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.

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	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

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	# *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.

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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).

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	• 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.