

Pharmaceutical Use Outside of Approved Indications

Guidance on “Off-label” Prescribing

Department of Veterans Affairs (VA) Center for Medication Safety
And Veterans Health Administration (VHA) Pharmacy Benefits Management Strategic Healthcare Group and the VA
Medical Advisory Panel

Executive Summary

1. Prescribing that is outside approved indications by the Food and Drug Administration (FDA) is often referred to as “off-label” use.
2. This often involves use outside of specified populations, or in different diseases or stages of diseases. Other types of off-label use may involve changes to dosing or dosing schedules or in chronology and sequence of use of pharmaceutical agents.
3. Familiarity with the evidence before using a drug off-label is important since there is heightened concern when there is little or no supporting evidence of benefit or safety in a population or for a condition.
4. When considering or reviewing off-label use, whether from an individual or institutional perspective, an evidence-based approach similar to the principles elucidated by the United States Preventive Services Task Force is recommended (see Appendix 1).
5. Evidence of benefit (and importantly, risk) should be explicitly reviewed in the context of standard therapies for the population or condition and recommendations for (or against) use should be based on the quality of evidence as well as the net benefit (potential benefits minus potential harms) [see Appendix 1]. Selective use of studies to support a position is strongly discouraged and in the event of a negative outcome, may not withstand the rigor of a thorough peer review.
6. Since off-label use occurs with non-formulary as well as formulary drugs, clinicians must be aware of their own prescribing practices. When prescribing outside of FDA indications, it is recommended that clinicians understand and follow local protocols and procedures, for example from their Pharmacy & Therapeutics (P&T) Committees. In these cases, the burden of responsibility rests with the prescriber.
7. Consultation with local VA P&T Committees is recommended for agents that do not already have established protocols for off-label use.
8. Pharmacy & Therapeutics Committees are responsible for considering effectiveness, equity, safety, and outcomes – and as a secondary point, cost – when making decisions about pharmaceuticals. As such, these Committees may approve or disapprove requests, based on the level and quality of evidence, in the context of local policies and procedures.

Background

Off-label use refers to a range of prescribing that is outside approved indications by the Food and Drug Administration (FDA). This may involve areas such as bioequivalence (e.g. generic products or modified-release dosage forms), dosing (e.g., above maximum or subtherapeutic), dosing schedules (e.g., using more often than approved), dosing regimens (e.g., using a drug approved for combination therapy as monotherapy) or chronology (e.g., using an agent as first line therapy instead of its approved second line usage). More often, off-label use refers to utilization outside of specified populations (e.g., by gender or age or weight) or in different diseases (or stages of diseases) than originally approved.

Benefits of therapies should not be assumed across populations or for conditions even when there exists plausible epidemiological evidence, biological plausibility or cohort studies – all of which contributed to use of hormone replacement therapy in women prior to the randomized trial that outlined the potential hazards [Women’s Health Initiative, 2002]. With emerging drug therapies, especially, it is important that safety be addressed explicitly. A frequent assumption is that a product is as safe in one population as another; without considering possible drug-disease interactions and/or to possible lower efficacy rates. For example, beta-carotene is relatively harmless in the general population yet it appears to increase the risk of lung cancer in heavy smokers [Alpha-Tocopherol, Beta-Carotene, 1994; Omen 1996]. Hence, just as efficacy and effectiveness of a medication cannot necessarily be extrapolated to new indications or uses, the safety of pharmaceuticals should not be considered constant across diseases or populations.

In general, off-label use becomes a heightened concern when there is little or no supporting evidence of benefit or safety in a population or for a condition. This may occur, for example, soon after a new drug is released and/or when marketing is expanding ahead of published evidence. Under these circumstances, both the risks and benefits of utilization become more difficult to gauge. Hence, new evidence concerning emerging off-label use of a drug must be viewed in the context of standard therapies for a disease or population since these often have far more data on effectiveness and safety. In some instances, older drugs may be prescribed for newer (off-label) uses and while there may be relatively reassuring data on safety, there is often little on efficacy or effectiveness for the proposed use.

