

Review of Laws, Regulations, and Uses of Off-label Drugs in Indonesia

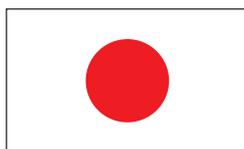
Final Report

June 2017



**THE ACCESS AND
DELIVERY PARTNERSHIP**

New Health Technologies for TB, Malaria and NTDs



From the People of Japan

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Acknowledgments

This report details the results of the off-label medicine study conducted by the Indonesian team (Dr. Prastuti Soewondo, Vetty Yulianty Permanasari, MPH, and Mira Nurfitriyani, BPH, of the Faculty of Public Health, Universitas Indonesia) as part of the collaboration with the Health Intervention and Technology Assessment Program (HITAP). The two reviews were supported by PATH through the Access and Delivery Partnership (ADP), a project funded by the Government of Japan and led by the United Nations Development Programme (UNDP).

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About the Access and Delivery Partnership

The adverse impact of tuberculosis (TB), malaria and neglected tropic diseases (NTDs) on development outcomes has resulted in new approaches and partnerships to tackle the global deficiencies in research and development, and treatment access. One such initiative is the strategic partnership between the Government of Japan and UNDP, which promotes research and development, and expedites access to and delivery of health technologies used to address TB, malaria and NTDs. This partnership comprises two complementary components, which reflect the Government of Japan's and UNDP's strategic goals on global health¹:

The Global Health Innovative Technology (GHIT) Fund, which focuses on the promotion of innovation and research through the development of drugs, diagnostics and vaccines for TB, malaria and NTDs. The GHIT Fund stimulates research and development of new health technologies through funding research and product development partnerships between Japanese and non-Japanese organizations.

The Access and Delivery Partnership (ADP), which aims at assisting low- and middle-income countries (LMICs) enhance their capacity to access, deliver and introduce new health technologies for TB, malaria and NTDs.

Led and coordinated by UNDP, the ADP is a unique collaboration between UNDP, TDR (the Special Programme for Research and Training in Tropical Diseases, which is hosted at the World Health Organization) and PATH. Working together, the project partners will leverage the expertise within each organization to provide the full range of technical skills necessary to strengthen capacity in LMICs. The ADP emphasizes consultation, collaboration and implementation with partner-country governments and stakeholders, working to develop LMICs' capacities to access and introduce new technologies.

New health technologies are broadly defined as drugs, diagnostic tools and vaccines that are relevant for the prevention, treatment or cure of TB, malaria and NTDs, but are not yet available for market introduction or have not been introduced in LMICs. The introduction of new health technologies can place burdens on existing health systems, including new requirements for drug regulation, supply and distribution and health personnel training. Accordingly, the ADP will focus on providing LMIC stakeholders with the necessary skills to develop the systems and processes required to effectively access new health technologies and introduce them to populations in need.



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Abbreviations

ADR	adverse drug reaction
Badan POM	Badan Pengawas Obat dan Makanan (Food and Drug Monitoring Board)
CATAG	Council of Australian Therapeutic Advisory Groups
DG Binfar	Direktorat Jenderal Kenfarmasian dan Alat Kesehatan (Directorate General of Pharmaceutical Care and Medical Devices)
EMA	European Medicines Agency
FDA	Food and Drug Administration
FORNAS	Formularium Nasional (National Formulary)
HCT	hydrochlorothiazide
HITAP	Health Intervention and Technology Assessment Program
HTA	health technology assessment
INA-CBG	Indonesian case-based group
JKN	Jaminan Kesehatan Nasional (universal health coverage)
NIE	nomor izin edar (marketing authorization)
MOH	Ministry of Health
NICU	neonatal intensive care unit
PAH	pulmonary arterial hypertension
PPJK	Pusat Pembiayaan Jaminan Kesehatan (Center for Health Financing and Insurance)
PRON	Pusat Rujukan Obat Nasional (National Referral Center for Drugs)
PROS	Pusat Rujukan Obat Spesialistik (Referral Center for Specialist Drugs)
SAS	Special Access Scheme
TGA	Therapeutic Good Administration
WHO	World Health Organization

Background

The use of off-label drugs is a worrying regulatory issue.^{2,3} Off-label use is defined as the use of a drug outside the scope of its approved label—that is, at different doses or frequencies, in different indications, in different age groups, administered by an alternative route, or in a formulation not approved for use in specific age groups (i.e., in children).⁴

In the United States, physicians sometimes prescribe drugs without adequate knowledge of label requirements, such as approved indications, dosages, routes of administration, or patient age.³ A 2006 study—also in the United States—reported that 20 percent of the 500 most commonly used drugs are prescribed off-label and that 73 percent of off-label use has little or no scientific support.²

Japan faces different issues in off-label use, where there are many drug indications that remain unapproved in Japan, despite being approved elsewhere and backed with strong supporting evidence. Many of these unapproved indications are then prescribed off-label and are not covered by the Japanese health insurance system. In response to this issue, in 1999 the Ministry of Health, Labor and Welfare of Japan stated that it would approve a new supplement for a drug indication without clinical trials, under certain conditions. This approval scheme involved practical application and evaluations using literature-based evidence.⁵ This situation where many drug indications are unapproved by the national health insurance is similar to the issues currently faced by the Indonesian government while it is on its way to implementing its universal health insurance system.

In Canada, on a randomly selected day (March 5, 2014), a total of 2,145 drug prescriptions were extracted from children hospitalized in a mother-child tertiary-care hospital. The off-label drug use rate was 38.2 percent (161 substances; 819 prescriptions).

The study stated the following reasons for off-label drug use:

1. Unapproved age group (53.2 percent).
2. Dosage (27.6 percent).
3. Frequency (25.2 percent).
4. Indication (5.5 percent).
5. Administration route (5.6 percent).

Only 39.3 percent of these off-label drug prescriptions had strong scientific support.⁶

In India, research on drugs used for anesthesia in surgical wards of a teaching hospital was conducted with 400 patients from general surgery, pediatric surgery, and orthopedics departments. A total of 3,705 drugs were prescribed to the 400 participants—an average of 9.26 (SD ± 3.33) drugs per patient—and off-label drugs constituted 20.19 percent of all the drugs prescribed. At least one off-label drug was

prescribed to 82.5 percent of the patients. The study indicated that inappropriate dosage was the most common form of off-label use.⁷

Similar to the previous studies, a study was undertaken to evaluate off-label antibiotic use involving 616 children in the three European countries of the United Kingdom, Greece, and Italy. The study collected data on all 110 patients admitted to the participating neonatal intensive care units (NICUs)—62 in the UK, 38 in Italy, and 10 in Greece—and all 506 admitted to general pediatric wards—265 in the UK, 94 in Italy, and 147 in Greece—over a two-week survey period between February and May 2009. In addition to the details of all the antibiotics prescribed (compound, route of administration, dosage, and indication for use), the study also collected data on each respondent's age, date of birth, weight, relevant medical history, and diagnosis. A total of 1,244 antibiotic prescriptions were issued (290 in NICUs and 954 in pediatric wards) in the two months studied. The study concluded that off-label antibiotic use is very common among European pediatric patients, due mostly to off-label doses and indications but rarely to age. The authors recommended educational programs for doctors regarding licensed antibiotic use in children and further clinical studies of unlicensed antibiotics to determine the appropriate administration for children.

In reviewing literature related to the effects of off-label drug use, a study in a pediatric ward of an Indian tertiary-care public teaching hospital tested the hypothesis that off-label status is a risk factor for adverse drug reactions (ADRs). The results stated that off-label and labeled use were responsible for 34 (67 percent) and 17 (33 percent) ADRs, respectively. This study concluded that the use of off-label medicines was more likely to be implicated in an ADR than labeled medicines.⁸

A systematic review that assessed the extent of the use of off-label and unlicensed drugs among hospitalized children was recently published. This study systematically searched MEDLINE/PubMed for papers published between 1994 and 2012 that addressed off-label/unlicensed drug prescriptions for the pediatric population. From the 34 studies that met the inclusion criteria, it was found that:

1. Off-label/unlicensed prescribing is widespread among the hospitalized pediatric population worldwide.
2. There is no consensus on a definition of either off-label or unlicensed drugs.
3. Preterm newborns receive the most off-label/unlicensed drugs.⁹

In Indonesia, there is a lack of evidence related to the practice and use of off-label drugs. The literature review found a study conducted in Harapan Kita National Heart Center which mentioned the Center's high use of drug-eluting stents (coating stents with drugs) with off-label indications when doing coronary revascularization with Percutaneous Coronary Intervention.¹⁰

Another Indonesian study investigated off-label prescribing practices for pediatric patients ranging from zero to five years old in Bandung, Jawa Barat. It was a retrospective and population-based study that included 4,936 prescriptions (with multiple prescribed drugs) written by pediatricians for patients in 14

selected community pharmacies in 2012. The results showed that 18.6 percent of the prescriptions contained at least one off-label drug. Furthermore, 7 percent of the 16,516 prescribed drugs were categorized as off-label. Doxycycline and domperidone were the most prescribed drugs with off-label indications.¹¹

The two studies in Indonesia showed a significant number of off-label drugs prescribed, reinforcing the urgent need to scrutinize under evaluated off-label prescribing practices that may compromise patient safety. To date, there has not been any study that has analyzed the laws and regulations related to the use of off-label drugs in Indonesia.

