

## Off-label (unlabeled) Use of Drugs

**O**ff-label use of drugs is widespread and unavoidable, especially when treating the young, the pregnant, the old and those with cancer. Some of the most striking advances in dermatology have followed the off-label use of drugs. This review examines some of the issues surrounding off-label use of drugs by dermatologists, illustrates the need for such use and looks at possible changes in the regulatory system.

### *Off-label use of drugs is widespread*

Under the Federal Food, Drug, and Cosmetic (FD&C) Act, the labeling approved by FDA for a drug is limited to those uses for which the sponsor has submitted information regarding the safety and efficacy of that product and which information has been reviewed by the FDA; other uses for which the sponsor has chosen not to submit data to the FDA may be demonstrated in the clinical literature before and after the product is approved by the FDA. The FD&C Act does not, however, limit the manner in which a clinician may use an approved drug.<sup>1</sup>

*Dermatologists, like other physicians, face a dilemma when attempting to use only drugs with regulatory body approved indications. Neither industry or regulators want to be accused of experimenting on children, pregnant females or old people!* In pediatrics, only about 20% of all drugs marketed in the US have been labeled for use by infants and children<sup>2</sup>, such an exclusion results in widespread off-label use.<sup>3,4</sup> One study found that in 36% of 707 admissions, children received one or more courses of an unlicensed or off-label treatment.<sup>3</sup> In 731 pregnant patients, 23% took

more than one drug for off-label indications.<sup>5</sup> Many drugs used in oncology<sup>6</sup> and drugs prescribed for pain relief<sup>7</sup> also have off-label uses.

### *Delays in obtaining supplementary indications cause problems*

*Delay, hesitancy or indecision by regulatory bodies in granting a drug supplementary approval, after it has been peer-reviewed and proven to be clinically effective and safe, results in widespread off-label prescribing and a very frustrated profession. Some examples illustrate this point:*

- Several years delay in granting minoxidil approval for treating male-pattern baldness resulted in illicit importing, off-label prescribing and instances of faulty extemporaneous compounding.
- Methotrexate was found to be of benefit in the treatment of psoriasis, but approval was delayed and it was prescribed off-label for several years.

During the period that a new drug is passing through the bureaucratic maze, opinion provided by recognized authorities, and/or treatment protocols generated by expert panels, sometimes recommend the use of the drug for a new indication. Such direction provides support to the dermatologist or physician prescribing the drug for this new indication.

It is worthwhile understanding what happens next. This new, unapproved use, after discussion at clinical meetings, publication in journals and acceptance by a cross-section of authorities with a special interest in the field, is found to be of great benefit to patients, leading to widespread acceptance by the profession and listing in peer-reviewed publications such as the USPDI<sup>8</sup> and the AHFS.<sup>1</sup>

## **Practical implications**

FDA approved drugs for off-label indications, and unlabeled drug uses, have played a significant role in the way in which we treat skin disease. A good example is the use of thalidomide to treat the cutaneous manifestations of erythema nodosum leprosum, first reported in 1965, recommended by the WHO in 1988 and finally approved by the FDA in September 1997.<sup>9</sup>

If the unlabelled use of a drug is for treatment rather than research, this constitutes *innovative therapy* and appears to be within the physician's ethical and legal prerogative supported by FDA regulations, common law, and ethical cannons.<sup>10</sup> Although the off-label use of a drug is not necessarily an improper use of the drug, there is no regulatory body approved information on risk/benefit available. In this situation, the prescriber has to utilize consultation with colleagues, plus information gained from the package insert and a review of the medical literature.<sup>11</sup> The ethical and legal implications of this situation are not always clear. Although no specific informed consent appears to be required, unlabelled drug use best serves the patient and protects the physician from liability when it is accompanied by informed consent that adequately informs the patient of the innovative nature of the therapy together with the greater uncertainty of risk.<sup>10</sup> As recent well-known cases have shown, extra care must be taken to ensure that the physician and the patient are both well-informed of the risks and benefits, so their collaboration can result in the best possible clinical outcome.<sup>12</sup>

*Ultimately, regardless of the legality of unlabelled drug use, if an approved drug is used for unlabeled purposes, a physician should carefully weigh the risk/benefit of the use of the drug before, during and after treatment.*<sup>10</sup>

## **The position of the FDA is challenged**

The FDA's long-standing policy prohibiting drug companies from distributing information to physicians about off-label use of drugs or devices, or those applications outside the use specifically approved by the FDA, was recently overturned by a federal judge (July 30, 1998).<sup>12,13</sup> In the judge's opinion, the FDA cannot prevent manufacturers from distributing articles or portions of studies on unapproved uses published in a bona fide, peer-reviewed professional

journal; cannot block drug or device makers from distributing textbooks from independent publishers, and cannot prevent industry from suggesting content or speakers to independent program providers putting on continuing medical education symposiums.<sup>13,14</sup>

