Drug repurposing patent documents vs peer review: patent information comes more than 600 days earlier on average

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Drug developers require access to scientific information in as close to real time as possible. The commonly employed formal sources are peer-reviewed journals and conference presentations. Another extremely important information source, the intellectual property documents, is widely ignored.

For many years, we have been screening the international patent applications of the World Intellectual Property Office (WIPO, Geneva, Switzerland) – which are the formal disclosures made under the Patent Convention Treaty (PCT) – for several thematic categories including *inter alia* and drug repurposing. It soon became apparent that this subset of intellectual property documents offers a particularly pronounced information advantage over the subject matter represented in peer-reviewed journals. As this is almost totally uncharted territory [1], we decided to investigate how many of these documents have peer-reviewed companion papers and when they are published in relation to the corresponding patent document.

The WIPO's online database, PatentScope [2], was used as the sole source of patent information. It offers no option to search for documents that deal with known active pharmaceutical ingredients in unapproved or previously unknown therapeutic applications. Therefore, we examined all document titles and abstracts published under IPC Code A61K (which covers drugs) for known substance classes, drugs, drug candidates or other compounds for which the wording was suggestive of drug repurposing; in other words, for use in a new therapeutic indication that is not simply a use extension, such as from one type of cancer to another. These documents were flagged and in a second round of investigation body text and claim sections were examined to confirm or reject drug repurposing status.

The third step consisted of a PubMed search to identify a peer-reviewed companion paper – defined as having at least one patent inventor as an author and a substantial part of the patent application as a subject – for each drug repurposing patent document. An author search was carried out for all inventor names in each patent document as a first tier and each hit was examined for contextual congruence with the respective patent, in a time window starting 3 years prior to the publication date of the intellectual property document up to the present. If no congruence was found, pivotal keywords (compound nonproprietary names, drug targets, mechanisms or pathways) were extracted from the patent document and combined with the institutional applicant. If this returned a clearly congruent peer-reviewed hit within the same time frame, the hit was also considered a companion paper. The earliest public availability date (the 'Epub' online date, or the print date if no Epub date was available) and the digital object identifier were recorded and linked to the respective patent document.

We found that the number of PCT drug repurposing patent applications has risen consistently between 2015 and 2019 and did so more strongly than the total number of A61K publications, raising their share from 0.69% in

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Table 1. Numbers and shares of Patent Convention Treaty drug repurposing patent applications that had their peer-reviewed companion (if any) published before or after the patent document, 2015–2017.

Year	Patent earlier than peer review	Patent later than peer review	No peer review companion	Total patents
2017	31 (27.4%)	25 (22.1%)	57 (50.4%)	113
2016	23 (25.0%)	20 (21.7%)	49 (53.3%)	92
2015	27 (32.9%)	18 (22.0%)	37 (45.1%)	82

2015 to 0.91% in 2019, while increasing their numbers from 82 in 2015 to 142 in 2019. A total of 550 intellectual property documents related to drug repurposing were identified during this 5-year interval.

An interesting finding emerged when we started to correlate and analyze publication dates for patent/peer-reviewed document pairs from the 2015 to 2017 period. From our current general experience in the pharmaceutical sciences and from an analysis in the vascular risk management sector that we had published several years ago [3], we had assumed that peer-reviewed documents would become public quicker (if they existed at all) than the corresponding patent documents. In contrast, our data show that the fraction of patent applications that get a peer-reviewed companion paper published only after the public disclosure of the invention (or not at all, at least not within 2–5 years) is between 67 and 75% (Table 1). Looking at patent disclosures published in 2015, those that were ahead of their peer review companion papers (if any) had an average time advantage of 629 days. Those that lagged behind their companions did so by 400 days. In total, PCT documents published in 2015 that had a peer review companion paper were 218 days ahead of it on average. Because even some patent documents published in 2015 had peer-review companions with Epub dates in the last quarter of 2019, we did not extend this analysis to documents published in 2018 and 2019. The fact that the share of patent documents without peer-reviewed companions consistently continued the rise evidenced in Table 1 during these most recent years (data not shown) suggests that many patent documents from this interval may still get their peer review counterparts published.