In 2015, the Health Intervention and Technology Assessment Program (HITAP), in collaboration with PATH—through the Access and Delivery Partnership (a project through the United Nations Development Programme)—assisted the Ministry of Health (MOH) of Indonesia to conduct an economic evaluation study of using sildenafil to treat pulmonary arterial hypertension (PAH).

However, drug manufacturers have not registered this medicine in Indonesia’s Formularium Nasional (FORNAS), or National Formulary, thus it is considered an off-label medicine and not eligible to be covered in the universal health coverage scheme by Indonesian law. After completion and socialization of this study, there are reports that the government is now considering allowing access to sildenafil for PAH for a limited time through the Special Access Scheme (SAS).

This study intends to help fill the evidence gap in the laws, regulations, and uses of off-label drugs in Indonesia, unequivocally addressing both positive and negative aspects, the benefits, and risks of off-label use in any setting.

Objectives

This report aims to meet the following objectives:

- To describe the current situation of off-label use of medicines in Indonesia, including but not limited to sildenafil for PAH.
- To describe the advantages and disadvantages in terms of health, plus economic and ethical impacts, of limiting off-label use of medicines as is currently the law in Indonesia.
- To describe the policy mechanisms, the laws, and the regulation of the use of off-label medicines in Indonesia.
- To identify nonlegal barriers that inhibit off-label use of medicines in Indonesia.
- To formulate policy recommendations regarding off-label use of medicines in Indonesia, including possible policy mechanisms and revisions of law and regulation, based on the study review results.

Literature review

As indicated above, off-label use is most often defined as the use of a drug outside the scope of a drug's approved label—that is, at different doses or frequencies, in different indications, in different age groups, administered by an alternative route, or in a formulation not approved for use in specific age groups (i.e., in children).⁴ In their 2015 study, Patil and team state that when a drug is used in a way that is different from that described in a drug label approved by a regulatory body, it is said to be “off-label use.”⁷

In the United States, once a drug is approved for a specific purpose, the drug can then be used for any purpose, even if the Food and Drug Administration (FDA) has not approved its use for that specific purpose. Using the drug for a purpose not indicated on its FDA-approved label is called an “off-label” practice. According to Fox, off-label practices can happen in the following three ways:

1. Used by patients.
2. Prescribed by physicians.
3. Marketed by manufacturers.¹²

More specifically, it is considered off-label when a physician prescribes a drug to treat “unapproved conditions or in unindicated combination, dosage amount, or frequency.”

Based on US government regulations, the FDA does not have the authority to limit a physician from prescribing a drug for off-label purposes, because the FDA does not regulate the practice of medicine. Furthermore, the FDA does not have the power to regulate how the individual patient will then use the medication prescribed. However, the FDA is authorized to regulate one of the three off-label practices: the manufacturers' marketing and selling of the drug. A drug manufacturer is considered to market a drug off-label when it promotes its product for non-FDA-approved purposes, users, dosages, and/or combinations. In 1997, the US Congress passed legislation to allow the FDA to regulate how a drug manufacturer disseminates off-label information. Prior to 1997, a manufacturer could only promote an FDA-approved drug for its FDA-approved purposes. However, the 1997 Act was an effort “to protect the public's health and safety by ensuring distribution of only truthful, non-misleading information regarding uses of prescription drugs.” More specifically, the Act provided the FDA with the authority to control how a drug manufacturer distributed information on a drug's off-label uses to physicians.¹³

In 2006, the European Union passed the Paediatric Regulation (Regulation [EC] No. 1901/2006 of the European Parliament and of the Council), which aimed to reduce off-label use of medicines in pediatric pharmacotherapy. To evaluate the possible impact of the regulation on the prevalence and the frequency of off-label prescriptions, a 2011 study was conducted in Kuopio University Hospital in Finland, which was a repeat of a similar study conducted in 2001 (ten years earlier). For two weeks, the prescriptions for patients below 18 years old were reviewed in three wards—NICU, general pediatric ward, and pediatric surgical ward—in April and May 2011. The study population included 123 patients, of which 119 received a total of 1,054 prescriptions in 2011. Results of the study indicated that the proportion of

patients with at least one prescription for off-label use or for an unauthorized medicine was significantly higher in 2011 (79 percent) than in 2001 (58 percent). For newborns, significantly more prescriptions were for off-label use in 2011 than in 2001 (51 percent versus 22 percent). Therefore, the study concluded that the prescribing of off-label medicine was more prevalent in 2011 than in 2001 and that the European Union's recent pediatric legislation has had only minor, if any, impact on the prescription of drugs for pediatric inpatients in specialized care.¹⁴

A study in Japan was done with the purpose of investigating the factors that contribute to the approval of individual medicine applications by the Japanese approval system and of assessing their efforts in facilitating the approval of off-label drugs. Eighty drug approvals were obtained from the official review reports of the Japanese regulatory agency. The following criteria were studied to analyze individual applications: review time; therapeutic class; application category under Japanese regulations; international approval status; post-approval monitoring plan; and variety and quantity of literature evidence. The study indicated that the variety and quantity of literature evidence provided for a specific application showed no consistent trend with respect to international approval status.

Interestingly, this study concluded that in the case of Japan, foreign authorities' approval did not appear to be essential for approval in Japan. Instead, the safety and effectiveness of medicine as defined by standard textbooks or guidelines was used consistently to obtain approval for off-label use in Japan.⁵

Several other countries have policy mechanisms related to the use of off-label drugs, such as practice guidelines, codes of ethics, financial mechanisms, and provision of published evidence. For example, Australia, Singapore, and the United Kingdom have practice guidelines for the use of off-label drugs.

In Australia, the Council of Australian Therapeutic Advisory Groups (CATAG) developed some guiding principles before prescribing off-label drugs (CATAG 2015).¹⁵ These are summarized in Figure 1.

The main principles are to:

- Consider the off-label use of medicine only when all other options, including medicines approved by Therapeutic Goods Administration, are unavailable, exhausted, not tolerated, or unsuitable.
- Use high-quality evidence to determine appropriateness of off-label medicine use.
- Involve the patient/patient caretaker in shared decision-making recommending an off-label medicine.
- Consult the Drug and Therapeutics Committee when prescribing an off-label medicine, except when the use of an off-label medicine is considered routine.
- Ensure the appropriate information is available at all steps of the medicines management pathway.
- Monitor outcomes, effectiveness, and adverse events.
- Consider liability and accountability when using off-label medicines.

Figure 1. Guiding principles developed by CATAG for off-label drug use.



¹CATAG; DTC

In Singapore, A Good Practice in Prescribing Medicines was developed. Included in it is the topic “prescribing medicines for use outside the terms of their license (off-label).” This regulation is aimed at serving the patient’s needs apart from the available licensed drug, with the following requirements:

1. There should be a sufficient evidence base or experience of using the medicine to demonstrate its safety and efficacy.
2. The physicians must take responsibility for prescribing the medicine and make a clear, accurate, and legible record.
3. Physicians must also state the advantages of and reasons for using these medicines.

¹ Council of Australian Therapeutic Advisory Groups (CATAG); Drug and Therapeutics Committee (DTC)

Besides the practice guidelines, a code of ethics can be used as one of the policy mechanisms related to off-label drug use. In Singapore, physicians are required to treat their patients according to general methods and only use licensed medicines for appropriate indications, as stated in the Singapore Medical Council's 2016 Handbook on Medical Ethics: "A doctor shall not offer to patients management plans or remedies that are not generally accepted by the profession, except in the context of a formal and approved clinical trial."

In the United Kingdom, the General Medical Council, which develops the prescribing guidance, recommends that a medicine should usually be prescribed in accordance with the terms of its license. However, unlicensed or off-label medicines may be prescribed when, based on an assessment of the individual patient, the prescriber concludes, for medical reasons, that it is necessary to do so to meet the patient's specific needs.

The other policy mechanism is financial, which is applied also in Australia and Singapore. In Australia, the Pharmaceutical Benefit Scheme Schedule lists the medicines available to patients at a price subsidized by the government. Then the scheme subsidizes only medicines that are approved by the Therapeutic Goods Administration (TGA). In Singapore, there is a Handbook for Healthcare Professionals published by the MOH stating that off-label uses of medicine are non-claimable or not allowed for reimbursement in some conditions.

