# Aligning legislation with clinical practice: off-label prescribing under the microscope

In the United Kingdom, there was much controversy regarding off-label prescribing of bevacizumab for age-related macular degeneration in favour of ranibizumab due to lower cost. The British General Medical Council, which regulates the medical profession in the United Kingdom, advised doctors against off-label use of bevacizumab as doctors should not prescribe unlicensed medicines when licensed alternatives exist, but this advice was criticised for conflating laws designed to regulate drug marketing with those relating to drug prescribing.[1,2] Inevitably, this guidance deterred doctors from using bevacizumab.[3] After years of wrangling, the UK's High Court ruled in favour of the off-label use, noting that the regulator did not have the exclusive authority to determine appropriate uses of medicines.[4]

This episode raises important questions regarding the intersection of therapeutic goods regulation and good medical practice. Therapeutic goods regulation is directed at regulating products and drug sponsors, not clinical practice. As a result, the Therapeutic Goods Administration (TGA) recognises that off-label prescribing does not fall under their jurisdiction.[5] However, as prescription medicines are indispensable tools for physicians, there is inevitably some crossover. This is particularly true when non-clinical factors come into play, such as affordability.[6-8] Off-label prescribing of medicines provides important insights into this intersection as the medicine is approved for a specific use, but not the use for which physicians prescribe them. Surprisingly, despite its ubiquity, the legal status of off-label prescribing has never been analysed in terms of the *Therapeutic Goods Act 1989* (Cwlth) and related instruments.

## General framework and definitions

In Australia, the *Therapeutic Goods Act 1989* and related instruments provide the legal framework for regulation of the movement of therapeutic goods across borders and between entities.[9] Under the Act, unless explicitly exempted (eg, Personal Importation or Clinical Trials schemes) or specifically permitted via an authority (eg, Special Access or Authorised Prescriber schemes), it is a criminal offence and civil contravention to import, export or supply medicines or biologicals not included in the Australian Register of Therapeutic Goods (ARTG).[8] The technical definition of a "therapeutic good" provided for in the Act is broad and includes how the product is represented or likely to be perceived (Box). If a good is represented or perceived to be for therapeutic use, it is a therapeutic good. A "therapeutic use" is a legal phrase with a broad meaning (Box). A medicine used for a different "therapeutic use" to the approved use could be interpreted as a different product and therefore potentially an unapproved medicine. The focus of the analysis in this ethics and law article is Part 3-2 of the Act, which requires all medicines used in Australia to be included in the ARTG unless explicitly exempted or excluded. Specific and general offences relating to the use of unapproved medicines are also described in Part 3-2 of the Act.

## Off-label medicine uses are legally distinct from their on-label use

Section 16 of the Act describes the grounds on which a therapeutic good is considered "separate and distinct from other therapeutic goods". Seven distinguishing characteristics are specified, the most relevant for our purposes being "different indications" or "different directions for use". This means that when a medicine is prescribed for an indication not listed in the ARTG (ie, off-label), it would be considered a distinct and unapproved therapeutic good. Medicines can be used despite not being included in the ARTG, either via an exemption or issuing of an authority to use non-ARTG medicines, as provided by certain provisions in the Act (see ss18, 18A, 19, 19A), which are elaborated on in the relevant sections of the Therapeutic Goods Regulations 1990. These provisions make no mention that off-label uses of medicines, or practices that could be interpreted as such, are exempted therapeutic goods. It follows that offences relating to importing, exporting or supplying unapproved therapeutic goods described in Part 3-2 are applicable to off-label medicines (see ss19B, 19D).

The TGA may interpret off-label uses as unapproved therapeutic goods and this is apparent in their guidance regarding clinical trials.[10] On their clinical trials website, it is stated that "therapeutic goods already included in the ARTG to be used in a manner not covered by the existing entry" would be deemed an unapproved therapeutic good. This guidance appears to be based on the provisions of s16, and therefore is also applicable outside of the clinical trial context.

## Supply of off-label medicines

The Act includes offences for importing, exporting, manufacture and supply of unapproved products but, for our purposes, the most relevant provisions relate to "supply" of therapeutic goods. "Supply" is broadly defined in the Act and includes virtually any form of exchange with another person, whether for money or as a gift, or for the purposes of treatment or advertisement (eg, samples) (Box). It also includes "supply by way of administration to, or application in the treatment of, a person". This means doctors who administer off-label medicines would be contravening the Act, but "supply" does not seem to extend to prescribing medications. On the other hand, a pharmacist who was to supply a medicine based on an off-label script would have contravened the Act. Importantly, these violations do not apply to individuals who do not qualify as a "sponsor", and somewhat paradoxically, persons who supply medicines do not qualify as a sponsor (Box). Therefore,