Overall, thoughtful and evidence-based use of medications is good clinical practice. This is true for all medication use, whether used within or outside of approved FDA indications, especially because FDA labeling and indications depend on submissions and requests to (and from) that agency. Contemporary prescribing must also consider new evidence as well as data that may or may not have been submitted to the FDA. Also, when the FDA approves a drug, it typically considers safety in relationship to the approved indication and other therapies. For instance, when a drug is approved as a second or third alternative, or for a relatively serious medical condition, a more significant side effect profile may be acceptable even though it would not be so for a less serious situation, or for first line therapy. These issues must be kept in mind when considering and reviewing off-label use of pharmaceuticals.

Focus

The following guidance applies to issues outside of bioequivalence and modified dosing forms, for which use, unless stated otherwise for a particular drug, is generally considered standard practice.

Goals

The Center for Medication Safety in conjunction with the Pharmacy Benefits Management Strategic Healthcare Group and its Medical Advisory Panel outline below the general principles and recommendations when considering pharmaceutical use outside of approved dosing, chronology, disease or disease stage or populations.

Our intention is to offer an educational and dynamic document to assist healthcare providers, as well as Pharmacy & Therapeutics (P&T) Committees and other policymakers, to better understand and oversee “off-label” use and to use principles of evidence-based medicine, as described in Appendix 1, in reviewing such use.

General Principles

1. First and foremost, pharmaceutical prescribing should be evidence-based, whenever possible (i.e., when sufficient evidence exists for a robust review).
2. The ultimate responsibility for the safety and efficacy of off-label prescribing resides with the prescriber. He/she should be familiar with the evidence of benefit and with the safety profile before using a drug. He/she should know and understand local protocols for use of the agent or consult with local pharmacist.
3. Consultation with the VA P&T Committee is recommended for agents that do not already have established protocols for off-label use.
4. Proper assessment of evidence for off-label use should involve as comprehensive and balanced review as possible and feasible. A review of available scientific literature, with assessment of study quality and net benefit, is necessary, to better understand safety and efficacy. Evidence should be viewed in the context of other more standard therapies. Selective use of studies to support a position is strongly discouraged and in the event of a negative outcome, may not withstand the rigor of a thorough peer review.
5. Pharmacy & Therapeutic Committees, as agents of an institution, and pharmacists can and should assist clinicians, when requested, to assure effective (and cost-effective) and safe use of medications, as substantiated by scientific evidence.
6. Clinicians may request review by Pharmacy & Therapeutics Committees for off-label use, but equally so, the P&T Committee may ask the requestor to provide evidence of benefit and safety for requests as part of the review process.
7. Pharmacy & Therapeutics Committees are considered the arbiters of such matters and have the right to approve or disapprove submitted requests, based on the merit of scientific evidence and on local policy and procedures.

General Recommendations:

An evidence-based approach that underscores evidence assessment, such as that used by the United States Preventive Services Task Force [Harris, 2001], is recommended when prescribing or when reviewing requests for off-label use. Some pharmaceutical references summarize existing evidence (e.g., Facts and Comparisons <http://www.factsandcomparisons.com/> or MICROMEDEX) and these may be helpful, depending on the circumstances. One method to provide context on risk and benefit is to assess number needed to treat (NNT) for specified end point(s) and number needed to harm (NNH) for specified adverse events. The American College of Physicians' Journal Club defines various terms and definitions, including NNT and NNH, at <http://www.acpj.org/shared/glossary.htm>.

If a medication's efficacy or safety profile is relatively unknown or cannot be quantified, or if new data are emerging that suggest possible adverse effects that were previously unknown or unclear, then providers and overseeing Pharmacy & Therapeutics committees should be very wary of use. In certain circumstances, use may reasonably be subject to additional stipulations from P&T Committees (see under, **Other Issues**, below). As with any pharmaceutical use, on or off label, local formulary and non-formulary policies and approvals procedures should apply.

Note that the examples that follow should be considered illustrative and not definitive statements, since information and evidence change constantly.

