

New Indications & Cross-Label Dispensing

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Executive Summary

Innovation is a continuous process, and appropriate incentives are needed to encourage development of the full potential of healthcare innovations including medicines. Over the lifecycle of a medicine, company sponsors pursue development of new medicinal uses for previously discovered medicines. When these are approved, they are referred to as “new indications” and are usually added to the list of approved uses for the product. However, this requires considerable investment to generate both non-clinical and, more significantly, clinical evidence to support the application for these additional indications to the regulatory authority and for approval for use in healthcare. Without appropriate incentives that make it possible for this investment to be recovered, these important extensions to the therapeutic value of a medicine may not be possible and patients will have fewer new treatment options to improve care.



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1. Innovation is an Incremental, Continuous Process

- * When a medicine is first discovered, **not all of its potential benefits for treatment are known** and evaluated. Many medicines go on to be successfully researched, tested and evaluated in additional areas of treatment. This process requires the company sponsor to invest in further research and development to provide rigorous evidence, both non-clinical and clinical, in order to demonstrate that the medicine delivers patient benefit in the proposed new use (also referred to as an “indication”) and that the benefit/risk ratio¹ for that medicine in use for that medical condition is acceptable. From a societal perspective, it is clearly desirable that the best possible use is made of established safe medicines and that these subsequent uses are supported by thorough clinical assessment.

2. Second Medical Use Patents Are Good for Patients

- * **Developing new indications for existing medicines has considerable value for patients and healthcare. However, these new indications are only developed with considerable investment by innovating companies.** Appropriate incentives are needed to ensure the necessary investment is made to extend the uses of known medicines into other areas of treatment to benefit more patients.
- * **We believe that an effective patent system is an essential mechanism to incentivise the development of innovative new medicines and innovative new uses for existing medicines.** It allows appropriate returns to be made in an exclusivity period that is fixed and relatively short, vis-à-vis the many years over which a medicine is typically used.
- * **If patent rights are not effective to provide exclusivity for the invention, the incentive for investment is undermined and the link to future innovation is weakened.** Exclusivity incentivises new and additional investment to deliver new treatment options for disease and symptom management.
- * **However, because of the problem of cross-label dispensing, patents alone may not be effective incentives to develop new uses for existing products.** Although generic² prescribing and dispensing of generic products for non-patented uses should be permitted, the cross-label dispensing for patented uses significantly undermines the incentive to develop products for new uses.
- * **Additional mechanisms are needed to ensure that only the originator product is prescribed and dispensed for the patented use while allowing generic products to be dispensed for other uses.** One way of doing this would be to have prescribing systems/software which make it clear that only

¹ The **benefit/risk ratio**, or *risk-benefit balance* as it is described in the European pharmaceutical legislation is an evaluation of the positive therapeutic effects of a medicinal product in relation to any risk relating to the quality, safety or efficacy of the medicinal product as regards patients’ health or public health. (Article 1 point 28, Directive 2001/83/EC as amended).

² Generic prescribing describes prescribing by reference to the International Non-Proprietary Name (INN).



the original medicine should be prescribed (by reference to its brand) and dispensed for the patented indication during the period of patent exclusivity.

3. How Second Medical Use Patents Work

- * Effective measures conferring exclusivity for the new indication for a period of time are essential incentives to encourage research into such new uses.
- * A '**second medical use patent**'³ establishes protection for a known medicine in a specific new use / indication. However, this type of patent may not be effective on its own to provide a sufficient incentive to undertake development of new indications because of what is known as "cross-label dispensing".