Finally, in Table 2 we disclose the patent application/peer-review document pairs for 2015, the latest year for which the great majority of peer-reviewed papers can be assumed to have been published.

Life scientists, including those working in drug development, tend to ignore patents as a regular information source. While the reasons for this negligence are numerous, one often-heard statement – that any worthwhile information from patents can be found in the peer-reviewed literature – requires qualification. This is especially true in the field of drug repurposing which has experienced an impressive rise in peer-reviewed publications during recent years. In each of the 3 years that we analyzed in this respect (2015–2017) the patent document was more likely to reach the public earlier, in some cases years earlier, if it existed at all – which was not the case for about half of all patent documents published during this period.

Our data from 2015 to 2019 also show that interest in international patenting drug repurposing findings seems to rise quicker than peer-reviewed publication rates. One conceivable explanation for both phenomena might be that drug repurposing work can lead to relatively quick results, requiring prompt patent filings which then trigger a tightly paced disclosure process. In any case, scientists and analysts working in this field would do well to include international PCT patent disclosures in their monitoring.

Our analysis, which we believe to be the first of this type to be published, has an obvious limitation: patent documents were identified by manual screening of PatentScope titles and abstracts. Documents which revealed drug repurposing only in their body text or claims section could have been missed. From our unrelated work with pharmaceutical patents we believe that this miss rate is less than 10% and in any case is not likely to have changed the outcome of our analysis.

The type of search employed by us is suited to machine learning, which could include the entire patent texts [4] while searching for alternate compound designations and chemical structures [5] which in our work could rely only on the searcher's experience. The system could then be expanded toward the companion peer review paper searches and proper pairings. Our dataset could serve as a comparator and means of calibration for such systems.

Table 2. The drug repurposing Patent Convention Treaty patent application/peer-reviewed document pairs of patents published in 2015 and their temporal offset.

