IMI) was launched to accelerate the discovery and development of medicines for Covid-19. A public-private partnership Included 37 different partner organisations comprising of scientists from academia, research centers, small medium enterprises, European Federation of Pharmaceutical industries and associations (EFPIA) member companies and

ITEM	DESCRIPTION
	IMI associated partners from Belgium, China, Denmark, France, Germany, the Netherlands, Poland, Spain, Switzerland, the UK and the US
Output	Facilitating and developing public-private partnerships to initiate, accelerate and help finance the repurposing of drugs
Best time to apply and time window	Private-public collaboration groups could be initiated from the start of a newly identified drug repurposing development idea. Early-stage collaboration, however, is not the only option; late-stage collaboration may be a tactical de-risking policy for Big Pharma.
Expert tips	**PROs:** • Find new opportunities for repurposing of existing drugs • Helps resourcing projects (with funding/ partners complementary expertise) to accelerate these projects • Will facilitate the drug development processes and help translation of drug repurposing from research to practice in more time and cost-efficient manner **CONs:** • Time investment to build the right partnership (agree on scope and legal framework) where analysis should be handled with care in informing drug development decisions to avoid errors in execution. **KEY DRIVERS FOR EFFECTIVE AND SUCCESSFUL COLLABORATION BETWEEN ACADEMIA AND INDUSTRY** • Intellectual Property agreements such as - is the compound to be repurposed patented? IP owner? Expiration date? Supplementary protection certificates? Freedom to Operate? • Access to raw data, regulatory master file, Pharmacovigilance reports and safety data of the original product • Business constraints and expectations (Pipeline, strategy, opportunity for the private partner) • Robustness of the Proof of Concept; industry/market feasibility; cost-effectiveness • Human factor consideration (“fit” between stakeholders, resources and commitment) • Clinical Trial strategy and time to CSR

Drug Repurposing Guidebook

Building Block I463

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ITEM	DESCRIPTION
Building Block (BB) Title	Pre-competitive space working
References	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4990051/ https://futureoflife.org/data/documents/PreCompetitiveCollaborationInPharmaIndustry.pdf https://www.ncbi.nlm.nih.gov/books/NBK210038/ https://www.nature.com/articles/nrd3602 http://csmres.co.uk/cs.public.upd/article-downloads/Renal-precompetitive-consortium-(RPC2)-discovering-therapeutic-targets-together.pdf https://lawreview.law.ucdavis.edu/issues/48/4/Articles/48-4_Vertinsky.pdf
Description	Opportunity to combine complementary resources, expertise and skills across different organisations to help de-risk and/or support efficient evidence generation, and fast track development programmes. Key aim to bring multiple stakeholders together to address common joint issues (e.g., lack of natural history data, need for novel endpoint validation), and create a framework to develop an agreed solution that can benefit all. It enhances multi-stakeholder collaboration, which could produce faster and less resource intensive advances in a wide spectrum of activities versus working individually. Collaboration may come from a single organisation proposing to work together with another / others after identifying an issue, or from a group of organisations who have common goals and agree to conduct an activity jointly. Actual collaborative aspects may take different forms with varying degrees of formality.

ITEM	DESCRIPTION
Category	Engagement with MA
Type of BB	Development practice
Geographical scope	International
Availability	Some jurisdictions have specific programmes with specific calls in particular areas from established frameworks (e.g. the European Innovative Medicines Initiative [IMI] - Public Private partnership), versus the opportunity to create a bespoke collaboration.
Scope of use	Need to clearly identify the boundaries and specific area that might benefit from precompetitive space working.
Stakeholders involved	Industry, academics, not-for-profit, patient groups, government institutions.
Enablers/ Requirements	To agree the framework, rules of engagement and boundaries of the scope of the interactions in advance. Need to consider aspects such as ownership of intellectual property, data and extent of information sharing.
Output	Improved productivity, helping to de-risk / share risk
Best time to apply and time window	Depends on the scope of the pre-competitive space activity.
Expert tips	Consider the costs involved in delivering a collaborative project, the need for available resourcing, create agreements and Terms of Reference in advance of starting the project, seek legal advice.