4. The Problem of Cross-Label Dispensing

- * Regulatory authorities in the EU do not take account of patent status when considering whether or not to approve a generic or biosimilar version of an approved medicinal product. In most cases, the generic or biosimilar product will have the same labelling – including the same indications – as the reference medicinal product. However, in recognition of the rights conferred by second medical use patents, applicants for generic or biosimilar products are permitted to exclude the patent protected indications from the list of approved indications for the generic/biosimilar product. This carve-out of the patented indications gives rise to a so-called "**skinny label**" that only refers to non-patented indications.
- * When the basic patent expires for a medicine which has multiple indications, some of which are covered by a second medical use patent, some of the medicine's indications will be open to generic competition while those in the second medical use patent continue to be protected. In these circumstances, a generic or biosimilar product with a skinny label may be dispensed to patients suffering from any of the non-patent-protected indications; only the original medicine should be dispensed and/or intentionally administered to and used in patients diagnosed with the patent-protected indication.
- * Under this scenario, from the patient perspective, access to the medicine for those suffering from the non-patent protected indication(s) is improved through the availability of the generics, while therapeutic options are expanded for others as a result of the originator's investment in discovering further indication(s).

³ Second medical use patents are recognised in Art 54(5) of the European Patent Convention 2000, provided that the specific use is novel (i.e. not comprised in the state of the art). Art 54(5) of the European Patent Convention 2000 is implemented by primary legislation in the UK through section 4A of the Patents Act 1977 (as amended by the Patents Act 2004). Second medical use claims were included in patents before this in the form of 'Swiss claims' following G1/93, a decision of the Enlarged Board of Appeal of the EPO.



- * However, the logic of distinguishing the patented and off-patent indications may not be reflected in way medicines are procured, prescribed and dispensed. In particular, the practices of generic prescribing⁴ or allowing generic substitution may make it very likely that a pharmacist will dispense a generic product without reference to the indication for which the medicine was prescribed and without regard to whether the generic medicine has a “skinny label”. The dispensing of a generic medicine for an indication for which the innovating company still holds a patent and for which the generic medicine has not been authorised/labelled is described as **cross-label dispensing**⁵. It significantly undermines the effectiveness of the second medical use patent as an incentive for developing new indications.

5. Conclusions

- * Cross-label dispensing is a serious problem. Failure to address it has a **significant impact on the encouragement to develop medicines for new indications and uses**. While the healthcare professional’s essential clinical independence is both supported and respected, in order to continue to support medical innovation, it is also important that intellectual property protection is recognised and upheld, in a way that does not undermine the essential goal of prescribing or dispensing practice of delivering the right medicine to each patient.
- * Tender procedures which fail to differentiate between the protected and unprotected uses may exacerbate the problem by offering volumes which can in practice only be met legitimately by the originator and expose both generic companies and those issuing the tenders to claims of patent infringement.

6. Recommendations

- * **We can solve cross-label dispensing without compromising clinical freedom.** The basis on which a patient receives a specific medicine is primarily a question of clinical judgment on the part of their healthcare professional. Second medical use patents do not restrict the physician’s freedom to prescribe a particular medicine for a particular indication to an individual patient. They only limit whether that medicine should come from the patent holder or a generic source. Subordinate to this decision, it is possible to define how choices between equivalent medicines should be made, for example, to require that when a medicine is prescribed for a patent-protected indication, there is a benefit to the innovator.
- * One means of doing this would be that, where only the original medicine should be prescribed **for the patented indication, the prescription should be automatically written by reference to its brand name** and the pharmacist should dispense only the original medicine and be reimbursed at the

⁴ Cf. footnote 2

⁵ This practice can sometimes be incorrectly linked to the off-label or unlicensed use of a medicine, which refers instead to the clinical decision to use a medicine which has not been subject to regulatory evaluation and approval for that use.



correct price for that medicine. Of course, if the indication is off-patent – and is therefore one of the authorised indications on the generic label – then prescribing by INN can take place and the generic product can be dispensed by the pharmacist. Other solutions may be appropriate, dependent on the prescribing/dispensing system in the particular Member State.

- * Adaptations of relevant local or national **prescribing and dispensing software** can and should be used to separate patented from non-patented indications for a specific molecule, so that the relevant (branded) medicine is prescribed and dispensed accordingly for the patented indication.
- * **Guidance** regarding the correct application of existing European tender procedures, such as the negotiated procedure without publication, would also contribute to avoiding patent infringement and ensure that both innovators and generics were able to supply the market appropriately.



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