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POLICY BRIEF

Off-label medicines: Rational or Irrational?

- The use of off-label medicines is an unexplored area for healthcare priority setting, though it is common practice in countries and can have a significant positive or negative effect on health outcomes and the efficiency of health care systems. It is therefore important to have a rational and evidence-informed approach to make decisions about these issues on a case-by-case basis.
- The review of laws, regulations, and use of off-label medicines in Australia, Indonesia, Singapore, Thailand, and the United Kingdom (UK) found that all countries except for Indonesia legally allow the use of off-label medicines in their public health insurance schemes.
- Health technology assessment (HTA) [1] can play a significant role in assessing the safety, clinical benefit, value-for-money, budget impact, and social and ethical effects of off-label medicine use to inform public health authorities whether to be for or against the use of off-label medicines.
- Policy recommendations for various relevant actors ranging from research funders, healthcare payers and authorities, HTA agencies, health professional groups, civil societies and patient groups, and industry are proposed to ensure the desirability of off-label medicine use and its positive impact on medicine access.

Common Use

Off-label medicine use involves prescribing currently available and marketed medicines for a medical indication that the Food and Drug Administration or a similar authority did not approve. Its use can be common, especially amongst patient populations that are less likely to be included in clinical trials such as pregnant women, children, and extremely elderly and mental health patients. For example, some studies suggest that 79% of paediatric patients discharged from the hospital receive at least one off-label medicine prescription [2].

Benefit and Risks

Off-label medicine use can be controversial because the medicines have not undergone a rigorous assessment process to ensure thier safety and clinical benefit. Nevertheless, obtaining approval for a new medical indication can be resource- and time-consuming and industry players are not willing to invest, particularly when medicines are not patented. For example, the use of aspirin to prevent coronary arterial disease is one of the most widely used off-label medicines because of the low cost of the generic version. Consequently, companies will not invest in its registration due to the potential of having many free-riders.

[1] WHO definition. *http://www.who.int/medical_devices/assessment/en/*

[2] Wittich CM, Burkle CM, Lanier WL: Ten Common Questions (and Their Answers) About Off-label Drug Use. Mayo Clinic Proceedings 2012, 87:982-990.

Country Challenges of Off-label Medicine Use

Given that the thematic knowledge strands of the International Decision Support Initiative (iDSI) includes "Methods for Fair and Affordable Priority-Setting" and "Smart Purchasing for Universal Healthcare Coverage (UHC)," the priority setting for off-label medicine use is one of the important areas of country support. Off-label medicine use is an unexplored area for UHC technical aspects, e.g. benefits package or essential medicines list development and strategic purchasing. In Indonesia, the UHC scheme Jaminan Kesehatan Social cannot include off-label medicines as part of its benefits package due to legal constraints, e.g. patients with pulmonary arterial hypertension are unable to use the less expensive and more effective sildenafil because the product-is unregistered for this indication despite its registration in other countries [3]. In other countries of work, it is the opposite – because the Health Benefit Package lists medicines without specifying what medical indications they should be reimbursed for, doctors freely prescribe medicines, including many medicines prescribed for various off-label indications. This results in wasted resources because the government pays a significant budget for medicine use that may not have scientific evidence of clinical benefit. Thus, while the iDSI advocates neither for nor against the use of off-label medicines, it is important to have a rational and evidence-informed approach, ensuring that their benefits are tapped and the risks mitigated.

The Two Studies

Two studies were conducted to understand the political economy of off-label prescription and identify policy solutions for countries that may have legal constraints regarding the use of off-label medicines. An academic team from Indonesia explored the laws, regulations, and use of off-label medicines in Australia, Singapore, Thailand, and the UK. These two studies' results are summarized in this policy brief and also offers recommendations for priority-setting of off-label medicines for countries where they are legally available for use.

Key Findings

Off-label medicine use is widely practiced in all five countries, prominently for paediatric, cancer, and mental health patients. By law, all countries prohibit industries from marketing off-label medicine use. However, health professionals are aware of off-label indications from peers, direct industry communications, and published literature. Of the five countries, except Indonesia, their public health insurance allows for the reimbursement of off-label medicines. Australia and the UK developed a clear process and rigorous mechanism for priority-setting of off-label medicines, while Singapore and Thailand apply general approaches of HTA to consider inclusion of off-label medicines in their medicines formulary.