Drug Repurposing Guidebook

Building Block U229

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ITEM	DESCRIPTION
Building Block (BB) Title	**Initiative updating old labels – BPCA + PREA**
References	https://www.fda.gov/science-research/pediatrics/pediatric-labeling-changes https://www.fda.gov/media/122694/download https://www.accessdata.fda.gov/scripts/cderworld/index.cfm?action=newdrugs:main&unit=4&lesson=1&topic=7 https://www.nichd.nih.gov/research/supported/bpca https://www.federalregister.gov/documents/2019/04/23/2019-08167/best-pharmaceuticals-for-children-act-bpca-priority-list-of-needs-in-pediatric-therapeutics
Description	This building block describes the Best Pharmaceuticals for Children's Act (BPCA)/Pediatric Research Equity Act (PREA) legislative initiatives by which FDA drug labels can be updated (irrespective of original sponsor's willingness to engage).
Category	Regulatory and HTA engagement
Type of Building Block	Regulatory
Geographical scope	US

Availability	BPCA/PREA uses drug sponsors, NICHD/NIH, and the Pediatric Trials Network (PTN) to conduct the studies in collaboration with FDA. The program only apply to FDA-approved prescription drug labels.
Scope of use	- BPCA can be used in select settings when trying to update an FDA drug label for safety, efficacy, PK/PD, dosing, etc. for a drug used in a pediatric population.
Stakeholders involved	FDA, Sponsors (drug and biological product application holders), NIH (administers BPCA), Pediatric Trials Network (PTN) (conducts trials for BPCA), Pediatricians/Parents (BPCA)
Enablers/ Requirements	- Drug must be prescribed to pediatric populations/neonates - Drug must be off-patent (if BPCA off-patent clause is to be used) - The original sponsor/NDA holder has the right of first refusal to expand the label themselves. If they decline, and the drug is off-patent, NIH can decide to support someone else to conduct the studies to do it, and to serve as the sponsor to FDA or get the company to agree to submit the data package that was developed, typically by the Pediatric Trials Network (PTN) with NICHD support. - Funding is needed to conduct the studies, which are funded by NIH (but it is an unfunded congressional mandate, so the funding primarily comes from NICHD) and the trials are run primarily by the Pediatric Trials Network. - The FDA has to be in agreement with the trial design/data to be used/etc. - The group conducting the trial typically needs to be willing to serve as the sponsor or needs to be able to work with the original sponsor/NDA holder or another manufacturer to serve this role. - There needs to be access to the drug product still. - If sponsor replies to the Written Request themselves and is willing to conduct the study, they can receive 6 additional months of marketing exclusivity for their product. -
Output	BPCA:

	- New dosing, PK/PD, safety, or efficacy data added to FDA labels of drugs (including those that are off-patent) -
Best time to apply and time window	Can apply at any time; BPCA – multiyear process. For full approvals of entirely new indication in pediatrics, it has taken close to 10 years to get those approvals (and there have only been 2). The BPCA network goes through a rigorous prioritization process to identify disease/therapeutic areas of interest. Drugs or studies best positioned to meet those priorities are most encouraged to apply. BPCA engages with the FDA Review Divisions to determine what sort of trials would be necessary.
Expert tips	BPCA: Contact Perdita Taylor-Zapata, MD from NICHD about BPCA-related topics (taylorpe@mail.nih.gov) https://www.nichd.nih.gov/about/org/der/branches/opptb/taylor-zapata Interested parties can also participate in the BPCA prioritization process.

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Building Block U230

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ITEM	DESCRIPTION
Building Block (BB) Title	ROADMAP initiative
References	https://cdcn.org/roadmap/ https://everycure.github.io/
Description	The Repurposing Of All Drugs, Mapping All Paths (ROADMAP) project lead by the Castleman Disease Collaborative Network (CDCN), supported by a grant from Chan Zuckerberg Initiative (CZI), and partnered with 147 organizations. The ROADMAP initiative aims to: 1. Answer fundamental questions about the experience of various stakeholders (rare disease organizations, physicians, researchers, patients and loved ones) in drug repurposing. 2. Produce a "roadmap" for RDNPs to support the pursuit of drug repurposing, including options as to promising drug identification and the steps required to get from there to a success outcome (FDA approval or otherwise); including roadblocks and recommendations from experienced organizations as to which paths are best to pursue.
Category	Supporting tools
Type of BB	Development resource
Geographical scope	USA

ITEM	DESCRIPTION
Availability	The ROADMAP drug repurposing tool was launched in February 2023. It will provide guidance for rare disease organizations seeking to pursue drug repurposing, based on real world experiences.
Scope of use	Supporting both rare disease nonprofit organizations who are new to drug repurposing, as well as those who are in the process but need additional guidance
Stakeholders involved	Rare disease nonprofit organizations primarily; secondarily - their researcher, physician, patient and loved one communities.
Enablers/ Requirements	There are no requirements needed to use the tool, but it is going to be most helpful to US-based rare disease nonprofit organizations
Output	Insights as to next/best steps in your organization's drug repurposing project based on data from the ROADMAP project
Best time to apply and time window	Anytime in the drug repurposing process
Expert tips	Can be utilized several times in different parts of the process; over time, this project will benefit from updates and fresh data, which means checking in occasionally and contributing data would be very valuable.