*The court rejected the idea that the FDA is the font of all medical knowledge in this country.*

Richard Samp, Washington Legal Federation.<sup>14</sup>

## **Reasons for FDA policies on off-label use<sup>6</sup>**

The current situation permits a company to promote the labeled use of a new drug. Permitting sponsors to promote off-label uses would diminish or eliminate the company's incentive to carry out clinical trials and obtain definitive data. Such activity could result in harm to the patient, or fail to show that the drug is effective. If there is a deliberate attempt to diminish the use of evidence-based medicine in arriving at safety and efficacy decisions concerning a drug, the regulatory process will be eroded.<sup>6</sup> Drug companies could get approval for a drug for some narrow use and then heavily promote it for much broader uses that had not been adequately tested.<sup>15</sup> *What if preliminary findings are not subsequently borne out by further study, or are refuted by other studies?*

*Decisions on efficacy should be based on significant results, obtained from well designed and administered clinical trials, published in peer-reviewed journals. Peer judgment and review is essential for balanced results.*

## **The drug company position**

There is an inherent conflict of interest because most studies involving drug safety and efficacy are funded by the manufacturers.<sup>6</sup>

*However, in the real world who is going to carry the costs involved in bringing drugs to market if drug companies won't! There are costs of millions of dollars involved in obtaining drug approval, and cost considerations influence the number of indications established, the number of indications applied for, and the priority given to each of these applications. The number of patients needed for trials and the time required to complete the trials both increase if indications are broadened. Furthermore, during the regulatory review the 'patent time clock' is ticking down.*

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## A listing of some drugs and their unlabelled indications

These listings were compiled from the USPDI<sup>8</sup>, AHFS<sup>1</sup> Drug Information as well as suggestions from editorial advisors, other world experts and our peers.

<b>Drug</b>	<b>Unlabelled Use Relevant to Dermatology</b>	<b>Approved Dermatologic Indications include</b>
<b>Acyclovir</b>	<i>Laser resurfacing, prophylaxis Chemical peel Wire-brush surgery</i>	Herpes genitalis, simplex & zoster-prophylaxis Varicella – treatment
<b>Azelaic acid</b>	<i>Melasma caused by hyperfunctioning melanocytes</i>	Acne vulgaris – mild to moderate
<b>Cimetidine</b>	<i>Urticaria, acute in combination with an antihistamine Warts</i>	
<b>Clindamycin topical</b>	<i>Eczema, infected Folliculitis caused by <i>S. aureus</i>.</i>	Impetigo, localized caused by <i>S. aureus</i> and beta-hemolytic streptococci, including <i>S. pyogenes</i>
<b>Clofazimine</b>	Has Orphan Drug status for: <i>Leprosy, lepromatous (Hansen's disease) Leprosy, dapsone resistant Other leprosy associated disease or inflammatory reactions.</i>	
<b>Corticosteroids</b>	<i>Pemphigoid Sarcoid, localized cutaneous Vitiligo</i>	Many inflammatory diseases are listed as corticosteroid responsive.
<b>Cyclosporine</b>	<i>Atopic dermatitis Pyoderma gangranosum??</i>	Transplant rejection – prophylaxis & treatment Psoriasis, chronic severe WHEN under the care of a qualified, suitably equipped specialist.
<b>Dapsone</b>	<i>Actinomycotic mycetoma Cicatrial pemphigoid – desquamative gingival lesions Dermatosis, subcorneal pustular Granuloma annulare Lupus erythematosus, systemic – certain skin lesions Pemphigoid lesions with oral manifestations Ptychondritis, relapsing Pyoderma gangrenosum</i>	Leprosy (Hansen's disease) in combination with other agents Dermatitis herpetiformis

