

The Ethics Around Drug Labels and Generic Medicines

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Abstract

The labels of off-patent medicines can be obsolete and even misleading when compared to the contemporary, evidence-based use of the medicine. Apart from serious adverse drug reactions that can lead to rapid changes to the label, regulatory agencies can only review and approve proposed changes to the label submitted by the sponsor of the medicine. There are many reasons why a sponsor may not wish or have incentive to submit proposed changes, particularly once a medicine is off-patent. The problem of misleading and potentially dangerous medicines labels post-patent expiry needs to be addressed. Consideration is needed of the roles of the label at patent expiry, how well that role is fulfilled and the possible alternatives. Our preference is for a 'partnership' approach to support production and maintenance of up to date, and relevant information for generic medicines that is pragmatically situated within the context of other sources of high quality information and advice. Reform is clearly needed but progress will be dependent on convincing stake-holders of that need and will require much lateral and innovative thought from all stakeholders best facilitated by an 'honest broker' such as the DIA.

The importance of drug labels

A medicine is more than a pill, solution for injection or a topical product. It includes at least as significantly, the medicines information that optimizes the chance for safe and effective therapy in individual patients. This information is contained within the product 'label', 'approved product information' [PI] or 'summary of product characteristics' [SPC]—henceforth referred to as the 'label'. The label, which is the Regulatory agency's officially approved information document, accompanies each registered medicine.

Despite these expectations, for reasons that will be discussed below, it is unavoidable that the longer a drug has been available on the market the more the official information in the label is likely to be obsolete, less relevant or even misleading. Furthermore, information for the patient, for example the corresponding patient information that is derived from the 'label', may also be inconsistent with the contemporary use of the medicine or the indication/s for which the medicine is being prescribed. Labels or consumer information that are not up-to-date and consistent with contemporary, evidence-based practice can, therefore, lead to stress and uncertainty for clinicians or patients who want to make use of this information.

One revealing example of the importance of drug labels involves the off-patent medicine, metformin. This medicine is a member of the biguanide class of hypoglycemic agents and considered by international authorities, for example Inzucchi et al (2012)¹, as the first-line pharmacotherapy for Type II diabetes mellitus. It is advantageous because, unlike the sulfonylurea anti-hyperglycemia medicines, it is not associated with weight gain and often promotes weight loss. Further, hypoglycemic reactions are rarely a feature, again contrasting with sulfonylurea medicines. Metformin was not registered in the USA until 1994 although it had been registered in Canada in 1972 and has long been 'off-patent'. Of particular significance to the difficulties associated with drug labeling, metformin was a replacement for phenformin, also an anti-hyperglycemic medicine of the biguanide class that was withdrawn because it induced lactic acidosis at an unacceptable rate. While metformin is chemically related to phenformin, it has quite different physicochemical properties and clearance mechanisms². In contrast to phenformin that is cleared by metabolism via the cytochrome P450 enzyme system largely in the liver, metformin is cleared completely by the kidney. Not surprisingly, concentrations of metformin increase as renal function decreases. This knowledge, together with concerns about the class of medicine and the evident propensity for lactic acidosis, led to the official label contraindicating the drug in patients with glomerular filtration rates below 60 mls/min³ despite a paucity of data proving that this was clinically necessary.

One of the commonest causes of renal impairment and eventual end stage kidney disease (ESKD) is type II diabetes. Thus the long-standing, official contraindication to the use of metformin in renal impairment has deprived hundreds of thousands of patients of the proven benefits of this medicine⁴. Meanwhile, evidence has accumulated that a direct causal relationship between metformin use and lactic acidosis when used in otherwise well patients is highly unlikely.⁵ In fact, many physicians have been prescribing the drug 'off label' safely to patients with renal impairment' at least down to glomerular filtration rates (GFRs) of 30 ml/min' for many years⁶. Reputable guideline groups have been supportive of this practice⁷. Recent research has extended the possibility for safe use of metformin in patients with GFRs less than 30 ml/min down to 15 ml/min and studies are under way to test the safety and efficacy in patients with ESKD⁸.

With this degree of consensus across the medical profession and guidelines groups, it would be expected that the 'official' drug label would be brought up to date to reflect safe and effective use, and to advise on appropriate monitoring. However, the label has not changed.

This situation is at best confusing, may be deemed negligent for depriving people from potential benefits, and is at worst dangerous, yet is unfortunately, far from rare. Other important examples of drug labels that are not reflective of good clinical practice again include metformin, this time for Polycystic Ovary Syndrome (PCOS), which is not labeled for this indication even though this indication is 'evidence based'⁹ and accepted by authoritative guidelines reference sources such as the Australian Medicines Handbook¹⁰. Methotrexate was used off-label for many years for the treatment of rheumatoid arthritis despite overwhelming evidence of efficacy and safety¹¹.

Barriers to accurate drug labels

This raises the question of why drug labels and corresponding information are so often incomplete and/or out of date. The answer lies in the fact that the major regulatory agencies around the world can only review and approve changes to the label that are submitted by

the sponsor of the medicine. The only exception is when serious adverse reactions are identified, in which case mandatory and rapid submission to the agency is required that, if substantiated, will be incorporated into the label expeditiously. In all other instances, for example when substantial and sufficient evidence for a new indication for a registered drug has been assembled and incorporated into respected treatment guidelines, it is up to the sponsor whether or not they apply to have their label updated.