Summary of Recommendations from Australia [4]

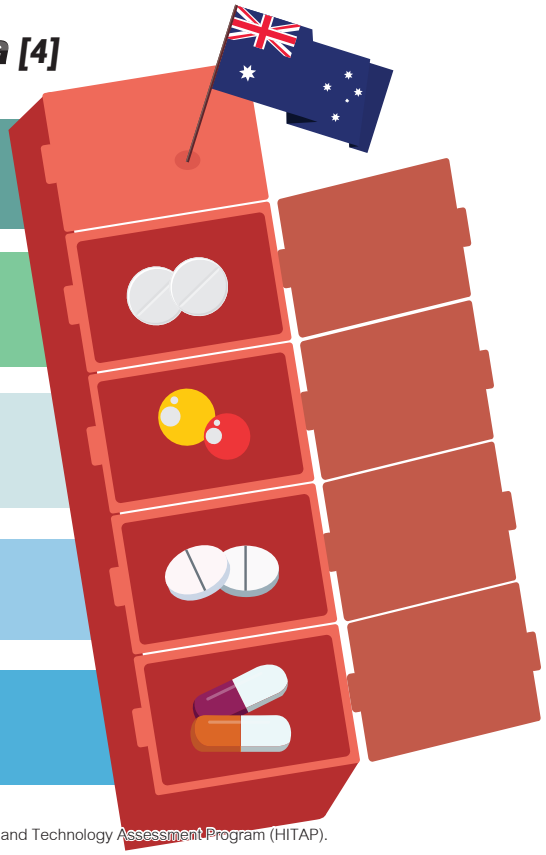
Consider only when all other options are unavailable

Use high-quality evidence to determine appropriateness of use

Share decision-making with patient when recommending one

Consult the Drug Therapeutic Committee when prescribing, except when the use of a medicine is considered routine

Ensure appropriate information is available at all steps of the medicines management pathway