Providing published evidence is also one of the policy mechanisms on the use of off-label drugs. In the United Kingdom in 2011, the National Institute for Health and Care Excellence announced that it would provide advice on the use, in special circumstances, of unlicensed and off-label medicines. This advice will not be formal guidance but is intended to be a summary of the available evidence to inform decision-making by healthcare professionals.¹⁶

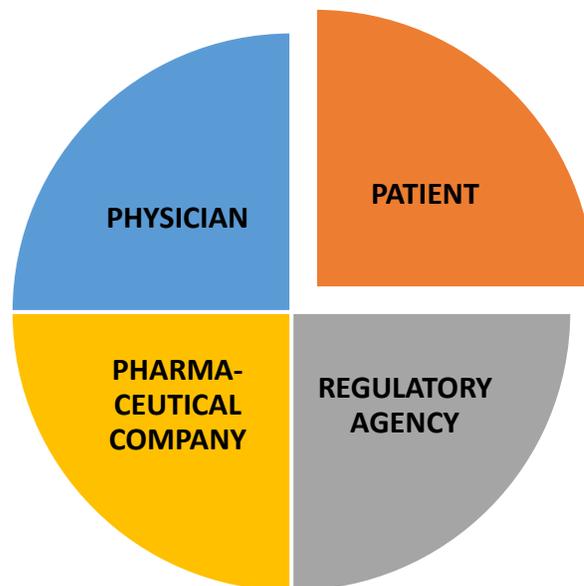
The policies described above are worth considering and studying to see which aspects could be applied and well received in Indonesia, in the interest of providing protection for both physicians and patients alike.

Unfortunately, there is a research gap on studies focusing on analyzing laws and regulations related to the use of off-label drugs in Indonesia, therefore limiting the ability of decision-makers to gain a comprehensive picture of the current situation and to take appropriate action.

Perspectives of the study

This study aims to analyze the laws, policies, and uses of off-label drugs from the perspective of physicians, pharmaceutical companies, and regulatory agencies (Figure 2). Due to the scope, this study did not include patients' perspectives.

Figure 2. Perspective of the study on the laws, policies, and uses of off-label drugs.



There were several activities in this study:

- Conduct the review as outlined in the Scope of Work for HITAP and regularly communicate on the progress of the study.
- Facilitate interviews, data collection, meetings, and other necessary activities to obtain data.
- Assist in the organization of stakeholder consultation meetings to discuss and consult on the plan for the review and discuss the findings of that review.
- Assist in the organization of and attend a policy forum in Indonesia to finalize the policy recommendation.
- Prepare final report and policy brief.

Methods

Study design

This is a qualitative study, which used an action research approach with the following data collection methods: desk review, in-depth interviews, and consultative policy forum with relevant stakeholders.

Study locations

The interviews of several key informants were conducted in Jakarta, Yogyakarta, Surabaya, Bali, and Palembang. The policy forum was also conducted in Jakarta. The preliminary result of this study was presented at the Side Meeting Event of the Prince Mahidol Award Conference in Thailand on January 30, 2017. To capture the current practice of off-label drug use, physicians in three public hospitals and one private hospital were interviewed.

Implementation time

The projected duration of this study was five months, from October 21, 2016 to March 21, 2017.

Interviewees and key informants

The key informants that have been interviewed and involved in the policy forum are as follows:

- Secretary, Director, and staff of the Directorate General of Pharmaceutical Care and Medical Devices (DG Binfar), MOH Indonesia.
- Director at the Directorate General of Health Services, MOH Indonesia.
- Director and staff of the Food and Drug Monitoring Board in Indonesia (Badan POM).
- Member of the National Committee of Drug Assessment, Badan POM.
- Head of Sub-Directorate and staff at the Center for Health Financing and Insurance (PPJK), MOH Indonesia.
- Representatives of three pharmaceutical companies (public and private).
- Pediatrician, internist, anesthesiologist, psychiatrist, obstetrician, surgeon, endocrinologist, and cardiologist from three public hospitals and one private hospital.
- One expert on Clinical Pharmacy from Airlangga University.

- Dean of the Faculty of Public Health, Universitas Indonesia.
- Deans of the Faculty of Pharmacy, Universitas Indonesia and Pancasila University.

Study instruments

The instruments used in this qualitative study include:

- In-depth interview guidelines: this study collected primary data by conducting in-depth interviews with key informants.
- Guidelines for conducting a policy forum.
- A document checklist for desk review.

To collect primary data through interviews, desk review, and a policy forum, we used a voice recorder to record all the processes of the interviews and the policy forum. All the dialogues were then transcribed and analyzed using content analysis. The secondary data (policy, laws, regulations) were also reviewed to answer the objectives of this study.

Ethical issues of the study

The study proposal and the completed instruments of this study were approved by and passed the review of conduct of the Ethical Committee at the Faculty of Public Health, Universitas Indonesia.

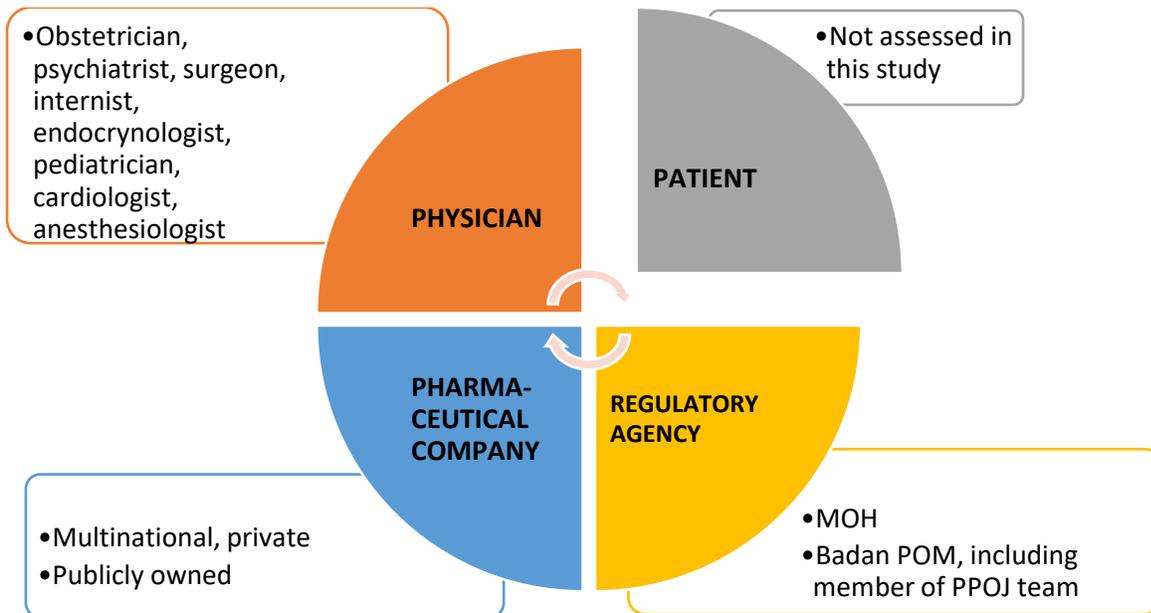
The ethical aspects considered in this study were:

- Self-determination: the informants/respondents were informed about the objectives, process, and possible effects of this study and then given the freedom to decide whether or not to participate. If they were willing to do so, they were then asked to sign an informed consent form.
- Privacy and anonymity: the identity of the informants/respondents was protected so they would not be recognized individually.
- Confidentiality: the identity of respondents and the data gathered were kept confidential.

Results

The results of this study are presented from three perspectives (Figure 3). The first perspective is that of regulatory agencies, which consists of data gathered from interviews with Badan POM, including the National Committee of Drug Assessment and DG Binfar, MOH Indonesia. The second perspective is that of pharmaceutical companies, both multinational, private companies and publicly owned companies. The physician's perspective is also considered, consisting of data gathered from obstetricians, psychiatrists, surgeons, internists, endocrinologists, pediatricians, anesthesiologists, and cardiologists.

Figure 3. Stakeholder groups whose perspectives were considered in this study.



²PPOJ

The term “off-label drug” used in this study is defined as the prescription of medicine for indications other than those on the approved drug label by Badan POM (the Indonesian FDA)—including different usage of dose, route of administration, and patient population (i.e., pediatric)—or for new side effects that are outside of label indications when approved. In theory, the actual use of the medicine is often not problematic as a pharmacotherapy; however, clinically it is used based on need and the physician's own knowledge/experience.

There are many important challenges regarding off-label drugs, including legality, evidence base, risks for patients, and health costs. Off-label prescriptions often occur due to the following reasons: limited drug review, limited informative drug data, and a lack of scientific evidence on the benefits of the medicine, especially in phase 1 and phase 2. Justifiably, it is true that an off-label drug prescription is each doctor's prerogative: doctors may be informed by new publications (journals, newsletters), workshops, and

² Panitia Penilaian Obat Jadi, National Committee of Drug Assessment (PPOJ)

experiences from other colleagues and peer groups and may believe that the old drugs were yet to be effective or are too expensive. Information on off-label drugs that remain indicated with the medical and pharmaceutical aspects was included in our study.

The perspective of the regulatory agencies

There are two main regulatory agencies related to drug policy in Indonesia: Badan POM (the Indonesian FDA) and DG Binfar, MOH.