1. Off-label use is appropriate when there exists properly conducted scientific studies of high quality and of sufficient size to firmly establish risks and benefits of therapy, as described by the United States Preventive Services Task Force (USPSTF, see Appendix 1), for the disease and/or population. In practical terms this means a Level of Evidence I (high-grade evidence linked to a health outcome), with a substantial or moderate net benefit, that reaches a Strength of Recommendation of A (strongly recommended) or B (may be useful). Criteria for use and for approval are at the discretion of local Pharmacy & Therapeutics Committees, unless stated otherwise.

An example would be use of spironolactone for reducing mortality in advanced systolic heart failure (level I evidence) [Pitt, 1999]. The use of spironolactone in this circumstance yielded moderate net benefit on an important health outcome and would receive a strength of recommendation of B.

2. Off-label use may be appropriate when there exists Level II-1 (high-grade evidence linked to an intermediate outcome), or Level II-2 or II-3 evidence (moderate evidence linked to a health outcome), with small to substantial net benefit, leading to a Strength of Recommendation of B (may be useful) or perhaps C (intervention may be considered) [Appendix 1]. Typically, such a recommendation either requires multiple sources of (consistent) moderate level evidence in order to quantify the anticipated benefits and possible adverse effects of therapy or, in some cases, small randomized control trials with an important health outcome (Level II-1) to substantiate the request, though the strength of recommendation tends to be relatively weak (e.g., a “C”). Further consideration may be given if the designated use is documented in standard resources or references. These may include but are not necessarily limited to: (a) general or specialty specific textbooks, (b) standard drug references such as MICROMEDEX®, Drug Facts and Comparisons, United States Pharmacopeia Dispensing Information, or American Hospital Formulary Service Drug Information, (c) review papers from widely recognized or specialty-specific peer review journals; (d) properly conducted meta-analyses and evidence based medicine reviews (e.g., Cochrane Collaboration) or (e) locally approved guidance such as a pre-approved protocol by an institution’s P&T Committee; or (f) within VA (or VA/DoD) Guidelines. Again, criteria for use and for approval are at the discretion of local Pharmacy & Therapeutics Committees, unless stated otherwise.

An example is use of pramipexole for restless legs syndrome, as noted in MICROMEDEX®, with 2 open label trials (Becker, 1998; Lin, 1998 [total of 35 participants]) and one randomized double blind trial (Montplaisir, 1999 [10 participants]) providing fair evidence (Level II-1) of small to moderate benefit. This would provide a recommendation of B (or perhaps C) but in considering use, this must be balanced against a safety profile that includes case reports of sudden onset of sleep during daily activities [per package insert]. In this case, pramipexole may be considered, though perhaps not as first-line therapy, on a case-by-case basis, if reasonable clinical rationale can be provided.

Another example is use of modafinil for fatigue associated with Multiple Sclerosis. Evidence of small to moderate net benefit was demonstrated in a small (n = 72) prospective, single blinded (patient only) study, with phased placebo and titration design [Rammohan, 2002]. Per Appendix 1, an assessment yields a Level of Evidence of II-1, with small to moderate net benefit and hence at best a recommendation of B. As with the case above, use may be considered, though perhaps not as first-line therapy, on a case by case basis if reasonable clinical rationale can be provided

3. Off-label use should be far more cautionary, and appropriateness is less clear, where there exists Level III evidence (no linkage to health outcomes) or Level IV (insufficient evidence) without any of the resources or references above. In considering use, there should still be some supportive evidence of net benefit available such as case reports, abstracts from national or international conferences, small studies of some scientific merit or studies that include a selected subpopulation and where extrapolation to the population at hand may be relevant due to, for example, biological plausibility. At best, these situations give a graded recommendation of Insufficient Evidence (I). Importantly, safety should be addressed as explicitly as possible since there exists the potential to do harm. Use may also be considered under very selected circumstances, such as when no other option exists or when theoretical reasoning is compelling (for example, when an argument can be made for extrapolating results from one population to another or when based on pathogenesis of a disease). In general, providers should not utilize pharmaceuticals under these circumstances without prior P&T assessment and approval (or precedent for such). Moreover, when requests are sent to P&T, these should typically be reviewed on a case-by-case basis and be subject to one or more stipulation, as described below.