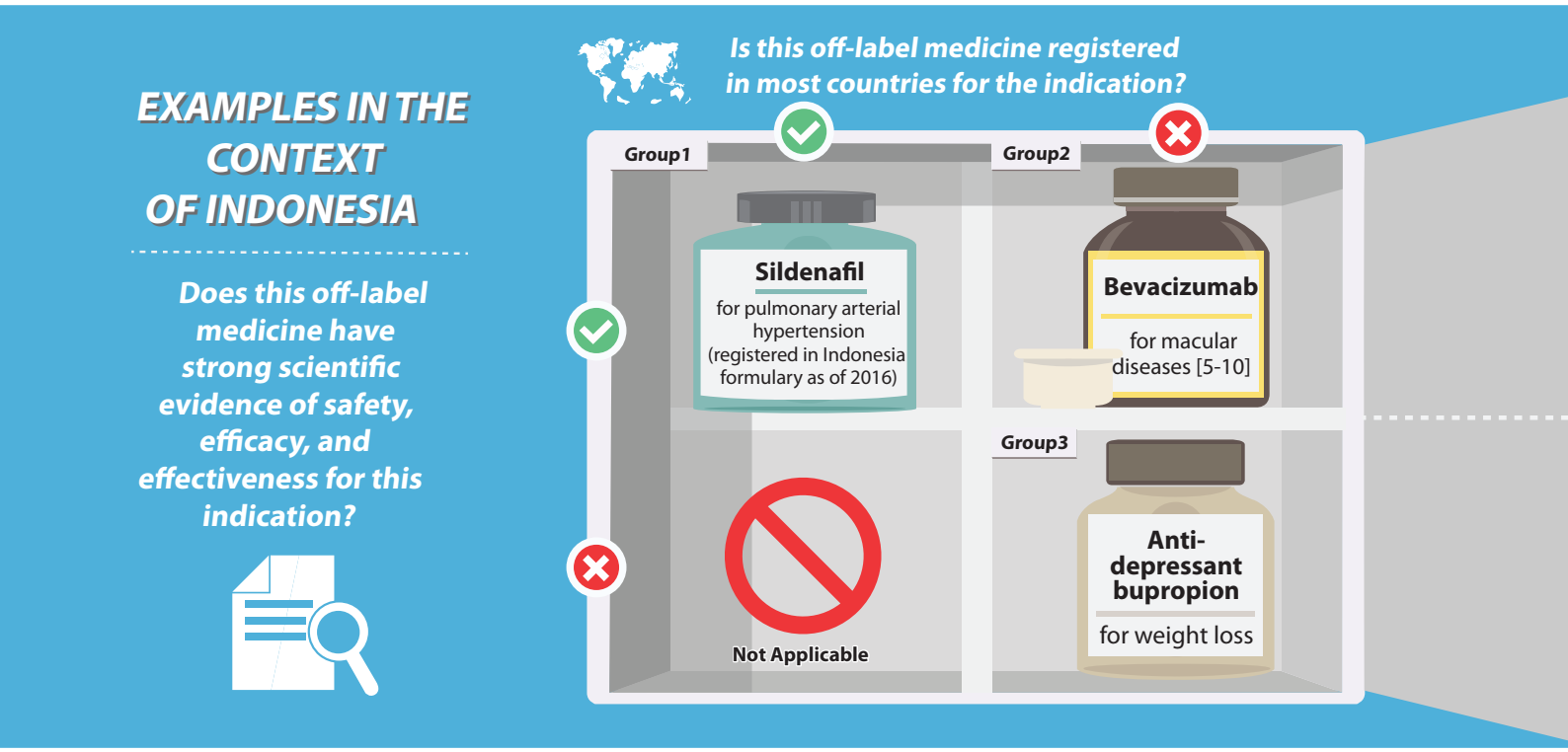


[3] Policy Brief: Health Technology Assessment for Sildenafil as Treatment for Pulmonary Arterial Hypertension in Indonesia. Health Intervention and Technology Assessment Program (HITAP).

[4] Gazarian M, Kelly M, McPhee JR, Graudins LV, Ward RL, Campbell TJ: Off-label use of medicines: consensus recommendations for evaluating appropriateness. Med J Aust 2006, 185:544-548

Discussions

Figure 1 offers a simple framework to classify off-label medicine use into three categories per the following criteria: whether it is registered for that condition in most countries except the country of interest, and whether the medicine in question has high quality of evidence to support its use.



Group 1 reflects ethical issues in pharmaceutical markets. If the evidence for safety and clinical effectiveness exists for these medicines, they should be registered with the FDA in all countries to ensure medicine accessibility for patients in need. Recognizing the limitations of generic medicine producers in obtaining market approval of medicines, transnational pharmaceutical companies should invest more effort and resources to register the product. If evidence supports their use, such as in Group 2, the UHC system should include them in the reimbursement list regardless of industry registration. Priority-setting institutions should evaluate products in Groups 1 and 2. Health authorities should try to monitor, detect, and prohibit the use of off-label medicines in Group 3. If necessary, the products may be used alongside evidence development such as prospective evaluation of outcome (e.g. efficacy and safety). Registries for monitoring the outcome of off-label medicines as well as informed consent from patients who are prescribed off-label medicines should be introduced for medicines in Group 2 and 3. Industry, research grants agencies, and public health authorities should invest resources to determine safety and clinical effectiveness for Groups 2 and 3. In many cases, industry players may have perverse incentives to do so such as the case of bevacizumab for macular disease. As such, public health resources should be available to subsidize outcome studies of widely-used off-label medicines. The review also indicates examples of policy mechanisms to balance the risks and benefits of off-label medicines, included in the policy recommendations.