With the implementation of Jaminan Kesehatan Nasional (JKN—i.e., universal health coverage) in 2014, there have been many major policy changes, the foremost being DG Binfar’s introduction of the first National Formulary of drugs, also known as FORNAS, under the Minister of Health’s Decree No. HK.02.02/MENKES/523/2015.¹⁷ All drugs listed in FORNAS had been approved by Badan POM and registered, as part of the approval process, specific indications of each drug. Therefore, all the drugs listed in FORNAS are considered “on-label.”

“There is no off-label drug registered in the National Formulary (FORNAS) in the National Health Insurance, since the FORNAS planning team follow the approval and nomor izin edar [marketing authorization] or registration number from the Food and Drug Administration.” —Badan POM representative

FORNAS lists each drug by its generic name, indication, type (tablet, injection, suspension, syrup, etc.), maximum dosage, and type of health provider to provide the drug (primary healthcare, secondary hospital, tertiary hospital). Figure 4 shows examples of some drugs listed in FORNAS.

Figure 4. Examples of drugs listed in the National Formulary (FORNAS).

DAFTAR OBAT FORMULARIUM NASIONAL

KELAS TERAPI	SUB KELAS TERAPI/NAMA GENERIK/SEDIAAN/KEKUATAN DAN RESTRIKSI PENGGUNAAN	FASILITAS KESEHATAN			PERESEPAN MAKSIMAL
		TK 1	TK 2	TK 3	
1. ANALGESIK, ANTIPIRETIK, ANTIINFLAMASI NON STEROID, ANTIPIRAI					
1.1 ANALGESIK NARKOTIK					
1	fentanil				
	inj: Hanya untuk nyeri sedang hingga berat dan harus diberikan oleh tim medis yang dapat melakukan resusitasi.				
	patch: Untuk nyeri pada pasien kanker yang tidak teratasi dengan analgetik non opioid.				
	1. inj 0,05 mg/mL (i.m./i.v.)		√	√	5 amp/kasus
	2. patch 12,5 mcg/jam		√	√	10 patch/bulan
2	hidromorfon				
	1. tab lepas lambat 8 mg		√	√	30 tab/bulan
	2. tab lepas lambat 16 mg		√	√	30 tab/bulan
3	kodein				
	1. tab 10 mg	√	√	√	20 tab/minggu
	2. tab 20 mg	√	√	√	20 tab/minggu

“If the off-label drug that is not suitable for the indication is verified by the Social Security Provider [BPJS], the payment cannot be claimed. This method leads doctors to give on-label prescriptions.” — Badan POM representative.

One of the benefits of JKN is that doctors must refer to the medicine and indication listed in FORNAS for the claim to be reimbursed. A patient utilizing their JKN service will likely receive proper caution in drug administration, since doctors must refer to FORNAS, and in the process the physicians can gain a clearer understanding on whether the drug is on- or off-label.

Previously, there were not any regulations prohibiting the prescription of off-label drugs in Indonesia. Prior to JKN and FORNAS, many physicians were unaware of “on-label” or “off-label” versions of the prescribed drugs because their knowledge is most often derived from seminars, workshops, and international journals provided by their professional organizations. However, with the implementation of FORNAS, doctors are exposed to the registered indication for each drug.

Unfortunately, a challenge still lies ahead, as there are no available data to track drugs used in the hospitals or whether they are “on-label” or “off-label,” since hospital claim data does not include drug information under the Indonesian case-based group (INA-CBG) payment system. Data could possibly be obtained through a special assessment by tracking back to the patients’ medical records to analyze the prescription pattern for specific diseases.

Nevertheless, much progress has been made with the new policies in place, since doctors can now easily refer to clear and consistent information about approved drugs and their indications through the FORNAS listing—although whether the physicians will access FORNAS and comply is a different issue.

In drug approval, Badan POM is responsible for ensuring the efficacy, safety, and quality of the drug. The process of drug registration in Indonesia is determined by Badan POM Regulation No.

HK.03.1.23.10.11.08481 of 2011 on Drug Registration. In this regulation, to receive marketing authorization, drugs must meet the following criteria:

- Adequate efficacy and safety, proven through the test of nonclinical and clinical trials or other evidence in accordance with the status of the development of relevant scientific knowledge.
- Quality that meets the criteria concerning the production process according to good manufacturing practices, specifications, and methods of analysis of all materials used in the finished product with valid evidence.
- Use of labeling and product information that contains information that should be complete, objective, and not misleading, to ensure the rational and safe use of drugs.
- Administration that is in accordance with the real needs of society.
- Especially for new psychotropic drugs, the presence of a clear advantage compared to approved drugs circulating in Indonesia; and for contraceptives or other drugs used in the national program, a possible requirement for clinical trials in Indonesia.

“First of all, drugs that are being prescribed should be an on-label drug. It depends on the pharmaceutical company to register the drug for the specific indication. Then, we have experts that consist of Professors of Pharmacology called the National Committee of Drug Assessment [Panitia Penilaian Obat Jadi—PPOJ]. They will set a meeting to discuss and decide on the approval of that indication.”—Badan POM representative

The perspective of Badan POM

A key part of Badan POM's role is the registration and approval of drugs based on the safety, efficacy, and quality of the product—all of which is done in response to inquiries from pharmaceutical companies. In other words, Badan POM does not proactively assess drugs without a request from a pharmaceutical company, despite its knowledge of the country's needs and current conditions.

As the main drug regulatory agency, Badan POM is aware of off-label practices in Indonesia.

“The use of off-label drugs in Indonesia is quite common. This situation happens as a result of the health workforce's experience. Sometimes, the practice happens because of the patient's need—for example, Amitriptylin. It is used for antidepressant treatment; however, it can be used for neuropathy chronic pain.” —Badan POM representative

Regarding this and many similar cases, Badan POM is aware that there is a need for patients to use off-label drugs as their therapy choice, while physicians also should have a right to decide the appropriate clinical intervention for their patients.

From the perspective of Badan POM, the usage, availability, accessibility, and affordability of the drug is the responsibility of the MOH. According to the Badan POM officials, the policy on drug use is under the MOH's authority, as stated in the interview statement below:

“The Ministry of Health or doctors'/specialists' associations have the authority to regulate the utilization of off-label drugs, since they have the authority on clinical use. On the other hand, we, Badan POM, have responsibility for ensuring the quality, safety, and efficacy of the drug. In addition, the Ministry of Health has the authority on the treatment process and the drug's availability, accessibility, and affordability. Hence, it is outside of the scope of Badan POM.” —Badan POM representative

Despite its passive nature, Badan POM has made itself open to requests. For example, the interviewees stated how it would have been helpful if there had been a request from the physicians' association and patients' association to the MOH. The MOH would then give a formal written recommendation to Badan POM to request an approval for the indication. Following the recommendation from the MOH, Badan POM would assign the National Committee of Drug Assessment to evaluate it based on the evidence, which would then advise the head of Badan POM whether or not to approve that indication.

Pharmaceutical companies should register other indications of their drug in order to gain NIE. Unfortunately, there is little incentive for Indonesia's pharmaceutical companies to register a drug for more than one indication due to the requirements of submitting scientific and clinical studies for that specific indication. This, coupled with the lengthy bureaucratic process, causes them to be more reluctant to register their products for additional indications. The average time spent by pharmaceutical companies is around one and a half to three years just to obtain the registration of one indication.

During the in-depth interviews, Badan POM staff also admitted that there has been no discussion yet related to off-label drugs with the MOH or doctors'/specialists' associations. In the future, Badan POM should be more sensitive and open-minded in finding a solution that caters to the needs and wants of patients.

The perspective of DG Binfar, MOH

As mentioned above, the use of the drug and ensuring its availability, accessibility, and affordability are the responsibility of DG Binfar. In regard to off-label use, the MOH is aware that there are several off-label drugs which are urgently needed by patients, although DG Binfar has no data on the practice of off-label drugs in Indonesia.

“We don’t have data related to the use of off-label drugs, and we cannot guarantee there is no off-label drug use in the market. As an example, we know there is use of Viagra® or sildenafil 50mg and 100mg, not for treatment of erectile dysfunction. Or Hidroxicloroquine, the malaria drug, but being used for Lupus.” —MOH representative [Viagra is a registered trademark of Pfizer Inc.]

There are some other off-label drugs also prescribed for rare diseases and for life-saving purposes. According to the DG Binfar officials, the primary off-label use in Indonesia is due to the existence of unregistered, but necessary, drugs, such as sildenafil, as mentioned above. In the case of rare diseases such as Lupus, pharmaceutical companies do not want to register the drug for that specific indication because the use of the drug is very limited due to the small number of cases. There is no incentive for the pharmaceutical company to produce such drugs; thus, going through the lengthy bureaucratic process will not bring it any economic benefit.

“In reality, if there are a lot of consumers, the pharmaceutical company will register its product, and vice versa. For example, for a rare disease, the pharmaceutical company will not register its product for it because the market is limited and not beneficial for them. But, we still market it whether the market is limited or not.” —pharmaceutical company representative

In another case, there was a pharmaceutical company that packed a drug needed in Indonesia, but the company, after packing the drug, sold it to a neighboring country and not to Indonesia.

