



# Oversight of Off-Label Prescriptions: Singapore Developments

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## Definitions and Scope

- OLU: prescribing licensed drug outside approved indication
  - Dosage, route, population, or duration.
- Distinguished from unlicensed/compassionate and research use
- Rationale: innovation, rare conditions, evidence gaps

# Prevalence and Evidence

One US study: ~21% of commonly used medication prescriptions involve OLU; ~79% in paediatric hospital discharged patients

WHO EML: 60% OLU

Most common areas: Infectious diseases (30.5%) and oncology (25.2%)

Evidence for OLU varies: RCTs, other trials with limitations, observational studies, expert opinions to case reports

# Promotion and Scientific Exchange of info

Physicians may prescribe;  
manufacturers cannot promote  
unapproved uses

For e.g., Singapore Association  
of Pharmaceutical Industries  
*Code of Conduct* (2025), Part 3  
prohibits promotion but allows  
scientific exchange of relevant  
information concerning a drug

# Ethical Foundations

Balance beneficence and non-maleficence

Informed consent critical depending on uncertainties involved

Justice concerns: access inequities driven by evidence gaps; funding policies

Professional responsibility: Heightened justificatory burden and documentation when deviating from label.

# Recent Singapore Case Law

- *Ang Yong Guan v SMC* (2024)  
SGHC (Medical professional disciplinary proceedings)
- Patient with a complex orthopaedic/neurological, psychiatric and social history
- Polypharmacy - Court scrutinised multi-drug prescriptions with risk of serious adverse interactions
- High-dose combinations of drugs in excess of label specifications
- Patient ultimately died
  - COD: “multi-organ failure with pulmonary haemorrhage, due to mixed drug intoxication”

*Ang Yong  
Guan v  
SMC*

- Principles articulated:
  - (1) ... once it is proven that a treatment is not indicated for a condition, or a stipulation in a product insert has been departed from, **the evidential burden** shifts to the defending medical practitioner to negative an assumption of inappropriate treatment or otherwise to justify such a departure
  - SMC need not go further to show that each deviation was unjustified, that the risks outweighed the benefits, or that the medical practitioner did not exercise proper clinical judgment.
  - **The burden instead lies on Dr Ang to show the converse.**

*Ang Yong  
Guan v  
SMC*

- Principles:
  - (2) A medical practitioner can justify his departures from the applicable standards of care... if:
    - (a) he has considered the rationale behind that standard and concluded after a **risk-benefit analysis of a prospective departure from it that it is justified**;
    - (b) the medical practitioner's conduct is **objectively defensible in the circumstances**, as determined with reference to the **prevailing test for medical negligence**; and
    - (c) at least in certain circumstances, the medical practitioner has **first discussed a prospective departure with the patient including any safety measures, and the patient must have consented to such a departure.**

# Why an “evidential burden of proof”?

- SMC Ethical Code and Ethical Guidelines (2002) para 4.1.3 - Prescription of medicine
  - A doctor may only prescribe medicines that are legally available in Singapore and must comply with all the statutory requirements governing their use.
  - A doctor shall prescribe, dispense or supply medicines only on clear medical grounds and in reasonable quantities as appropriate to the patient’s needs.
- SMC ECEG (2016) now provides:
  - B5(2) You must prescribe, dispense or supply medicines only on clear medical grounds arrived at through sufficient clinical information and after considering the available evidence and what is accepted by the profession as good clinical practice.
  - B5(9) **If you use “off-label” drugs**, you must ensure that it is in the patients’ best interests, there is rational basis, patients have justifiable medical indications, you have assessed the risks and benefits of such use and patients’ consent to such use has been obtained if they are able to give it.

# Clinical Practice Guidelines: Value and Limits



Presumptive standard of care?



Deviations require justification, but evidence underlying OLU may be conflicting, difficult to access and assess



Evidence gaps and update lag

# “Informed consent”

- Obligation not seen as automatic under the auspices of off-label treatment/separate ethical requirement.
- What counts as information that a reasonable or particular patient would attach significance to?
  - Must the patient be specifically told that a prescription is “off-label”
  - Or do we focus on risks, benefits and the uncertainties involved?
- Would seem to also have to disclose reimbursement implications.

# Beyond professional responsibility

- Patient safety and welfare generally –
  - Studies consistently demonstrate a higher incidence of adverse drug events associated with off-label prescribing.
  - Oncology – may lead to heightened toxicity, increased patient costs
- Public health implications
  - Anti-microbial resistance resulting from off-label use of antibiotics
- Atul Gawande: “Punishment and more training were not going to solve the problem. Instead, you need systems.”

# Policy options for better systems responses

- Evidence-based consensus lists of accepted OLU (central or specialty bodies) to reduce variability and clinician burden.
- Formal expert approvals for specified OLU (French TRU model) with active pharmacovigilance.
- Strengthen post-marketing surveillance (EHR-based sentinel systems) and public trial registration.
- Streamline label expansions for well-supported uses; calibrate reimbursement to evidentiary strength and patient need.

Thank you!

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