Table 1: Examples of Desirable and Undesirable Use of Off-label Medicines

Desirable Use of Off-label Medicines [8]	Undesirable Use of Off-label Medicines [11-12]
Since November 2012, based on strong clinical evidence on effectiveness derived from systematic review and meta-analysis, the Thai government recommends the use of off-label bevacizumab as treatment for macular disease under its universal healthcare coverage scheme because the on-label medicine, ranibizumab, for these medical conditions is 50-60 times higher in cost. As of 2016, there have been more than 10,000 patients with access to bevacizumab, with a Thai HTA agency confirming the safety and efficacy of bevacizumab compared to ranibizumab through prospective studies conducted between 2013-2015.	Eli Lilly's Zyprexa had been approved for treatment of psychotic disorders but the company promoted the use of off-label medicines to the elderly population with dementia. In 2009, the United States government fined the company US$1.4 billion for promoting an unapproved use of Zyprexa. Another case is AstraZeneca's Seroquel, which was approved for treatment of schizophrenia and bipolar mania. However, the United States government alleged that the company promoted Seroquel for many unapproved indications such as aggression, sleeplessness, anxiety, and depression, resulting in a US$520 million fine to the company in 2010.

[5] Comparison of AMD Treatments Trials (CATT): Lucentis - Avastin Trial [https://nei.nih.gov/catt]
[6] WHO Model List of Essential Medicines. World Health Organization; 2015.
[7] Abouammoh M, Sharma S: Ranibizumab versus bevacizumab for the treatment of neovascular age-related macular degeneration. Curr Opin Ophthalmol 2011, 22:152-158.
[8] Anothaisintawee T, Leelahavarong P, Ratanapakorn T, Teerawattananon Y: The use of comparative effectiveness research to inform policy decisions on the inclusion of bevacizumab for the treatment of macular diseases in Thailand's pharmaceutical benefit package. ClinicoEconomics and Outcomes Research: CEOR 2012, 4:361-374.
[9] Jolley D: Italy Fines Novartis and Roche in Collusion Case. In The New York Times; 2014.
[10] Moja L, Lucenteforte E, Kwag KH, Bertele V, Campomori A, Chakravarthy U, D'Amico R, Dickersin K, Kodjikian L, Lindsley K, et al: Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. Cochrane Database of Systematic Reviews 2014.
[11] Pharmaceutical Giant AstraZeneca to Pay $520 Million for Off-label Drug Marketing [https:// HYPERLINK "http://www.justice.gov/opa/pr/pharmaceutical-giant-astrazeneca-pay-520-million-label-drug-marketing" www.justice.gov/opa/pr/pharmaceutical-giant-astrazeneca-pay-520-million-label-drug-marketing]
[12] Eli Lilly and Company Agrees to Pay $1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa [https://www.justice.gov/archive/opa/pr/2009/January/09-civ-038.html]

Policy Recommendations

For Healthcare Payers and Public Health Authorities

- Fund the use of off-label medicines with strong scientific evidence for the benefits package.
- Control the marketing and use of off-label medicines that have no evidence of clinical benefit and safety or if there is clear evidence of harm.
- Provide financial and non-financial incentives for industry to register medicines for off-label medicine indications.
- Implement national guidelines on the use of off-label medicines.

For HTA Agencies

- Conduct HTA of off-label medicine use to inform policy decisions of healthcare payers and public health authorities.

For Civil Societies and Patients

- Be aware and understand that the use of off-label medicines can have both benefits and risks.
- Monitor the use of off-label medicines, especially those with potential harms.
- Encourage patients to discuss the benefits and risks of their treatments with health professionals.
- Support the HTA of off-label medicine use through participation – and encouraging others to participate – in good clinical trials.

For Research Grant Agencies

- Provide resources for independent researchers to assess the safety and clinical benefit of common or important (e.g. only choice for patients) off-label medicine use for particular indications.
- Provide resources for monitoring and assessing the impact of off-label medicine use to set research priorities for their country.

For Health Professionals

- Work with the government to develop codes of conduct or ethical guidelines regarding off-label medicine use.
- Collaborate with HTA agencies to conduct HTA of off-label medicine use. Support registries for monitoring outcomes.
- Inform and discuss with patients the non-routine use off- label medicines. Informed consent should be given for these types of off-label medicine use.

For Industry

- Register products for off-label indications if the evidence is available.
- Develop evidence for off-label indications.
- Non-promotion of medicines for off-label indications.
- Monitor the use of medicines for off-label indications and inform stakeholders if these are identified.

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