“For a rare disease, there is a drug named Sinemet® [carbidopa and levodopa] that is packed by Merck Sharp & Dohme Corp. Pharma in Pasuruan, East Java, Indonesia. However, they sell it in Malaysia without prescription and at an affordable price. Then, the question is, why don’t they sell it in Indonesia, where the drugs are needed.” —MOH representative [Sinemet is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.]

To date, the solution for cases such as these is to register those drugs for the SAS, in which the drugs are directly purchased by the government without going through the formal Badan POM process.

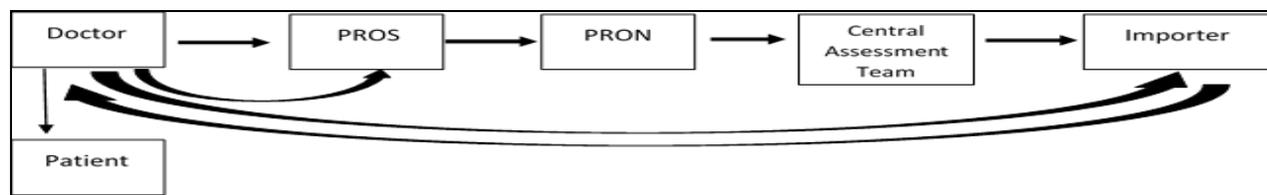
The procurement of drugs through the SAS pathway in Indonesia is regulated by Health Ministerial Decree No. 1379A/Menkes/SK/XI/2002 on the Management and Use of Drugs, Medical Devices, and Special Health Food.¹⁸ The regulation includes drugs, medical devices, and foods that are needed for people but that have no NIE. One such drug is an orphan drug, a drug that is needed only for treating rare diseases (less than 200,000 patients in Indonesia), and so its safety and effectiveness have not been tested and proven. Another is a drug that is needed by more than 200,000 patients in Indonesia and yet has no commercial value.

Patients, who have the right to access the drugs, medical devices, and special health food they need, are divided into two categories (see Figures 5 and 6, and Table 1):

- Category A: patients who are in a terminal state or who have a life-threatening disease; they might pass away after a short time without medical treatment.
- Category B: all patients except those in category A.

There is a Referral Center for Specialist Drugs—*Pusat Rujukan Obat Spesialistik* (PROS)—which has mechanisms for managing the use of drugs, medical devices, and special health foods. The center is usually in tertiary teaching hospitals in all parts of Indonesia. In addition, Rumah Sakit Umum Pusat Dr. Cipto Mangunkusumo hospital and its assessment team act as the national coordinator for PROS.

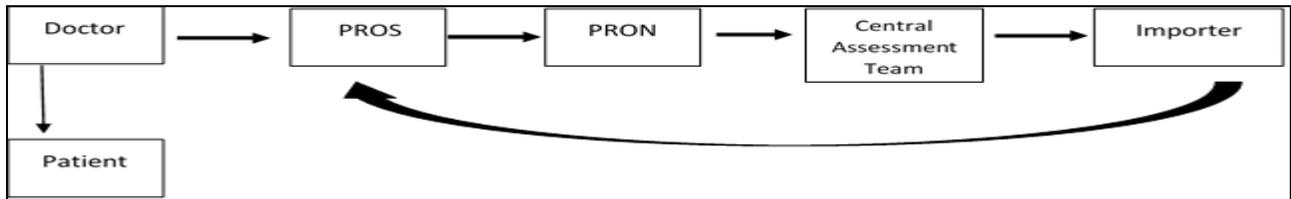
Figure 5. The pathway of drugs, medical devices, and special health food procurement for category A patients.



3

³ Pusat Rujukan Obat Spesialistik (PROS); Pusat Rujukan Obat Nasional (PRON)

Figure 6. The pathway of drugs, medical devices, and special health food procurement for category A patients.



4

Table 1. Procurement of drugs, medical devices, and health food service procedures.

Number	Category A patients	Category B patients
1	Doctor makes patient's condition statement	Patient submits proposal to nearest PROS
2	Doctor asks the informed consent of the patient/guardian	Patient fills the form of drug data that has been Provided
3	Doctor has full authority and no need to ask PROS/PRON for agreement	Patient makes a statement that no conventional therapy can control or treat the condition of the patient's disease
4	Doctor makes a request to importers orally as well as by completing a written request form	Doctor completes the application data with the data of clinical trials up to phase III
5	A copy of the form is submitted to PROS no later than four weeks after the request, with negligence liable to a fine of IDR10 million	Doctor requests informed consent from patients or their guardians regarding the treatment that the drug has not received marketing authorization in Indonesia
6	A copy is sent to PRON and the Central Assessment Team	PROS expert team assess and continue to PRON if it meets the requirements
7	A copy is sent to the importer/distributor	PRON expert team continue the assessment results and send it to the central assessment team
8	Doctors prescribe drugs rationally	Central assessment team assesses and refers the request to the importer
9	The available drug can be taken by the physician or the patient's family to the distributor with a prescription	Importers ship products to PRON based on PROS demand
10		Doctors prescribe drugs rationally
11		The available drug can be taken by the physician or the patient's family to the distributor with a prescription

⁴ Pusat Rujukan Obat Spesialistik (PROS); Pusat Rujukan Obat Nasional (PRON)

Outside of the SAS mechanism, DG Binfar has expressed its receptiveness for input on the drugs needed.

“The physician/patient associations can propose a drug to be included in FORNAS, then we would check the registration number, validity period, drug provider, and local or import. That information can be obtained from Badan POM. Then we will help.” —DG Binfar representative

Additionally, a previous case has allowed an off-label drug to become on-label by following certain steps, as described below:

1. A hospital, physicians’ association, or patients’ association makes a request to the MOH. The pharmaceutical company may not make a request directly to the MOH, in order to avoid conflicts of interest.
2. The MOH, Badan POM, and those who made the request will discuss the proposed drug.
3. The MOH will be willing to give a recommendation to Badan POM about the drug if there is urgent need for a specific indication to treat patients.
4. Pharmaceutical company then formally registers the drug with Badan POM.
5. The National Committee of Drug Assessment in Badan POM will review the proposal and assess the efficacy, safety, and quality of the drug for that specific indication.
6. If it is approved, Badan POM will release the NIE number.

“In a nutshell, the drug provider/company has to submit the information to Badan POM because the registration number is owned by the drug company. And, if in the future Badan POM needs some additional information, the company has to process it.” —MOH representative

Unfortunately, the MOH does not have a comprehensive list of off-label uses in Indonesia. Nevertheless, it has expressed its willingness to facilitate discussions to find solutions to and reforms for the use of off-label drugs in Indonesia.

“The clinical doctor has the authority to use off-label drugs. Therefore, to prepare the regulation related to off-label drugs, discussion with many stakeholders is very important.” —MOH representative

Although the key players in this situation are physicians, there should be a discussion among the MOH, Badan POM, and the physicians’ association related to the development of off-label drug policy.

The perspective of pharmaceutical companies

The representative of the one international pharmaceutical company interviewed stated that the company's head office has regulations in place that require marketed drugs to have been registered in Badan POM and to have an NIE number. There is a possibility that a drug which is registered for five indications with the US FDA has only been approved for two indications in Indonesia. Only those two indications may be marketed/promoted.

“XYZ is a multinational company with headquarters in America and has a branch in Indonesia. As a result, the Indonesian office still adheres to its head office regulations that must be obeyed in all branches. The regulation related to drug usage is clear, indicating that drug promotion to doctors can only be based on the indications approved and registered. Any promotion that isn't based on that is a mistake and in non-compliance.” —pharmaceutical company representative

Promotional materials should be checked and approved by the pharmaceutical company's medical and regulatory divisions before being used, most commonly by medical representatives to approach doctors. In addition, the company informs the medical representatives to avoid off-label marketing.

“If the marketing and sales departments promote the product, then they will print a binder or a brochure—promotional material. Before it spreads widely, we have to check the promotional material through the medical division and continue to the regulatory division. It will be checked whether the indication in the promotional material is in accordance with the indication as approved by Badan POM.” —pharmaceutical company representative

“...When the checking process was completed and done, and we verified that it is suitable, then it can be promoted. So doctors will be just like our representative to communicate with our customers. They will only explain the on-label, not off-label drug.” —pharmaceutical company representative

The pharmaceutical companies, both international and local, know of the practice of using off-label drugs under the clinical direction of physicians. However, if the physicians prescribe off-label drugs without informed consent from the patient, it would be considered “malpractice.”

One international pharmaceutical company in Indonesia had experienced an off-label drug becoming an on-label drug. A representative of the company recounted its experience with sildenafil, which with a dosage of 100mg and 50mg is prescribed for erectile dysfunction, but with a dosage of 20mg is prescribed for PAH. Sildenafil has now been approved by Badan POM for PAH cases with a new name: Revatio® (Revatio is a registered trademark of Pfizer Inc.).