PCT publication number	Peer review DOI	Offset of PCT vs peer review (days) [†]	Subject matter
WO/2015/189597	10.3892/ijo.2016.3567	-173	Low-dose naltrexone for priming of cancer cells for therapy
WO/2015/187847	10.1016/j.stem.2017.08.001	-629	Prostaglandin E1 and misoprostol for chronic myelogenous/myeloid leukemia
WO/2015/184260	10.1101/gr.190629.115	+49	Anticonvulsants for epigenetic mendelian disorders
WO/2015/181412	10.1371/journal.pone.0111184	+408	Theobromine for urolithiasis
WO/2015/173788	10.1016/j.antiviral.2017.03.024	-500	Anti-infective strategy against influenza and <i>Staphylococcus aureus</i> infection
WO/2015/170248	10.1186/1479-5876-12-128	+540	Nelfinavir, metformin and rosuvastatin for cancer
WO/2015/166277	10.1172/jci.insight.87001	-273	Aldehyde dehydrogenase inhibitors for fibrosis
WO/2015/165856	10.1111/bjd.16930	-1047	Artemisinin for seborrheic keratoses
WO/2015/157223	10.1371/journal.pone.0194868	-889	Various compounds for coronavirus infection
WO/2015/154820	10.1016/j.antiviral.2013.10.003	+725	Anti-inflammatory agents for viral infections
WO/2015/149706 WO/2015/149707	10.1073/pnas.1416166111	+304	Fingolimod for ischemic stroke
WO/2015/147411	10.1038/cddis.2014.266	+462	Mitochondrial complex I inhibitors for proliferative vitreoretinopathy
WO/2015/143367	10.1016/j.cct.2016.02.012	-160	Cenicriviroc for fibrosis
WO/2015/127163	10.3324/haematol.2019.226720	-1526	Pyridoxamine for sickle cell disease and thalassemia
WO/2015/120254	10.1093/carcin/bgt366	+646	Disulfiram for brain tumors
WO/2015/120206	10.18632/oncotarget.7283	-222	MAO inhibitors for brain cancers
WO/2015/110949	10.1038/leu.2016.5	-188	Imatinib for hypercholesterolemia
WO/2015/110593	10.1093/ofid/ofv155	-147	Endothelin receptor B antagonists for cytomegalovirus infection
WO/2015/108985	10.4088/JCP.13cr08917	+342	Ketamine for autism spectrum disorders
WO/2015/106678	10.24272/j.issn.2095-8137.2020.012	-1607	Progesterone for altitude sickness
WO/2015/095757	10.1073/pnas.1523005113	-298	Roxadustat for retinopathy of prematurity
WO/2015/091857	10.1038/nm.3827	+101	Modulators of intracellular chloride for Down syndrome
WO/2015/079413	10.1126/scisignal.2005537	+135	Synaptojanin-2 inhibitors for cancer
WO/2015/079031	10.1016/j.traccli.2013.03.005	+750	XPO1 inhibitors for beta-thalassemia
WO/2015/076430	10.1155/2014/973986	+281	Metformin for immune diseases
WO/2015/073804	10.1038/srep03743	+489	Various compounds for malaria
WO/2015/073697	10.1186/s12974-018-1208-3	-1120	Laquinimod for glaucoma
WO/2015/065136	10.1167/iows.15-18065	-313	Masitinib for vascular permeability disorders
WO/2015/065135	10.1007/s12272-016-0872-z	-590	Dasatinib for vascular permeability disorders
WO/2015/060702	10.1016/j.pbb.2017.07.009	-814	S-phenotropil for obesity
WO/2015/059114	10.1097/CEJ.0000000000000333	-1172	Yellow fever vaccine for breast cancer prevention
WO/2015/053452	10.1371/journal.pone.0094978	+374	Silmitasertib as a splicing regulator
WO/2015/049608	10.1016/j.eplepsyres.2017.08.006	-863	Propylparabene for neuroprotection in status epilepticus
WO/2015/046857	10.1089/thy.2017.0338	-1091	Metformin for autoimmune thyroid diseases
WO/2015/044762	10.1016/j.ejmech.2017.05.034	-771	Cefazolin as an inhibitor of IL-15 and IL-2 receptors
WO/2015/026939	10.1016/j.bcmd.2015.10.004	-243	Chemical inducers of fetal hemoglobin expression for sickle cell disease
WO/2015/026849	10.1038/ncomms3410	+541	Clemizole for epilepsy
WO/2015/023871	10.1111/adb.12106	+465	Ibudilast for alcoholism
WO/2015/013591	10.1007/s10620-014-3157-8	+273	Rifaximin for irritable bowel syndrome
WO/2015/011246	10.5665/sleep.5854	-489	Flecainide as a modafinil potentiator
WO/2015/007869	10.1016/j.redox.2018.05.014	-1225	Local anesthetics for cancer
WO/2015/006319	None (PMID: 24595578)	+306	Ivermectin for papulopustular rosacea
WO/2015/006305	10.1111/bjd.13408	-27	Ivermectin for rosacea
WO/2015/004470	10.1016/j.hrthm.2015.05.027	-132	Hydroxychloroquine for cardiovascular diseases
WO/2015/001799	10.1128/AAC.01614-15	-470	Clofazimine for babesiosis

[†] Negative values represent patents published ahead of peer review.

NOTE: If available, PubMed Epub dates were used. If these were only given as year and month, the 15th day of the respective month was used for calculation.

N/A: No peer-reviewed companion identified; PCT: Patent Convention Treaty.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References

1. Mucke HAM. Drug repositioning in the mirror of patenting: surveying and mining uncharted territory. *Front. Pharmacol.* 8, 927 (2017).
2. PatentScope. World Intellectual Property Organization (2019). <https://patentscope.wipo.int/search/en/search.jsf>
3. Mucke H. Relating patenting and peer-review publications: an extended perspective on the vascular health and risk management literature. *Vasc. Health Risk Manag.* 7, 265–272 (2011).
4. Bergeaud A, Potiron Y, Raimbault J. Classifying patents based on their semantic content. *PLoS ONE* 12(4), e0176310 (2017).
5. Akhondi SA, Rey H, Schwörer M *et al.* Automatic identification of relevant chemical compounds from patents. *Database* 2019, baz001 (2019).