An example would be using alendronate in 1997 for treating osteoporotic vertebral fractures in men who did not respond to standard therapies. Although early studies were done in women [Black 1996], other studies using this drug, for Paget’s Disease, had included men [Reid, 1997], and there was some anecdotal data on use of etidronate in men with osteoporosis, and hence it would not have been unreasonable to consider such off-label use for selected patients who had exhausted other standard modalities of treatment. A similar, more contemporary, situation arises for tegaserod in men with constipation-predominant irritable bowel syndrome; here again primary studies have focused on women [Novick, 2002].

4. Off-label use is generally not appropriate when only (expert) opinion is provided, without any substantiating evidence on a disease or an intermediate outcome for that disease. At best this represents a

grade of Level I (insufficient evidence), and it is important to note that in such cases harm is always possible.

Examples of inappropriate off-label use include using bosentan in patients with pulmonary arterial hypertension due to chronic obstructive lung disease, since these patients were excluded in the seminal study [Rubin, 2002] or requests for gefitinib in patients who do not have non-small carcinoma of the lung (e.g. adenocarcinoma of unknown origin) or as an adjunct to standard chemotherapy regimens for potential survival benefit (rather than for palliation after standard regimens have failed) [Kris, 2003; <http://www.fda.gov/cder/drug/infopage/iressa/iressaQ&A.htm>].

5. Off-label use is clearly not appropriate when there exists a Recommendation of D (possible harm) or when seminal studies suggest no benefit to the population or disease specified, which differs from situations when there is no or little evidence of benefit due to lack of appropriate studies.

An example would be use of interferon gamma-1b for interstitial pulmonary fibrosis, which in the seminal study showed no net benefit to progression free survival or quality of life or pulmonary function (Level I evidence, strength of recommendation D). [Raghu, 2004]. Note that this would take precedence over an earlier, small, open label cohort study [Ziesche, 1999] that suggested a possible benefit. Another example would be use of gabapentin for mood disorders, again a situation where early reports were promising but further studies failed to suggest substantive net benefit [Backonja, 1998].

Other Issues

1. Off-label use may be entirely appropriate in many situations, but when sufficient evidence from properly conducted randomized control trials is not available to justify efficacy/effectiveness and/or safety, additional requirements or stipulations are reasonable, at the discretion of the local P&T Committee. As a general rule, the stipulations and requirements should become more stringent as the benefits (e.g., NNT) and the harms (e.g., NNH) of therapy become more difficult to quantify. Examples of such stipulations and requirements may include:
 - a. A pre-determined therapeutic trial of clinically reasonable duration with a specified follow-up period and/or specified outcome.
 - b. Development of criteria for subsequent utilization and monitoring.
 - c. Documentation in the medical record by the requestor or delegate that a conversation on risks and benefits has taken place with the patient (or designated caregiver, as appropriate) and that the patient or caregiver understands that the drug has not been studied and/or approved for use in the proposed manner and that he/she accepts the attendant risks. For example, "I have discussed the risks and benefits with this patient and he/she agrees with the use of this agent, even though it has not been studied and/or approved for the proposed use."
 - d. Formal informed consent protocol document signed by the patient or caregiver prior to use (this protocol should be utilized rarely and generally only when there is the possibility of a life or organ threatening safety issue connected with use of a drug).
 - e. Referring the matter to the local Research & Development Service as possible investigational therapy (Note that this should be a very rare occurrence. The FDA policy on referral to an institutional review board is provided in Appendix 2).

Appendix 1

Determining Evidence Levels and Strength of Recommendations

The following evidence grading and assessment scales are based on those used by the VA National Clinical Practice Guideline Council. This method is very similar to that used by the U.S. Preventative Services Task Force (<http://www.ahrq.gov/clinic/3rduspstf/ratings.htm>). In general, assessments should be guided by as comprehensive a review of the available literature as possible and not selective interpretation of individual studies.