“Known widely, Viagra® is used for erectile dysfunction, while a low dosage of sildenafil called Revatio is used for pulmonary hypertension treatment for children and adults. Both of them have the same ingredients, but each has a different dosage (Sildenafil is 20mg, while Viagra® is 100mg or 50mg). The Ministry of Health invited me to join the Health Technology Assessment (HTA) one and a half years ago. The forum discussed Revatio®. At that time, there was an association of patients with pulmonary hypertension who wrote a letter to the Ministry of Health to ask XYZ to register that product in Indonesia. Fortunately, it has been approved sic by Badan POM.” —pharmaceutical company representative

A detailed breakdown of the process of how off-label sildenafil became on-label Revatio® is as follows:

1. The process began with a request from the Association of PAH Patients to the MOH stating the patients’ need for sildenafil in a different dosage for different indications.
2. They gained support from the Indonesian Cardiologists’ Association, which also sent a formal request to the MOH.
3. The HTA Committee of the MOH also gave its support and recommended that Badan POM examine the case.
4. The pharmaceutical company then registered the drug with Badan POM.
5. In Badan POM, the National Committee of Drug Assessment evaluated the drug. Pharmaceutical companies are required to provide clinical evidence (data on molecular structure, stability, quality, pharmacokinetic properties, clinical testing, etc.). Endorsement was also needed from the physicians’ association (epidemiological data, demographic data).
6. The company gained approval after 18 months of processing.

According to the pharmaceutical company, a request from the patients’ association, support from the physicians’ association, and a recommendation from the MOH are crucial elements in registering an off-label drug for on-label status. In the evaluation process, Badan POM will usually refer the submission to the FDA (US), the European Medicines Agency (EMA), and the TGA (Australia). If the drug with that specific indication has already been registered in those three associations, Badan POM is more likely to approve and release a marketing authorization number for the same specific indication in Indonesia.

“It was the first time to see an active association. They asked the Ministry of Health to provide the drug for them. Since they really need it. Then their request was discussed and followed up by the HTA Committee. However, we do not know if there will be something like that in the future. Since we cannot do it alone.” —pharmaceutical company representative

Representatives of both pharmaceutical companies stated that they will also be protected if there is a policy related to off-label drugs. In addition, the companies will comply and register the drug with Badan POM if there is a request from the MOH or other governmental agencies. Generally, the companies will consider several aspects before registering a drug with Badan POM, prioritizing the issues of the accessibility and safety of the drug and profitability for the company.

The companies disclosed issues that often occur when registering a drug with Badan POM. One of their examples was when the pharmaceutical company provided evidence from clinical studies which demonstrated the effectiveness of “Drug A” during a 30-day therapy. Unfortunately, Badan POM approved the registration for only a 15-day therapy despite the lack of evidence in support of the shorter treatment period. In situations like these, Badan POM receives feedback from the physicians’ association.

“Our principle is, we will produce and fulfill drugs needed in Indonesia. Since that is the most important issue. However, a certain drug is not available in Indonesia while it is available in Singapore, Malaysia, and Thailand. It happened because it has not been approved, and that is our problem. If there is a regulation that permits the industry to submit a list of drugs needed in Indonesia to the Ministry of Health, we can propose it. Then, the Ministry of Health can evaluate it. After being evaluated by an independent team from the Ministry of Health, they can determine the number of indications which have been submitted by the pharmaceutical industry. The result of an evaluation can help the pharmaceutical industry to register the drug to the Food and Drug Administration. Based on the Revatio® case, if there is a need from governments or patients, the process will not take a long time. Therefore, it will be easier for us to provide drugs to patients in Indonesia.” —pharmaceutical company representative

The perspective of physicians

Most of the physicians were not aware of any regulations prohibiting the practice of off-label drug prescription in Indonesia. However, some of them were aware of similar off-label drug policies abroad, such as those of the FDA and the American Society of Health-System Pharmacists in the United States, the EMA in European countries, and the TGA in Australia.

“There is no specific policy about off-label drugs; however, the off-label drug is not allowed to be used, that’s it. In the National Formulary [FORNAS], the indication of drug is stated, so we should comply with that.” —physician

“What I know is that in other countries the off-label drug can become on-label and be approved by the FDA after clinical trials have been conducted.” —physician

The majority of physicians interviewed have prescribed drugs for their patients for different indications than those registered in Badan POM, arguing that it has been in the patients’ interest (only one orthopedist claimed never to have prescribed off-label drugs). The reasons and examples varied greatly; for instance, there are some drugs that are still needed by the patients but are no longer registered, such as hydrochlorothiazide (HCT) and Serpasil™. When registration dates expire for older drugs, pharmaceutical companies are required to reprocess the registration, with the procedures consuming a minimum of six months, therefore leading to a stockout for those six months. Another example is methotrexate, which is in high demand but no longer exists in the market.

The physicians are also aware of the SAS mechanism but know it to be most often used for unlicensed drugs or for drugs that have not yet been registered in Indonesia. However, they agreed that the process is quite complex, which sometimes leads the patients to buy those drugs abroad or to import them themselves.

“A doctor can propose drugs which are not on the list of FORNAS or are a different indication than registered, if they are needed. Should the doctor be able to prove the advantages, the drugs can be used. For instance, the usage of drugs for Hipofisis Tumor can be proposed in certain hospitals. Due to limited availability, sometimes the patient will move to another hospital that permits proposing off-label drug usage. It turns out that there is nothing significantly special about the drugs, and other hospitals can administer the same drugs if they propose the drugs to FORNAS.” —physician

“Not all drugs in Indonesia are registered, especially the lower-cost drugs such as Serpasil™ and HCT. These drugs are not registered, and that means there is no indication, but there is a demand. If the drugs are too cheap, they will become lost from the market, such as HCT, which is called an orphan drug.” —physician

“In the meeting between BPOM and DG Binfar to discuss FORNAS, DG Binfar promised to accelerate and ensure the provision of unregistered drugs, but there is no real action. The example of the drug is methotrexate (MTX)—a cheap cytostatic tablet which is used for rheumatoid arthritis treatment. Cytostatic, which can be used to treat cancer patients, inhibits cell growth (an immunolabulator). It has been several months since it has been lost from the market, but it seems like no one is aware of this issue. If officials know, they will say there is a system for the provision through the SAS, but in reality, no one can use the SAS if there is no import act, and meanwhile the procedure is complex. Sometimes, patients with chronic disease import the drugs themselves. The patients should submit an approval letter to the Minister of Health. The content of the approval letter includes the name of the drugs and the dosage.” —physician

The secondary effect of certain drugs is another main determinant of physicians when prescribing off-label drugs. Additionally, many physicians stated the lack of information on the indications that are registered in Badan POM for certain drugs. Many were unaware that FORNAS has a complete indication list for all drugs registered. Several examples of off-label drug use that have been prescribed by the physicians interviewed are listed in Table 2.

Table 2. Drugs that have been prescribed off-label.

Drug name	On-label indication/route of administration	Off-label indication/route of administration
Asam Valproate	Anti-convulsion	Bipolar disorder
Amitriptyline	Antidepressant	Neuropathic pain
Morphine	Anesthesia	Cancer pain
Sildenafil	Erectile dysfunction	Pulmonary hypertension, with different dosage
Erythromycin	Antibiotic	Prokinetic
Probiotic	Diarrhea	Adjuvant anti-allergic
Insulin	Subcutaneous injection	Topical
Victoza® ⁵	Antidiabetic	Reduced body weight
Tiraks	Thyroid	Reduced body weight
Xenical® ⁶	Heart disease	Reduced body weight
Tramadol	Analgesic	Erectile dysfunction
Misoprostol	Gastric ulcer	Abortion
Metformin	Antidiabetic	Polycystic ovary syndrome
Cyproheptadin	Anti-allergic	Appetite enhancer
Mebendazol	Anthelmintic	Immunomodulator
Domperidone	Anti-nausea	Breastmilk production stimulant

Physicians acknowledged prescribing off-label drugs based on similar practices abroad, which were introduced through workshops, seminars, or international journals. For the use of sildenafil mentioned above, physicians followed the clinical practice guidelines released by their professional organizations (e.g., 2015 European Society of Cardiology/European Respiratory Society Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension). In addition, sometimes the use of off-label drugs is a result of clinical pathway development. Regrettably, there are some clinical practice guidelines that have not yet been approved and released by the MOH.

Unfortunately, there has been no dialogue between regulatory agencies and physicians on the practice of off-label drugs. The physicians suggested a forum to find solutions to this practice for health practitioners in Indonesia. There should be a policy that encompasses some main objectives, such as:

- Developing a clear transition mechanism from off-label drugs to on-label drugs.
- Ensuring the safety of off-label drugs for patients.
- Providing information on the legal aspects for physicians who use their clinical judgment when prescribing off-label drugs.

⁵ Victoza is a registered trademark of Novo Nordisk A/S.

⁶ Xenical is a registered trademark of Genentech, Inc.

