Should Off-Label Medicines Be Included In The Universal Health Coverage (UHC) Schemes? Why, When, and How?

Ully Adhie Mulyani [1]
[1)] HTA Program Mahidol University, Research Center Building, Faculty of Medicine Ramathibodi Hospital, Mahidol University 270 RAMA VI Road. Rachathevi, Bangkok 10400, Thailand.
Tel. (+66)2-201-1269 Fax. (+66)2-201-1284

Abstract

Off label medicine refers to any medicine that is used to treat any ailment beyond of its approved / licensed indication by National Regulatory Authorities, such us FDA in USA and BPOM in Indonesia. Off-label medicines are used because the available and approved drugs do not have the desired effect, then doctors try medicine that have not been licensed indications. Some other reasons in practice off-label medicines use and prescribing are that drugs in the same category have the same effect (although have not been approved by indication), the expansion to a lighter form than the licensed indication, or extension of use for certain related conditions. At the opposite, the disadvantage of the practice off-label medicine use is generally not included in any health insurance benefit package, also not covered by mandatory insurance scheme (JKN-BPJS). Patients should pay for the price of a drug that has not been assured or proven of its efficacy and safety. It needs strong evidence based on scientific research to ensure the safety and effectiveness of off-label medicines to be included in the list of medications (national formulary) to put it on National Health Insurance (BPJS) benefit package.

Keywords: off-label medicine, health insurance, pharmacy

Abstrak

Obat *off-label* adalah obat yang digunakan di luar indikasi yang disetujui oleh lembaga yang berwenang, kalau di Amerika *Food and Drug Administration* (FDA), sedangkan di Indonesia Badan POM. Obat *off label* digunakan karena obat yang tersedia dan *approved* tidak memberikan efek yang diinginkan, sehingga dokter mencoba obat yang belum disetujui indikasinya. Beberapa alasan lain adalah adanya dugaan bahwa obat dari golongan yang sama memiliki efek yang sama (walaupun belum disetujui indikasinya), adanya perluasan ke bentuk yang lebih ringan dari indikasi yang disetujui, atau perluasan pemakaian untuk kondisi tertentu yang masih terkait. Kerugiannya adalah obat *off-label* umumnya tidak dicover oleh BPJS sehingga pasien harus membayar sendiri harga obat yang belum terjamin efikasi dan keamanannya. Perlu dukungan penelitian yang kuat terhadap keamanan dan efektivitas obat off label agar dapat dimasukkan dalam daftar obat (formularium nasional) yang ditanggung BPJS.

Understanding off-label medicine

Off-label medicine refers to any medicine that is used to treat any ailment beyond of its approved/licensed indication. Practice of the off-label prescribing not only based on beyond licensed indication, but also apply to the use of a marketed medicine in different patient population (e.g. paediatric, geriatric, pregnant patient, etc.), dosage, or dosage form that does not have approval from the authoritative body.[1]

In a drug regulatory system, an authoritative body whose responsible for the drug approval in a country should approve it licensed indication based on the pre-clinical and clinical evidence that is provided and submitted by the drug manufacturer. This process is to confirm that the given licensed drug performs its safety and efficacy in the utmost scientific manner.

Approval of medicine by the National Regulatory Authorities can take years; this process is laborious and very-costly. A literature stated that the FDA approves not more than 60 percent of all drugs submitted for review and a period 6-8 years for a drug approval.[2] Process for drug approval is started after a drug is tested for preclinical and clinical trial phase III, while the time period for doing pre-clinical until successfully end the phase III trial might take over more than 10 years. The figure below, show the process from drug discovery until approval to the medicine regulatory authorities.

Acceptability and commonality of off-label medicine use in standard care

Paediatric patients is prone to receive off-label prescribing, as it has been reported in some countries, either prospectively or retrospectively that the extent of off-label prescribing in paediatrics range from 7 to 60%.[3] A study in a major paediatric teaching hospital in Australia year 2008, off-label prescribing occurred in infants and children (31.7% and 35.9% respectively); common reasons for off-label prescribing were dosage (47.4%) and age (43.2%).[3]

The high prevalence of off-label use and prescribingz shown that this practice is extremely common worldwide.