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ITEM	DESCRIPTION
Building Block (BB) Title	**Initiative updating old labels – Project Renewal**
References	https://aacrjournals.org/clincancerres/article/27/4/916/125031/FDA-Oncology-Center-of-Excellence-Project-Renewal https://www.fda.gov/about-fda/oncology-center-excellence/project-renewal https://www.fda.gov/about-fda/oncology-center-excellence/project-renewal-faq https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-updated-drug-labeling-including-new-indications-and-dosing-regimens-capecitabine https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approves-updated-drug-labeling-including-new-indications-and-dosing
Description	This building block describes the Project Renewal pilot initiative established by the U.S. Food and Drug Administration (FDA) Oncology Center of Excellence (OCE) by which FDA drug labels can be updated. Project Renewal is a collaborative program that leverages external oncology experts to review publicly available data in the literature to update certain older oncology drug prescribing information to ensure this information is clinically meaningful and scientifically up to date.
Category	Regulatory and HTA engagement

Type of BB	Regulatory
Geographical scope	US
Availability	Project Renewal is focused on the evaluation of long-standing oncology drugs with decades of clinical experience and use.
Scope of use	Oncology drugs on the market for over 20 years that are important components of standard multi-agent chemotherapy regimens, some of which have curative potential, but have standard of care uses that are not included in the labeling or have outdated information Project Renewal will not be used to modify FDA-approved product labeling for drugs initially approved in the past 15 years.
Stakeholders involved	External Scientific Expert Teams, Hematology and oncology fellows from academic training programs, FDA, Reference listed drug (RLD) holders
Enablers/ Requirements	The Project Renewal process is initiated and directed by the OCE in the following steps: - Identify and prioritize oncology products into a Candidate drug list (CDL) - Engage RLDs to confirm participation in Project Renewal - Identify and select potential off-label uses for each product - Identify and onboard research team members (RTMs) to evaluate evidence and discuss clinical use - Identify and onboard clinical fellow to support identifying and evaluating scientific literature - Identify and evaluate publicly available literature on selected off-label use(s), summarized in a draft product report - Discuss clinical use and the evidence to support potential labeling updates through a series of labeling evidence evaluation process (LEEP) meetings - Finalize the product report, summarizing available evidence and labeling considerations - Deliver final product report and draft labeling considerations to FDA for independent review - Document labeling considerations and decisions in a repository - Capture lessons learned about Project Renewal process for continual process improvement

	- Publish finding from labeling updates, as appropriate
Output	- Updated labeling information - Prescribing information in Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) format. - Project Renewal is intended to help inform the provider community responsible for caring for cancer patients. This includes oncologists, advanced practice providers, registered nurses, and pharmacists at community and specialty pharmacies who use FDA prescribing information to inform clinical decisions and patient care. When applicable, revisions made to the prescribing information are also included in Patient Information, using nontechnical language to ensure safe and effective use.
Best time to apply and time window	Project Renewal does not accept external applications, it makes its own choices about what drugs to put through the process. The process takes several years. However, may speed up as they gain more experience and work out the issues with the process.
Expert tips	Project Renewal is limited to updating labeling of older oncology drugs with decades of use, multiple supportive clinical studies, and substantial post-marketing experience. The focus of Project Renewal is not to update product labeling with all possible or reported uses, but rather to identify currently unlabeled uses, which could be supported by published studies meeting FDA's regulatory standard of substantial evidence of effectiveness There is flexibility in the type and quantity of data used to conduct the benefit–risk assessment supporting a recommendation for inclusion of new uses and dosing regimens. The product report produced by project renewal is just one resource that the FDA will use during their independent labeling review, and FDA may include additional evidence when creating their final recommendations to ensure product labeling contains essential scientific information, is not misleading, and provides adequate directions for use.