In some vertical hospitals where staff members were interviewed (Class A hospitals), there are internal policies related to off-label drug practices. For example, there is a drug for hypophysis tumor that can be prescribed in a tertiary hospital through special approval from its therapeutic and pharmaceutical committee but cannot be prescribed in other hospitals. In addition, there are hospitals with approval from the therapeutic and pharmaceutical committee that then repackage the drug. For instance, a meropenem injection is only available in a one-gram dosage for adults, but when it is needed for children at a dose of 100mg, the hospital repackages the drug from one pack of one-gram to ten packs of 100mg. Prior to this, the hospital conducted a study to ensure that the quality of the drug is the same after as before it is repackaged. Yet this kind of internal policy only transfers the risk of using off-label drugs from the physician to the institution/hospital.

The perspective of patients

Initially, this study did not assess patients' perspectives on the use of off-label drugs, but the literature review that was conducted found a study in India which assessed the awareness and views of parents on off-label drug use in children. The parents were informed of the concept of off-label drugs before being interviewed. The study found that only 30 percent of parents had been aware of off-label drug use in children; 93 percent asked to be informed whenever a doctor prescribed an off-label drug; most of the parents felt that off-label drug use would increase the side effects and that it was illegal to prescribe off-label drugs; and 57 percent would ask for a change to an on-label drug in the case of such prescriptions for their children. Many parents would allow their children to be given off-label drugs in the case of a life-threatening condition (59.8 percent) or in the case of a chronic illness (51.3 percent), but only a few of the parents would allow it when their children were healthy.¹⁹

Discussion

The current situation of off-label drug use in Indonesia

The results of this study revealed that the practice of prescribing off-label drugs is still prevalent in Indonesia, as described from the perspectives of several different stakeholders interviewed in this study (the list of off-label drugs was presented in Table 2). It is probable that the practice of off-label drugs existed long before the implementation of JKN, understandably so due to the lack of FORNAS. At that time, doctors did not have sufficient access to information about the drugs registered by Badan POM according to indication. In the era of Askes, the social health insurance agency for civil servants and pensioners, there was a formulary drug list, Daftar Plafon Harga Obat, covering 16 million people. At that time, price negotiations took place directly between Askes and pharmaceutical companies.

Since the initial implementation of JKN, the government has provided both a drug and an indication list in FORNAS, where doctors across Indonesia can easily access information on all the drugs already registered through Badan POM. With the introduction of FORNAS, the government is advocating for doctors to only prescribe drugs with NIE in accordance with the indication registered for JKN patients.

One of the advantages of FORNAS is that there is a clear guideline on which drugs are categorized as on-label and which are off-label. It helps to ensure the efficacy, safety, and quality of the drugs used, because all the drugs listed in FORNAS are already registered with Badan POM and have a marketing authorization number. The current challenge is to urge more physicians to access and comply with the list of drugs. Perhaps having the drug list with indications on Badan POM's website would be a beneficial supplement to the information on FORNAS. Some of the physicians who are aware that the indication is not registered with Badan POM still use the drugs for other indications because they expect the secondary effect of the drug will support the treatment of their patients. Unfortunately, after more than three years of JKN implementation, Indonesia is missing drug information in the INA-CBG package of hospital claims, making it nearly impossible to track whether JKN patients are treated on- or off-label.

In practice, doctors have the prerogative to prescribe drugs based on their experience and updated knowledge. Advice from their peer group or professional associations, information about new drugs through seminars and conferences, as well as international clinical practice guidelines also influence their drug prescription patterns.

Referring to Table 2, tramadol is an example of a drug that has the same registered indication in Indonesia, the United States, and Europe (Badan POM, FDA, and EMA). It is given as an analgesic (moderate to severe pain), not for treating erectile dysfunction as practiced in Indonesia. Another example is domperidone, which has indication as an anti-nausea in Indonesia. It has the same indication in Europe according to the EMA website, which states that domperidone should only be used to relieve symptoms of nausea and vomiting, that doses and length of treatment should be restricted, and that both should be adjusted carefully by the patient's weight where available for use with children. Domperidone is not

approved in any country, including the United States, for enhancing breast milk production in lactating women—and is not even approved in the United States for any indication at all. Interestingly, not all the off-label drugs in Indonesia are also off-label in other countries. For instance, amitriptyline—which has one registered indication as an antidepressant in Indonesia (Badan POM) and with the US FDA—also has one other registered indication in Europe (EMA). The other indications of amitriptyline are for the treatment of neuropathic pain, prevention of chronic tension-type headaches, and prevention of migraines.

From the Badan POM perspective, only drugs that have obtained an NIE number from Badan POM should be available on the commercial market. From the perspective of the MOH, doctors should only prescribe drugs for indications that are registered with Badan POM. For JKN patients, doctors should refer only to FORNAS for drug prescriptions. To date, there are currently no regulations that prohibit the practice of off-label drug prescriptions in Indonesia.

From the perspective of pharmaceutical companies, they have strict guidelines that avoid directly marketing to or communicating with hospitals or physicians about off-label drug use, although currently Indonesia has no law which prohibits companies from marketing off-label drugs. In European countries, European Union law prohibits companies from promoting off-label drugs due to concerns about the drugs' effectiveness, safety, and cost. Even in the United Kingdom, this European law is incorporated into national law.²⁰ The pharmaceutical companies in Indonesia would also be willing to register off-label drugs as candidates for on-label drugs—if the bureaucracy around registering a drug for an additional indication is simplified, with a reasonable cost and shorter registration process.

Lessons learned from the previous process is that a request from the patients' association (reflecting the need) and support from the physicians' association (in terms of epidemiological data, clinical study results, etc.) are very important in the process of registering off-label drugs to become on-label ones. In addition, the results from an HTA study on certain drugs can also provide the necessary evidence, since Badan POM will only approve a new drug that has strong clinical evidence. The HTA Committee of the MOH can play a role in developing off-label-related policy.

Drawing from the study results, both through interviews and the literature review, some of the reasons for the existence of off-label drugs in Indonesia, and in other countries, are listed in Table 3.

Table 3. Reasons for the existence of off-label drugs.

Perspective	Reason(s) given
Physicians	<ul style="list-style-type: none"> • Off-label drugs may provide the only treatment option for pediatrics, oncology, psychiatry, and palliative care • Off-label drugs allow patients to access innovative and potentially useful new medicines or older medicines for new indications, doses, or routes based on recent evidence
Patients	<ul style="list-style-type: none"> • Patients' best interest
Regulatory agencies	<ul style="list-style-type: none"> • The pharmaceutical companies currently do not pursue registering off-label drugs to become on-label ones
Pharmaceutical companies	<ul style="list-style-type: none"> • No incentive to register new indications: costly and time-consuming

Advantages and disadvantages of limiting off-label drug use

Limiting off-label drug use does have some advantages and benefits. From a healthcare perspective, it can ensure patient safety, since many off-label drugs have no adequate evidence of their clinical effectiveness. In the United States, 73 percent of off-label drug use had little or no scientific support.² A study in India also showed that only 29.3 percent of all physicians who have ever prescribed off-label drugs felt that they had adequate knowledge regarding the use of off-label drugs.²¹ From an economic perspective, the pharmaceutical companies stated that there is no incentive to register an off-label medicine, especially for treating a rare disease or for a low-profit drug. The registration process is costly and time-consuming. In terms of ethical and legal considerations, using off-label drugs without informed consent would be considered malpractice. Thus, limiting off-label drug use can protect doctors from medico-legal problems.

Relating to the ethical aspect of the issue, the Beauchamp and Childress model of modern bioethics indicates that patient–physician relationships should be guided by: (1) beneficence; (2) nonmaleficence; (3) fidelity; (4) justice; and (5) autonomy. Beneficence means assisting others, especially those in danger or disadvantaged. Patients in chronic pain deserve a beneficent relationship with a physician. The use of drugs in off-label practice to relieve pain is essentially intended to be in the patient's best interest. Nonmaleficence means "First do no harm." Physicians are acting with beneficence toward their patients in prescribing an off-label drug to treat pain by ensuring the clinical benefits so that harm to the patient is minimized. Fidelity means trust and honesty in a relationship. Patients place their trust in a physician to act and advise purely based on the patient's best interest. A physician acts as a fiduciary in advising the patients honestly. Justice here is understood as accessibility or availability of technologies to relieve suffering. Autonomy may be viewed from the perspective of a patient, as well as a physician. Patient autonomy means that individual patients may make their own decisions, which must be free from controlling pressures. Autonomy is most often expressed in healthcare through the process of informed consent. Proper informed consent includes communication regarding: (1) medical condition and

prognosis; (2) nature of the proposed intervention; (3) risks, benefits, and consequences of intervention; and (4) available alternatives, including the risk, benefit, and consequences. Physician autonomy implies that, as physicians, they should be able to make medical decisions about a patient's treatment and be free from controlling influences.²²

On the other side, there are also some disadvantages to limiting off-label drug use. Physicians will lose options for giving better or more innovative treatment to patients, especially for the drugs that have evidence of strong clinical effectiveness. It is also considered unethical when knowledge says there is a strong clinical effectiveness for some off-label drugs, but regulatory agencies do not pay much attention to this evidence in the process of transitioning off-label drugs to on-label ones.