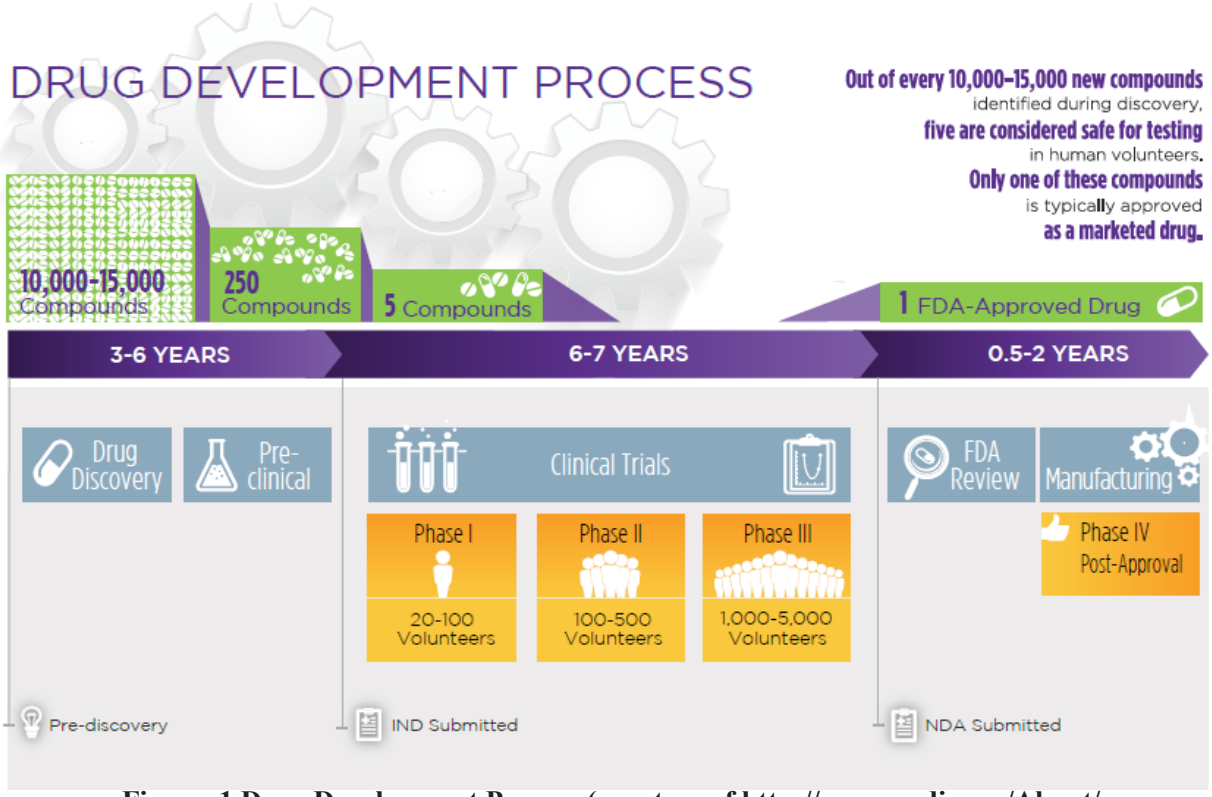

Figure 1 Drug Development Process (courtesy of http://www.ppdi.com/About/About-Drug-Discovery-and-Development)

Despite the fact that this practice is done without adequate clinical evidence.

Although on-label medicine is supported by the best evidence on its safety and efficacy, but in the real population setting the use and prescribing not represent the inclusion criteria for its study. Limitation in clinical trial setting is not involving vulnerable population such as paediatric, pregnant woman and elderly, orphan or rare diseases, even psychotic.