There may be some incentive for companies to apply for revision of labels for patented medicines, particularly where indications are likely to be expanded. However, once a patent expires, and generic versions of the medicine are marketed, the likelihood of new and relevant information being incorporated into the official label is slight. The reasons are clear: 1) the generic manufacturers often do not have full access to the new information because it has been generated independently e.g. via academic groups and gaining details of the work sufficient to satisfy regulatory agencies is challenging; 2) the originator company also may not own or have been involved with establishing the evidence for the new indication; 3) the originator company does not have much incentive to expend likely considerable resources on assembling and submitting the required data to the agency when the possible returns are not obvious; and 4) the regulator does not have the mandate or mechanisms needed to demand timely updating of labels. Furthermore there may be strong commercial incentives to avoid updating the label of drugs, such as when drug sponsors do not apply for new indications for drugs about to come off-patent if the new indication is likely to compete against a successor product.

Do we need drug labels for non-patented medicines?

This raises the question of whether we should consider doing away with drug labels altogether (or at least those parts that may become outdated) once medicines are 'off-patent'? This question could be approached by asking three further questions: What is or are the role or roles of the label at this time in the life-cycle of a drug? How well does the label fulfill those roles? And what, if any, alternatives are available?

As with labels for patented medicines, the roles of labels of generic medicines are to provide guidance on the safe and effective use of a drug which includes, amongst other features, summaries of important information about indications, side effects, contraindications, interactions, mechanism of action, doses, and route of administration, that is essentially identical requirements to patented medicines.

It is clear from the foregoing discussion that drug labels often do not serve these purposes especially when it comes to off-patent medicines. However, while labels are absolutely necessary for new medicines as a means of guiding practice, as new evidence emerges and clinical experience with a product develops, other forms of guidance may take precedence. This may include clinical practice guidelines that are endorsed by experts or authoritative bodies, robust systematic reviews of existing evidence such as Cochrane Reviews, and drug reference resources.

In this context the question becomes: how does the label 'sit' in relationship to good quality treatment guidelines that are widely available? In particular, should the label be 'competing' with these as a document to guide the safe and effective use of the medicine and, if so, how? It is to be expected that studies designed to support registration, and dealt with in detail in some labels, will be less pertinent at patent expiry in guiding the appropriate use of a medicine. Thus, the label will likely be 'out of touch' with clinical practice and emerging

evidence as reflected by the ubiquity of off-label prescribing in clinical practice, further indicating the decreasing relevance of the label.

Furthermore, because payer decisions are correlated to drug labels, particularly in countries such as Australia, out of date labels can lead to irrational economic situations where a generic drug proven to effectively treat an 'off-label' illness is more costly to the patient than a more expensive on-label drug for the same indication that is reimbursed by the payer.

Another pertinent question is whether the label and associated consumer information sheets are the best place for clinicians and patients to access information about potential adverse drug reactions after patent expiry. In theory, serious adverse reactions will have been, and will continue to be, incorporated into the label and consumer information in a timely manner, as mandated by regulation and law in all jurisdictions. However, other adverse drug reactions that are not classified as serious but that could be important for the individuals afflicted may not be reported to regulators and therefore not found in the label.

In this regard it is noteworthy that problems have also been identified in currently available, pre-patent expiry, labels. For example, Pfistermeister et al (2014), found large deficiencies and discrepancies in the information in labels from UK, USA and Germany¹². Of most concern, what were meant to be reciprocal warnings in labels of drugs involved in important drug-drug interactions that were identified as a contraindication to prescribing were found to be missing more than 40% of the time. There is also evidence, as illustrated with the metformin example, that prescribers and patients are likely to be misled and confused by seeking information from labels about safe use or adverse reactions as those reactions may no longer be reasonably related to the drug. Such 'reactions' are often still listed at rates identical to placebo as presented in the original label. Worryingly, Pfistermeister et al, (2014) also found that variation in contraindications listed in generic medicine labels for the same medicine were common¹². Consistency of the label for contraindications across all brands of particular generic medicines was found only 60, 10 and 20% of the time in the USA, UK and German 'labels' respectively.

Practical recommendations

It is beyond the scope of this article to argue for or against the ongoing availability of drug labels when medicines are off-patent. Before a decision can be made, further research is needed in order to understand the relevance and place (or lack thereof) of the post-patent label in the 'sea' of information about medicines.

If the decision is made to retain labels after patent expiry, then we will need to determine what form these documents should take. Should, for example, the 'legacy' document remain in the same form with essentially the same content as found on the day of registration perhaps 10 years or more previously? Should the detailed and pivotal clinical trial data accrued pre-registration still be prominent when there are more recent and relevant clinical trials – in particular comparative effectiveness studies—to guide therapy?

Should we wish to keep labels up to date, then we will need to develop effective scientific and governance processes for ensuring that this is done consistently and thoroughly (we believe that it would be better to have no labels at all than to have a mixture of trustworthy and misleading labels). The case has been made that the originator sponsor for a medicine

has complete responsibility for an up to date and relevant label, even after patient expiry, but this seems to us to be both unrealistic and unreasonable. Similarly, simply expecting and then organizing multiple generic companies to take combined responsibility for the label is unworkable currently. Regulation to demand this approach could be pursued however but there would be considerable barriers.

Our preference is a 'partnership' approach to support production and maintenance of up to date, and relevant information for generic medicines that is pragmatically situated within the context of other sources of high quality information and advice. Involvement of guidelines and evidence-based medicine (EBM) groups such as the Cochrane Collaboration, professional colleges, regulatory agencies and importantly, consumer organisations along with the originator and generic companies would be a good 'straw man' model to begin exploring this concept. Reform is clearly needed but progress will be dependent on convincing stake-holders of that need and will require much lateral and innovative thought from all stakeholders.

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