Further discussion of methods can be found at <http://www.ahrq.gov/clinic/ajpmsuppl/harris1.htm>. In addition, other resources for reference and tutorials include Cochrane Collaboration (<http://www.cochrane.org/index4.htm>), the American College of Physician's <http://www.acponline.org/sci-policy/guidelines/?hp> and the University of Toronto's Centre for Evidence Based Medicine (<http://www.cebm.utoronto.ca/>).

Assessment and grading of evidence and benefit is as follows:

1. Assess overall quality of evidence using the terms shown in Table 1.
2. Assess the net benefit (benefits minus harms) "substantial," "moderate," "small," or "zero or negative" as described in Table 2.
3. Based on ratings of the overall quality of the evidence and the magnitude of net benefit, grade the recommendation using the grid in Table 3 (Level of Recommendation)

TABLE 1: Overall Quality

I	High grade evidence (I or II-1) directly linked to health outcome
II	High grade evidence (I or II-1) linked to intermediate outcome or Moderate grade evidence (II-2 or II-3) directly linked to health outcome
III	Level III evidence or no linkage of evidence to health outcome
IV	Insufficient Evidence

Definitions

I: Evidence obtained from at least one properly randomized controlled trial.

II-1: Evidence obtained from well-designed controlled trials without randomization.

II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

II-3: Evidence obtained from multiple time series studies with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III: Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

TABLE 2: Net Benefit of the Intervention

Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering – or - A large impact on an infrequent condition with a significant impact on the individual patient level.
Moderate	A small relative impact on a frequent condition with a substantial burden of suffering - or - A moderate impact on an infrequent condition with a significant impact on the individual patient level.
Small	A negligible relative impact on a frequent condition with a substantial burden of suffering - or - A small impact on an infrequent condition with a significant impact on the individual patient level.
Zero or Negative	Negative impact on patients - or - No relative impact on either a frequent condition with a substantial burden of suffering - or - An infrequent condition with a significant impact on the individual patient level.

* generally this is in comparison to established standards (and/or placebo, when there is no comparison to other standard therapies)

TABLE 3: Determine Level of Recommendation

<i>Quality of Evidence</i>	<i>The net benefit of the intervention</i>			
	Substantial	Moderate	Small	Zero or -
I	A	B	C	D
II	B	B	C	D
III	C	C	C	D
IV	I	I	I	D

Definitions

- A A strong recommendation that the intervention is always indicated and acceptable
- B A recommendation that the intervention may be useful/effective
- C A recommendation that the intervention may be considered
- D A Recommendation that a procedure may be considered not useful / effective, or may be harmful.
- I Insufficient evidence to recommend for or against the intervention

Appendix 2

U.S. Food and Drug Administration

INFORMATION SHEETS

Guidance for Institutional Review Boards and Clinical Investigators

1998 Update

"Off-Label" and Investigational Use

Of Marketed Drugs, Biologics, and Medical Devices

"Off-Label" Use of Marketed Drugs, Biologics and Medical Devices

Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgement. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner when the intent is the "practice of medicine" does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB). However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight.

Investigational Use of Marketed Drugs, Biologics and Medical Devices

The investigational use of approved, marketed products differs from the situation described above. "Investigational use" suggests the use of an approved product in the context of a clinical study protocol [see 21 CFR 312.3(b)]. When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an IND or IDE may be required. However, according to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does not require submission of an IND if all six of the following conditions are met:

- (i) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
- (ii) it is not intended to support a significant change in the advertising for the product;
- (iii) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- (iv) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
- (v) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and
- (vi) it does not intend to invoke 21 CFR 50.24.

For additional information on whether or not an IND or IDE is required in a specific situation, contact:

For DRUG PRODUCTS contact:

Drug Information Branch (HFD-210)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
301-827-4573

For a BIOLOGICAL BLOOD product, contact:

Office of Blood Research and Review (HFM-300)
Center for Biologic Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852
301-827-3518

For a BIOLOGICAL VACCINE product, contact:

Office of Vaccines Research and Review (HFM-400)

Food and Drug Administration
8800 Rockville Pike
Bethesda, Maryland 20892-0001
301-827-0648

For a BIOLOGICAL THERAPEUTIC product, contact:
Office of Therapeutics Research and Review (HFM-500)
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852-1420
301-594-2860

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