Commonalities in off-label prescribing is broad, somehow physician are challenge to prescribe

Table 1 Some examples of the off-label uses of medicine (table is adopted from Wittich, et al1)

CATEGORY and DRUG	Example off-label uses(s)
Allergy	
• Diphenhydramine	Chemotherapy-related emesis, insomnia
Anaesthesiology	
• Propofol	Intracranial hypertension
• Dexamethasone, propofol	Postoperative nausea
Cardiology	
• Amiodarone	Supraventricular tachycardia
• Indomethacine	Pharmacologic closure of patent ductus arteriosus
Dermatology	
• Azathioprine	Atopic dermatitis, psoriasis
Gastroenterology	
• Erythromycin	Gastroparesis
• Omeprazole	Reflux-related laryngitis
Haematology/oncology	
• Alendronate	Hypercalcemia of malignancy
• Furosemid (nebulized)	Dyspnoea
• Rituximab	Idiopathic thrombocytopenic purpura
Infectious diseases	
• Linezolid	Infective endocarditis
• Sulfamethoxazole-trimetoprim	Sinusitis
Nephrology	
• Acetylcysteine	Prevention of contrast nephrotoxicity
• Erythropoietin	Anaemia of chronic diseases
Neurology	
• Atenolol	Migraine prophylaxis
• Isoflurane	Status epilepticus
• Lidocaine	Postherapeutic neuralgia
• Tricyclic antidepressants	Bulimia, insomnia, neuropathic pain syndrome
Obstetric	
• Magnesium sulphate	Premature labour
Paediatric	
• Morphine	Pain in children
• Sildenafil	Pulmonary hypertension in children
Pulmonary	
• Enflurane, isoflurane, halothane	Status asmathicus
Psychiatry	
• Beta blockers	Social phobia, public speaking
• Fluoxetine	Borderline personality disorder, diabetic neuropathy, fibromyalgia, etc.
• Trazodone	Insomnia in elderly patients
Urology	
• Sildenafil	Sexual dysfunction in women

off-label drug since the most available medicine to treat an indication is limited. A broad spectrum of off-label use of medicine is shown in this table below.

Sildenafil prescribing in Indonesia, the manufacturer is on process to license the new dosage form that is indicated for pulmonary hypertension In case of aspirin, this drug is approved for many ailments: pain, fever (the oldest indication), rheumatic diseases, wide range of cardiovascular diseases.[1] patients with history of revascularization procedure. Even aspirin is includes in a guideline-recommended practice as a prophylactic therapy for diabetic patients against cardiovascular diseases.[1]

In Thailand, the off-label use of bevacizumab for age-related macular degeneration and diabetic macular oedema is indicated in the National List of Essential Medicine (NLEM).[4] While in Indonesia, the prescribing of sildenafil to treat pulmonary hypertension is accepted and subsidized by government hospitals, i.e. Sardjito Hospital in Yogyakarta and Harapan Kita Hospital in Jakarta. Recent updates regarding the use of off-label.

Concerning legal and ethics in off-label medicine prescribing

Concerning legal aspect in off-label medicine use and prescribing, one short answer is that "it is not illegal." In New Zealand, there is common law require that off-label drug use is of an acceptable standard, that the patient be fully informed, and the patient gives informed consent.[5] An article explains that a legal theories used in a lawsuit in related to off-label use of medicine is due to failure to provide adequate informed consent for using and prescribing off-label medicine to patient, and medical negligence.[1]

A qualitative study done in Belgium, reveals that according to the respondents giving information about the working mechanism and risk associated with off-label treatment before starting it is important.[6] The information given to patients should be clear and comprehensive.[6] It means that by providing informed consent on the use of off-label medicine, patients held responsible in the shared decision making for their own treatment. In the future it saves physicians towards any legal lawsuit from the patients if the treatment seems to be failing.