The study found that some hospitals had their own policies related to off-label drug practice, such as prescribing off-label drugs with approval from their therapeutic and pharmaceutical committees. Essentially, this kind of internal policy only transfers the risk of using off-label drugs from the physician to the institution/hospital.

It is possible that this practice occurs mostly for non-JKN patients, since only 65 percent of the population is currently covered by JKN, with the remaining population receiving treatment through a fee-for-service payment scheme, such as private insurance or out of pocket. This fee-for-service payment scheme of most non-JKN patients allows for more flexibility for doctors to prescribe up-to-date drugs that have not yet been registered based on indications with Badan POM.

It is essential that the government establishes a monitoring system to capture the practice of off-label prescriptions and provide a conducive forum for enhancing communication between regulators, pharmaceutical companies, physicians, and patients. Physicians expect the regulators to bridge gaps and explore solutions for the practice of off-label drugs in Indonesia. There should also be a forum to accommodate the unmet needs of patients in obtaining the drugs they need. Off-label drug use could be related to several problems, such as safety for patients, costs for society, and legal risk for physicians; therefore, this practice should be used only when the benefit outweighs the risk. By considering the advantages and disadvantages, hopefully this forum can formulate policy mechanisms for off-label drug use in Indonesia.

Nonlegal barriers that inhibit off-label drug use

Currently, there is no law or regulation that prohibits off-label drug use in Indonesia. However, Indonesia has FORNAS, which lists the drugs and their indications as registered with Badan POM. Unfortunately, not all physicians regularly access this list before prescribing drugs for their patients. Moreover, there is no information in the INA-CBG package of hospital claims, making it nearly impossible to track whether JKN patients are being treated with on- or off-label drugs. Thus, only having FORNAS is not enough to inhibit off-label drug use in Indonesia.

Indonesia also has drugs listed under the SAS. These drugs are directly purchased by the government without going through the formal process of Badan POM. Of course, there are also some requirements to allow the drugs to be included under this scheme. The drugs include the orphan drugs, especially ones to treat rare diseases (needed by less than 200,000 patients), and the drugs that have no commercial value but are needed by more than 200,000 patients. Therefore, for these kinds of patient needs, the government already has a special mechanism to provide the drugs.

Increased awareness and knowledge of physicians about off-label drugs also potentially limit their use. When physicians realize that the drug to be used is off-label, they will ask the patient to sign an informed consent form, because they know that without informed consent it would be considered “malpractice.” This awareness will limit physicians who might otherwise easily prescribe off-label medicine.

Policy mechanisms, laws, and regulations for off-label drug use

A policy forum had been held in Indonesia to discuss the laws, regulations, and uses of off-label drugs. It was attended by the relevant stakeholders in Indonesia, including DG Binfar (MOH), DG Health Services (MOH), Badan POM, pharmaceutical companies, physicians, pharmacists, and universities (and observed by a representative from both PATH and the World Health Organization—WHO). At the forum, the physicians admitted to prescribing off-label drugs when necessary and claimed that they were trained to do so. DG Health Services also acknowledged the prevalence of off-label drug-prescribing behavior and received several questions from hospitals on the issue. These and other conditions that were discussed led to consensus among the policy forum attendees over the urgent need to develop a policy mechanism to regulate the use of off-label drugs in Indonesia, despite the challenges that will be faced in formulating the regulation.

DG Binfar expressed its support to enable pharmaceutical companies to register off-label medicines with Badan POM. At this forum, Badan POM also explained that there are three pathways for drug registration: 100-working-days approval (for orphan or life-saving drugs); 150-working-days approval (if the drug is registered in other countries); and 300-working-days approval (if the drug is undergoing parallel registration in other countries). In reality, registration takes longer than this (more than two years), and during that time the United States or other countries may have registered the medicine for one or more other indications. Badan POM cannot push the pharmaceutical companies to register for

more/other indications, since it has a mandate to protect public health, so the agency needs to ensure that the pharmaceutical companies have provided evidence that each drug meets the requirements of efficacy, safety, and quality. However, patients' associations, physicians' associations, and hospitals can request that a pharmaceutical company register one or more indications, as well as ask the MOH to support the registration process. Badan POM and pharmaceutical companies at this forum also raised the issue that the companies often have a patent in other countries for other indications; hence they cannot register those indications in Indonesia.

The forum also agreed on the criteria of off-label drugs that should be prioritized and considered when developing a policy mechanism: the drugs should have been registered in other countries and have strong evidence of clinical benefits. In addition, there was also a suggestion from universities to set up some standard criteria to determine what kind of clinical studies can be used as strong evidence— which led to another ethical issue, the fact that it is unethical when authorities know that certain drugs have strong evidence of clinical benefits but there is no action to formally register those drugs.

Within the limited time available, the forum discussed several options for a policy mechanism that should be chosen by Indonesia and the institution that should be responsible for developing it. DG Binfar has a committee which is responsible for developing FORNAS and deciding which drugs can be included under the SAS, so there is the possibility to include the management of off-label drugs under this DG. On the other hand, the MOH has a clinical advisory committee whose role is to resolve disputes, and its secretariat office is in PPJK, in the MOH, which makes PPJK one of the possible institutions to be responsible for developing the off-label drugs policy mechanism.

At the policy forum, the PATH representative said that due to the lengthy time needed to develop a regulation, the short-term focus should be on getting off-label drugs transitioned to on-label, whereas the WHO representative mentioned that the transition to on-label medicines is a big opportunity but should not be rushed, and instead all issues surrounding it should be addressed properly. Moreover, the question is whether there are enough HTA capacity and resources to support this endeavor. It would be important to look at other factors/justifications (e.g., magnitude of off-label use, health impact, and other issues around universal health coverage considerations). Given this positive progress, there is an urgent need for more evidence to inform policymakers and regulators.

Conclusion

This study concludes that off-label drug prescriptions are practiced in Indonesia, thus there is a call to ensure patient safety by ensuring the safety of off-label drugs, a need for protection for physicians when they are prescribing off-label drugs, and an appeal from pharmaceutical companies for faster and more reasonably priced drug registration. The policy forum that was conducted was successful in raising the issue of off-label drug use and acknowledging the urgent need for a policy mechanism to regulate it, as well as creating consensus over the criteria for off-label drugs that should be prioritized and considered in developing the policy mechanism.

Limiting off-label drug use can offer certain benefits, such as ensuring patient safety, protecting physicians from medico-legal problems, and avoiding economic losses for pharmaceutical companies that may occur when registering drugs for rare diseases. However, limiting off-label drug use can also offer some disadvantages. Physicians will lose options for giving patients better or more innovative treatment, and it is also considered unethical for regulatory agencies to just ignore knowledge of the strong clinical effectiveness of off-label drugs.

There are also some nonlegal factors that affect off-label drug use in Indonesia. One of the issues is that not all physicians regularly access FORNAS. Indonesia also has certain drugs listed under the SAS. If physicians prescribe drugs that are listed in FORNAS and the SAS, it will minimize off-label drug prescriptions. Lastly, raising awareness among physicians about off-label drugs also has the potential to limit the use of off-label drugs.

It is important to note that the findings of this study are limited to qualitative information, providing initial evidence derived from the qualitative assessments. The severity and magnitude of the actual practice of off-label prescription is yet to be captured but should be urgently followed up in further studies. Despite the lack of drug information from hospital claim data, a quantitative study of off-label practices can still be captured through a special assessment by retrospectively tracking back to JKN patients' medical records.

Further studies and evidence is necessary for use by policymakers in developing the most appropriate policy mechanism to be applied in Indonesia. With continued efforts from all stakeholders, hopefully Indonesia can soon adopt a suitable policy regulating the use of off-label drugs.

Suggestions

The vital overarching recommendations are as follows:

- This study suggests that a regulatory agency or university, with the financial support of international health non-governmental organizations, needs to conduct a quantitative study to ascertain the severity and magnitude of the actual practice of off-label prescription in Indonesia.
- There should be a separate study to identify off-label drugs that have strong clinical evidence and that have been registered in other countries for indications for which they currently are not registered in Indonesia. This study can be conducted by the MOH, a university, or other relevant institutions.

Policy recommendations

The vital policy recommendations are as follows:

- The regulatory agencies (MOH and Badan POM) should agree on who will be responsible for all things related to off-label drugs. Based on the policy forum that was conducted, there are two institutions deemed appropriate: PPJK and the Directorate of Pharmaceutical Services (under DG Binfar).
- The chosen institution should start developing a policy mechanism regarding off-label drugs and conduct a policy forum to gain support from relevant stakeholders to finalize any policy related to off-label drugs.
- The regulatory agencies must start identifying off-label drugs that have strong clinical benefits and that have been registered in other countries for indications for which they are currently not registered in Indonesia.
- The list of priority off-label drugs should then be processed following the new policy mechanism to become on-label drugs.

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