	Drugs selected for Project Renewal have decades of safety and other clinical data Several factors increase the acceptability of relying on published reports to support approval of a new use, including having multiple studies conducted by different investigators with consistent findings across studies, a high level of detail in the published reports (including statistical methods and analysis plans), appropriate endpoints that can be objectively assessed, robust results achieved by protocol-specified analyses, and studies conducted by research groups with a history of implementing high quality studies. After FDA independent review, FDA-reviewed draft labeling is sent to the reference listed drug company along with a letter requesting submission of a supplemental application. The company is encouraged to submit the FDA-reviewed product labeling, with or without further modifications, in their supplemental marketing application(s). The Project Renewal process is intended to facilitate submissions by companies, with a goal to reduce burden and maximize the efficiency of review of supplemental applications submitted to update older oncology product labeling. FDA OCE Project Renewal Lead: Dr. Sundeep Agrawal: Sundeep.Agrawal@fda.hhs.gov

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Building Block U232

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ITEM	DESCRIPTION
Building Block (BB) Title	**Initiative updating old labels - SRLC**
References	https://www.fda.gov/drugs/drug-safety-and-availability/drug-safety-related-labeling-changes-srlc-database-overview-updates-safety-information-fda-approved https://www.fda.gov/media/116594/download https://www.policymed.com/2013/08/fda-guidance-safety-labeling-changes.html https://www.sentinelinitiative.org/news-events/fda-safety-communications-labeling-changes https://healthpolicy.duke.edu/sites/default/files/2021-05/PostmarketSafety_PDS.pdf https://pubs.lib.umn.edu/index.php/innovations/article/view/495/489 https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm
Description	This building block describes the Safety Related Labeling Changes (SRLC) initiative by which FDA drug labels can be updated (irrespective of original sponsor's willingness to engage).
Category	Regulatory and HTA engagement

Type of BB	Regulatory
Geographical scope	US
Availability	SRLC – The FDA can request or order original sponsor(s) to make safety-related labeling changes based on new safety information that becomes available after approval of the drug or biological product. The program only applies to FDA-approved prescription drug labels.
Scope of use	These initiative can be used in select settings when trying to update an FDA drug label for safety claims (SRLCs) when new safety information becomes available.
Stakeholders involved	FDA, Sponsors (drug and biological product application holders)
Enablers/ Requirements	- Must be human prescription drugs regulated under New Drug Applications (NDAs) - Or prescription biological products regulated under Biologics License Applications (BLAs) - Or prescription drug with an approved abbreviated new drug application (ANDA), if the NDA reference listed drug (RLD) is not currently marketed - FDA expects that this results in changes to safety information in the Prescribing Information (e.g., ADVERSE REACTIONS BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS sections), but does not warrant inclusion in other sections of labeling (such as INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION), which would not normally trigger required safety labeling changes under section 505(o)(4).
Output	- New safety information added to drug labels of existing FDA approved products post-marketing - provides this safety information to the public, including health care vendors who integrate these important prescription drug labeling updates into systems frequently accessed by health care practitioners and/or patients - changes to safety information in the Prescribing Information (e.g., ADVERSE REACTIONS BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS sections), but does not warrant inclusion in other sections of

	labeling (such as INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION)
Best time to apply and time window	- sponsor has 30 calendar days to respond to FDA - then FDA will proceed within 15 calendar days either by sending a supplement approval letter or ordering the application holder to make the required labeling changes - FDA expects that new approved labeling will be available on the application holder's website within 10 calendar days
Expert tips	The definition of new safety information is broad to enable FDA to require application holders (sponsors) to add information about serious risks to the labeling of a drug New safety information for a SRLC is obtained through clinical trials, adverse event reports, post-approval studies, peer-reviewed biomedical literature, data derived from the post-market risk identification and analysis system, or other scientific data In response to a SRLC request the sponsor may submit a supplement with proposed labeling changes or a rebuttal statement. FDA allows 30 calendar days after sponsor's response for dialogue after which FDA can enforce the labeling change to take effect within 15 days. Application holders may submit labeling supplements for review at any time and without prior notification to FDA. Application holders may continue to submit labeling supplements using standard procedures (See 21 CFR 314.70 and 601.12). Approved updates to labeling are posted on FDA's Website FDA hosts a SRLC database that include safety labeling changes (SLCs) that were required by FDA as well as updates to safety information in the labeling recommended by the FDA or initiated by companies Any questions about the guidance for SRLC, contact Kristen Everett, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Building 22, room 6484, Silver Spring, MD 20993.