Integrating the best of clinical research, timely patent protection and market control to support access for patients

Unlocking the promise of drug repurposing

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Clinical programs directed to drug repurposing bear the promise of providing new therapies for yet non-treatable diseases based on available therapeutics. First and foremost, by repurposing, new patients may get access to therapy perhaps for the first time, or current treatment may be improved. Additional upsides can be that time to market, and therewith time to patient is shorter compared to drug development programs based on new drugs, and that costs are lower. These benefits are most likely apparent when the approved drug is assessed for a new use at the same dose and with the same formulation. Under these conditions safety has already been assessed, resulting most likely in saving on time-to-patient and costs.

Drug repurposing often involves drugs with a market authorization. For example, a generic version of a previously patented drug molecule. Alternatively, the active pharmaceutical ingredient (API) may still be patent protected. Then, when clinical data is supportive for the repurposing, the fate and success of the program is also determined by the involvement of the patent holder. They can repurpose the drug themselves, when freedom-to-operate to do so is apparent (no patent rights prohibit marketing the drug for the new indication). Alternatively, the patent holder may provide a license to explore the drug and to ultimately allow the/a licensee to make it accessible for new patient groups.

The advantages of a clinical program involving a patent-protected drug are manifold. The efforts and investments in time and financial resources are under protection of the patent law. Enforcement against infringers (copy-cats) is under control of the patent holder and their licensees. Requesting patients to voluntarily participate in clinical trials with yet uncertain outcomes of course comes with great responsibilities. On moral and ethics grounds, the chance for a beneficial therapy as a reward for the participant in the clinical research should be maximized. Patent protection at least contributes to the certainty that positive clinical results can be turned into access for patients. Investments in the chain of events from getting the new indication (1) on an approved drug label, (2) included in healthcare programs and (3) reimbursed, thrives certainly better when the trial sponsor can operate while having control under the protective umbrella provided by patents.

But what if the to-be-repurposed drug is off-patent and generic variants have a market authorization?

For generic drugs, in most cases, anyone is in principle allowed to explore potential new uses of such drug, and get regulatory approval for it. When the API no longer enjoys patent protection, this can provide new opportunities to freely investigate new therapeutic uses and pursue implementation thereof in clinical practice. Phase I clinical trials often will not be required. The suitable ready-to-use formulated and dosed drug will be readily available. Such aspects may foster repurposing of the drug. Notwithstanding the promise of faster and cheaper availability for the new patient group, the trajectory from (pre-)clinical research to approval, and to reimbursement of a fair and reasonable price, is still rather cost intensive. This because relatively large scale clinical trials will usually be required. Additionally, setting up manufacturing, logistics, and awareness campaigns (new standard of care for a yet underserved patient population) demand an investment before a new therapy eventually reaches patients. Securing the funds for clinical trials, market approval and beyond could certainly be aided by patent protection for the new use of the generic drug. As for patent-protected drug molecules, also a patented drug repurposing program provides a means for control and protection against e.g. companies not by far investing and contributing to the innovation to a similar extent. Accordingly, a patent may be a decisive factor when attempting to raise the funds required to transform for example a clinician driven drug repurposing program to the stage towards establishing the registration dossier accompanied by increased investment demands.

What and when to patent by whom?

The short answer is that for example in Europe and in the US almost any aspect related to the new use of the existing drug can in principle be patent protected. Once the first new and yet unpublished preliminary results indicative for the potential of the drug for the new patient group is apparent, patenting should absolutely be considered. "Patent before you publish!" Inventors (pharma and academic researchers, clinicians) involved in establishing the insightful (pre-)clinical data and in getting approval from an METC for conducting clinical research, should be encouraged to discuss patenting opportunities already in parallel. Just the indicative suitability of the drug for the treatment of a new disease, as for example established with preliminary though insightful model experiments, can in general suffice to support a patent directed to such a new use. Additional examples of aspects suitable for patent protection are amongst others, (1) a new dose; (2) a new formulation; (3) a new dosage regimen, either or not with a new route of administration; (4) patient stratification; and (5) a combination treatment, to name a few.

A patent backing a drug repurposing program provides means for control, similar to what is possible with an on-patent drug. Once market approval is obtained for the repurposed version of a drug, patent rights will discourage copy-cats from entering the market, and if they still do, the patent rights can be enforced against them in court. Monopolization provides control over the pricing and reimbursement negotiations to enable those who took the efforts and the financial risk to get a fair and reasonable award. Moreover, off-label use of products not approved for the new and patented indication, can be effectively halted at the level of manufacturers and sellers, without interfering at the level of drug prescribers. The odds that drug repurposing can fully deliver on its promise is to a large extent dependent on the timely recognition that there is a possibility as well as a necessity to apply for patent protection rather early in the program. In that regard, the drug repurposing program managers, and the team of researchers and clinicians involved, together have an important if not decisive key to success. They understandably and rightly feel a responsibility towards society and specifically towards the patients for which they are pursuing the drug repurposing program. Budget constraints and the lack of the ideal business case may hamper progress. Hence, for really connecting the demands from society to unlock drug repurposing potential and the opportunities available in the research centers, a fresh debate on investment models and business models seems to be a necessity. Likely on the national level rather than on the individual level of each university and university medical centers.

Fortunately, experts and stakeholders involved in all steps from initial idea to access for patients are aligning and teaming up to the benefit of smoothening the drug repurposing pathway. Without being complete, EU-funded consortia remedi4all and REPO4EU should not be left unmentioned in this context, as well as the Dutch

center of drug repurposing expertise FAST (Centre for Future Affordable & Sustainable Therapy Development). By collaboration, the promises of drug repurposing programs could be fully unlocked. For that, adapting current pharma regulation and current reimbursement policy may be required to smoothen drug repurposing programs up to fair and reasonable priced new therapies for new patient groups, which drugs are reimbursed and implemented in national healthcare guidelines.

Currently, with certain restrictions, the EU pharma regulation provides for an extension of the (clinical) data protection period with 12 months for a market authorization holder if a repurposed drug provides 'significant clinical benefit'. Although not yet established and implemented, a reformed EU pharma directive is on its way. Again, subject to limitations, the reform would extent the data protection period up to 4 years, providing improved protection for some drug repurposing programs. Although this would provide a major step forward, it still needs to be emphasized that patent protection can provide control for as long as 20 years. Moreover, starting with a centralized procedure for over 150 countries, patent protection for a drug repurposing program can be applied for in many highly relevant jurisdictions, not the least in 37 European countries including all EU member states, and in the US.

The prospect of a viable business case for an early stage drug repurposing program is often under debate, especially when it involves a generic drug. Securing patent protection (at the right moment) can help to significantly expand the potential market size beyond the Dutch borders, to the whole of Europe, and, for example, the US and Japan. An enlarged (potential) market increases the viability of the program at the time investments are needed for e.g. conducting the clinical trials for the registration dossier. Therewith, the opportunity of successful collaborative drug repurposing programs grows and chances for success, too.

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