Leaving a patient without adequate treatment is considerably unethical to physician's perspective, especially when an evidence is exist although beyond the formal authorization process.[7]

Concerning the reimbursement systems

In well developed country, e.g. Germany with two-tier health insurance systems, patients from private health insurance can use and get off-label prescription included in the insurance. In the opposite, for German citizen who is covered by public health insurance there is a strict regulation regarding off-label use and prescribing medicine that included in the reimbursement public health insurance systems. It must be proven for efficacy if it is used in an off-label manner. The restrictions are it is used for treatment of serious diseases, life threatening or seriously affects patient's health related quality of life, no other possible therapy and must be a reasonable expectation (benefit outweight it risk).[7]

Thailand has success story to include off-label medicine in the NLEM, i.e. (1) the use of intravenous immunoglobulin for the treatment of myasthenia gravis, and (2) bevacizumab for age-related macular degeneration and diabetic macular oedema. This policy is supported by strong evidence that the safety, efficacy/effectiveneso, and/or efficiency for the use of off-label medicine. [4] Putting off-label medicine in a NLEM or National Formlary is the first gate toget it covered in the reimbursement system.

Conclusion

To answer question **why, when, and how** off-label use and prescribing of medicine should be included in unversal coverage reimbursement system, here are some thought to be concluded:

Why off-label use and prescribing of medicine should be included in unversal coverage reimbursement system? Off label use and prescribing of medicine is not uncommon and can be seen in the standard of care. The practices of it mostly done in vurnerable population (population excluded from clinical trials), a licensed drug for certain indication is not available (e.g. oprhan or rare diseases), there is limited or even a broad evidence of the safety and efficacy/effectiveness

of certain licensed medicine to be used off-label but the manufacturer is reluctant to licensed it. It is not illegal to give treatment or care using off-label medicine. Lawsuit regarding off-label medicine are performed due to failure to provide adequate informed consent for using and prescribing off-label medicine to patient, and medical negligence (failure to provide adequate information). Leaving patient without a proper treatment is regarded unethical especially when physicians aware that there is a cure although not yet registered, and limiting the use of licensed medicine "only" in the reimbursement systems is somehow considered discouraging the efforts to provide equity for essential treatment and access to medicine.

When is off-label use and prescribing of medicine is included in the universal coverage system?
There are six proposed condition, i.e. (1). Presence of a severe, life-impairing or life-threatening condition; (2). Absence of authorized treatment or repeated treatment failure; (3) Absence of alternative treatments authorized for the condition; (4) The off-label use is supported by strong evidence in scientific literature; (5) The patient has been educated and has given his or her informed consent; (6) Presence of established reporting routes for adverse events and linked to off-label use.[6]

How is off-label use and prescribing of medicine is included in the universal coverage system?
The reimbursement system shall provide the easiness to access off-label use and prescribing of medicine especially it is supported by strong evidence that the safety, efficacy/effectiveness, and/or efficiency exists. Including an off-label medicine in a National List of Essential Medicine or National Formulary is a start to put it on the reimbursement systems. A system of registry and monitoring for serious adverse effects should be developed and established, to ensure the safety of off-label use and prescribing.

References

1. Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. Mayo Clin Proc 2012;87:982–90. (Accessed February 14, 2017).
2. Furey K, Wilkins K. Prescribing "Off-Label": What Should a Physician Disclose? AMA J Ethics 2016;18:587–93.
3. Czarniak P, Bint L, Favie L, Parsons R, Hughes J, Sunderland B. Clinical setting influences off-label and unlicensed prescribing in a paediatric teaching hospital. PLoS One 2015;10:e0120630. (Accessed February 14, 2017).
4. 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. Clinicoecon Outcomes Res 2012;4:361–74. (Accessed February 14, 2017).
5. Cook RJ. Off-label drug use as a consent and health regulation issue in New Zealand. J Bioeth Inq 2015;12:251–8.
6. Dooms M, Cassiman D, Simoens S. Off-label use of orphan medicinal products: a Belgian qualitative study. Orphanet J Rare Dis 2016;11:144.
7. Lenk C, Duttge G. Ethical and legal framework and regulation for off-label use: European perspective. Ther Clin Risk Manag 2014;10:537–46. (Accessed February 16, 2017).