<b>Drug</b>	<b>Unlabelled Use Relevant to Dermatology</b>	<b>Approved Dermatologic Indications include</b>
<b>Estrogen + cyproterone</b>	<i>Acne in females</i>	Acne in females (approved in Canada)
<b>Estrogen + Progestin</b>	<i>Hirsutism</i>	Acne in females also needing contraception
<b>Isotretinoin</b>	<i>Acne, less severe than nodular Folliculitis Fordyce disease Severe rosacea including nodulocystic rosacea and rosacea refractory to oral antibiotics Hidradenitis suppurativa Severe keratinization disorders such as ichthyosis &amp; keratosis follicularis (Darier's) Pityriasis rubra pilaris</i>	Acne vulgaris – <b>severe</b> recalcitrant nodular
<b>Methotrexate</b>	<i>Dermatomyositis, systemic (polymyositis) Sarcoid Vasculitis</i>	Mycosis fungoides, advanced Numerous cancerous conditions Psoriasis, severe, resistant, recalcitrant, disabling
<b>Mupirocin</b>	<i>Eczema, infected Folliculitis, localized caused by <i>S. aureus</i> Skin infections, minor</i>	Impetigo, localized caused by <i>S. aureus</i> and beta-hemolytic streptococci, including <i>S. pyogenes</i>
<b>Nitroglycerin</b>	<i>Anal fissures ?? Hemorrhoids ??</i>	
<b>Sulfasalazine</b>	<i>Psoriasis</i>	
<b>Thalidomide</b>	<i>Has Orphan Drug classification for: Apthous ulcers, in the terminally immunocompromised Graft v's host disease Kaposi's sarcoma Leprosy, reactional lepromatous Lupus erythematosus, cutaneous Mycobacterial infection</i>	Erythema nodosum leprosum
<b>Tretinoin (retinoic acid, vitamin A acid)</b>	<i>Actinic keratoses hands &amp; arms Disorders of keratinization such as keratosis follicularis Ichthyosis congenita &amp; vulgaris Melasma Post-inflammatory facial hyperpigmentation Verruca plana.</i>	Acne vulgaris Hyperpigmentation, mottled, facial due to photoaging Skin roughness, facial, due to photoaging Wrinkling, fine facial, due to photoaging
<b>Trimethoprim</b>	<i>Acne Pneumonia, <i>Pneumocystis carinii</i> (in the US)</i>	Pneumonia, <i>Pneumocystis carinii</i> in Canada but not in the US.

## Actions the FDA has taken

Many new treatment indications are granted each year—the FDA Center for Drug Evaluation and Research (CDER) approved 118 supplemental indications in the fiscal year 1996. In the future, when appropriate, clinical trials will enroll pediatric, female and geriatric patients. Other practical initiatives being discussed will affect the dissemination of information on off-label uses for approved drugs, as well as the information provided on labels and the granting of patent extensions. Future cooperation between the profession, government, industry and special interest groups will eventually help to remove some of the obstacles presently limiting our ability to prescribe drugs outside their approved indications.

## Summary

*Unlabelled drug use provides a realistic therapeutic option; patients demand the best and safest treatment and oftentimes there is no other treatment option available. With off-label uses, industry asks why they should be asked for more money, the regulators say that they weren't asked for an additional indication, and the Doctor is left holding the bag!*

## What makes it so difficult to find a practical process to screen new uses of drugs?

- The FDA's present mandate does not allow it to easily and quickly grant clearance for indications not backed by rigorous clinical studies.
- The pharmaceutical industry, already laboring under huge development costs (300–400 million dollars US over 10 years per drug) and erosion of their patent time, is reluctant to include extra indications that might further complicate their new drug submissions.
- In the past there was little incentive to encourage industry to apply for extra drug usage indications, either for new drugs under development, or for drugs already on the market. It has been suggested that if industry were granted extensions on their patent time, they might be more inclined to make such applications. A change in the law has recently been proposed which would extend the patent of a drug by six months if companies conduct pediatric studies.<sup>16</sup>

*“Regulatory boards should acknowledge that many drugs work for unapproved uses. The unapproved use only means that it is too costly to get formal data for every last disease that a drug might work for.”*

John Voorhees, University of Michigan, Medical School

Valid new uses for drugs are often first discovered via serendipitous observations and therapeutic innovations, and then subsequently may be confirmed by well-designed and controlled studies. Inclusion of such new uses in the FDA-approved labeling for a drug may take considerable time and, without the initiative of the manufacturer whose product is involved, may never occur. Therefore, accepted medical practice (state-of-the-art) often includes drug use that is not included in FDA-approved labeling.<sup>1</sup>