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**Key technical definitions from the *Therapeutic Goods Act 1989* (Cwlth)**

| Term | Definition |
|---|---|
| Therapeutic goods | Therapeutic goods means goods:<br>(a) that are represented in any way to be, or that are, whether because of the way in which the goods are presented or for any other reason, likely to be taken to be:<br>(i) for therapeutic use; or<br>(ii) for use as an ingredient or component in the manufacture of therapeutic goods; or<br>(iii) for use as a container or part of a container for goods of the kind referred to in subparagraph (i) or (ii); or<br>(b) included in a class of goods the sole or principal use of which is, or ordinarily is, a therapeutic use or a use of a kind referred to in subparagraph (a)(ii) or (iii); and includes biologicals, medical devices and goods declared to be therapeutic goods under an order in force under section 7, [additional clauses follow that describe goods which are not considered therapeutic goods (eg, "excluded goods") but are not relevant for our purposes]. |
| Therapeutic use | Therapeutic use means use in or in connection with:<br>(a) preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in persons; or<br>(b) influencing, inhibiting or modifying a physiological process in persons; or<br>(c) testing the susceptibility of persons to a disease or ailment; or<br>(d) influencing, controlling or preventing conception in persons; or<br>(e) testing for pregnancy in persons; or<br>(f) the replacement or modification of parts of the anatomy in persons. |
| Sponsor | Sponsor, in relation to therapeutic goods, means:<br>(a) a person who exports, or arranges the exportation of, the goods from Australia; or<br>(b) a person who imports, or arranges the importation of, the goods into Australia; or<br>(c) a person who, in Australia, manufactures the goods, or arranges for another person to manufacture the goods, for supply (whether in Australia or elsewhere);<br>(d) but does not include a person who:<br>(e) exports, imports or manufactures the goods; or<br>(f) arranges the exportation, importation or manufacture of the goods;<br>(g) on behalf of another person who, at the time of the exportation, importation, manufacture or arrangements, is a resident of, or is carrying on business in, Australia. |
| Supply | Supply includes:<br>(a) supply by way of sale, exchange, gift, lease, loan, hire or hire-purchase; and<br>(b) supply, whether free of charge or otherwise, by way of sample or advertisement; and<br>(c) supply, whether free of charge or otherwise, in the course of testing the safety or efficacy of therapeutic goods in persons; and<br>(d) supply by way of administration to, or application in the treatment of, a person. |

Source: *Therapeutic Goods Act 1989*.[9] ◆

while supply-related offences exist, they do not seem enforceable, and therefore not relevant for off-label prescribing.

## Use of off-label medicines

The Act also addresses offences related to the "use" of unapproved therapeutic goods. The relevant "general criminal offences" are described in s21A. Accordingly, if a person uses a therapeutic good in the treatment of another person, and the good is not included in the ARTG (such as an off-label use) or otherwise exempted from Part 3-2 of the Act, then the person has committed an offence. A strict liability offence also exists, meaning that no proof of fault is required, and the offender cannot make a defence on the grounds they made an honest and reasonable mistake.[11] The word "use" is, however, not specifically defined by the Act. The closest defined phrase is "therapeutic use", which includes the "use" of medicines "in connection with … preventing, diagnosing, curing or alleviating a disease". As prescription medicines cannot be used without a valid script, the act of prescribing seems to be circumscribed by this definition (Box).

## Improving alignment

Legislation can have a powerful influence on prescribing practice, both directly and via its downstream consequences. Most notably, the designation "off-label" can limit access to necessary treatments as such uses cannot generally be subsidised by the Pharmaceutical Benefits Scheme.[12] This is one of the motivations behind the TGA's recently launched Medicines Repurposing Program, which aims to make important public health related off-label uses, on-label. Pertinently, in defending its position proscribing the off-label use of bevacizumab for age-related macular degeneration, the British General Medical Council noted it could not recommend practices that are illegal, with the chief executive stating that "[t]he crucial factor is that our guidance must be lawful, and the law on this matter is unequivocal".[1] Although it is difficult to fathom therapeutic goods legislation being used to prosecute Australian doctors that prescribe off-label, the practice may be interpreted as illegal, at least in some circumstances, and this is a major oversight given how ubiquitous off-label prescribing is and the TGA's firm position against intervening in clinical practice.[5]

To align legislation with clinical reality, Schedule 5 or 5A of the Therapeutic Goods Regulations 1990 should be modified. These schedules explicitly set out products and scenarios where medicines are exempted from the registration requirement (via s19 of the Act). For example, medicines imported by patients from abroad (Schedule 5, Item 1), medicines compounded for use in hospitalised patients

(Schedule 5, Item 6A), and medicines used solely for experimental purposes in clinical trials (Schedule 5A, Item 3), are all exempted — with caveats — from inclusion in the ARTG via these schedules. The addition of an item that exempts medicines prescribed off-label by medical practitioners when used for treatment of another person (ie, not experimental purposes) in accordance with good medical practice would be sufficient to address any ambiguity.

## Conclusion

The governance frameworks for therapeutic goods and clinical practice should operate harmoniously to enable physicians to serve their patients' needs. Off-label medicines have existed in an administrative grey zone between approved and unapproved products since the advent of modern medicines regulation, yet it is an essential and ubiquitous part of clinical practice. This analysis, inspired by the bevacizumab case in the United Kingdom, is the first to investigate the status of off-label prescribing by direct reference to Australia's therapeutic goods legislation. It found that the legislation defines an off-label medicine as a distinct and unapproved therapeutic good and therefore offences related to the use of unapproved goods would apply. While the focus of this work was on sections of the Act that deal specifically with non-biological medicines, equivalent provisions exist for biologicals and the reasoning can also be extended to their off-label use. A simple amendment that could remedy this inconsistency is proposed.

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