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Stuart Maddin, Editor

## Update on Drugs

Class	Name/Company	Approval Dates and Comments
<b>Anti-AIDS</b>	<b>Efavirenz</b> Sustiva® Du Pont	Approved by the US FDA September, 1998 for the treatment of HIV-1 in both adult and pediatric patients. Efavirenz is a non-nucleoside reverse transcriptase inhibitor which has the advantage of once daily dosing.
	<b>Nevirapine</b> Viramune® Boehringer Ingelheim	Approved by the US FDA September, 1998 for use in combination therapy with other antiretroviral agents for treatment of HIV-1 infection.
<b>Antiherpes</b>	<b>Famciclovir</b> Famvir® SmithKline Beecham Pharma	Approved by the US FDA July, 1998 for the suppression of genital herpes in immunocompetent adults.
<b>Antihistamine</b>	<b>Cetirizine</b> Zyrtec® Schering	Approved by the US FDA June, 1998 for the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria in children aged 2–5 years; it was previously approved for patients six years of age and above.
<b>Anti-TB</b>	<b>Rifapentine</b> Priftin® Hoechst Marion Roussel	Approved by the US FDA June, 1998 for use in combination therapy of TB. Rifapentine will be given twice weekly for two months and then once weekly for the final six months.
<b>Cutaneous T-cell lymphoma</b>	<b>Denileukin diftitox</b> Ontak® Seragen®	An FDA committee has <i>recommended approval</i> of denileukin diftitox for treating cutaneous T-cell lymphoma, it has been designated an orphan drug by the FDA.
<b>Kaposi's sarcoma</b>	<b>Doxorubicin</b> Caelyx® Schering Canada	Canadian approval has been granted to this liposome encapsulated doxorubicin for the treatment of Kaposi's sarcoma.
<b>Skin substitute</b>	<b>Graftskin</b> Apligraf® Novartis	Approved by the US FDA in July 1998 for the treatment of venous leg ulcers; in Canada, it was approved for this same indication in April, 1997. <i>Apligraf® was the subject of a two part review in issues 2:5 and 2:6 of this Letter.</i>
<b>Drug Warning</b>		
<b>Dangers of alternative medicine</b>	<i>A New Engl J Med</i> 1998; 339: 839–841 editorial states that there is only medicine that has been adequately tested and medicine that has not, rather than two kinds of medicine—conventional and alternative. At present, the only requirement on herbal products is that they cannot claim to prevent or treat disease.  <i>Alternative medicine should pass the same FDA testing as conventional medicine.</i>	
<b>Protease inhibitors during pregnancy</b>	The National Institutes of Health have temporarily suspended enrollment of pregnant women into clinical trials of protease inhibitors, citing an unexpected number of premature births; of 10 babies studied, three were premature and one died in utero.	

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Articles are indexed by drug names, trade-names (marked ®), and disease terms.

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Lindane	2: 5	Quinolones ( 4th gen.)	5: 6	Trichophyton rubrum	2: 6
Lipitor®	4: 6	Recalcitrant rosacea	3: 3	Trichophyton violaceum	4: 3
Locoid®	2: 6	Red laser light	1: 3	Trichophyton	4: 3
Lustra®	5: 6	Regranex®	3: 6 / 4: 5	Tri-Cyclen®	4: 6
Lutetium texaphyrin	1: 4	Retin A® micro	4: 5	Trigger factors	3: 3
Male pattern hair loss	<b>4: 1,2,5</b> / 6: 6	Rhinophyma	3: 3	Trovaflaxacin	5: 6
Malignant melanoma	4: 5	Roaccutane®	5: 3,4	Trovan®	5: 6
Mectizan®	2: 5	Rogaine®	4: 2,5	Tumor necrosis factor alpha	2: 1
Melanoma	1: 5 / 6: 5	Rosacea	2: 6 / <b>3: 3,4</b>	UV induced discoloration	5: 6
Malassezia furfur	2: 6	Rosacea conglobata	3: 3	UVA / UVB penetration	6: 5
Mentax®	2: 6	Rosacea fulminans	3: 3	Vaccine – leprosy	5: 6
Metronidazole	2: 6 / 3: 3,4	SAER (spont adv. react. reports)	5: 3	Valaciclovir	2: 4,6 / 4: 5
Mycobacterium leprae	5: 6	Scabies	2: 5	Valtrex®	2: 4,6 / 4: 5
Microsporum canis	4: 3,4	Scars	1: 6	Vectavir®	4: 5
Minocycline (Minocin®)	3: 3,4 / 5: 6	Scleroderma	5: 6	Venous leg ulcers	3: 6
Minoxidil	3: 6 / 4: 2,5	Seborrhea	4: 5	Viral infections	2: 4
Mupirocin calcium cream	3: 6	Seborrheic dermatitis	1: 1	Virulizin®	4: 5
Mycosis fungoides	1: 4	Selenium sulphide	4: 3,4	Vitamin D deficiency	6: 5
Nail psoriasis	<b>6: 3,4</b>	Silicone based device	1: 6	Warts	2: 6
Nail ridging	6: 3	SKAR CARE®	1: 6	Wound healing	4: 5
Neoral®	1: 6 / 4: 5	Skin cancer	1: 3	Zidovudine	2: 6 / 5: 6
New drug treatments	4: 5	Skin Cap®	<b>1: 1,2,5,6</b>	Zinc pyrithione	1: 1,5,6
Non-melanoma skin cancer	1: 4	Skin discoloration	5: 6	Zoophilic fungus	4: 4
Non-steroidal anti-inflammatories	6: 1	Skin resurfacing	2: 3	Zovirax®	6: 6
Norgestimate / Ethinyl estradiol	4: 6	Skin sensitivity	1: 3		
Noritrate®	2: 6	Skin substitute	4: 5		
Ocular rosacea	3: 3	Sodium sulfacetamide	3: 3,4		
Onchocerciasis	2: 5	Solarase gel®	1: 6 / 5: 6		
Onycholysis	6: 4	Soriatane®	4: 5		