Pharmacovigilance, Drug Repositioning, and Virtual Screening

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According to the website of the Pharmaceutical Information and Pharmacovigilance Association or PIPA (URL: http://www.pipsaonline.org/), “Pharmacovigilance is the process of (a) monitoring medicines as used in everyday practice to identify previously unrecongnised adverse effects or changes in the patterns of adverse effects; (b) assessing the risks and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use; (c) providing information to users to optimise safe and effective use of medicines; (d) monitoring the impact of any action taken”. This definition, wider and more synoptic than many others, imbues Pharmacovigilance with both a wide meaning and an inclusive scope; yet its focus remains on Adverse Drug Reactions (ADRs). What perhaps this does lack is reference to the role that Pharmacovigilance might play in Drug Repositioning.

In 2009, I wrote: “Much as the world finds itself in financial crisis, so does the pharmaceutical industry, albeit for different reasons, namely: regulatory changes; dwindling corporate drug pipelines; recurrent patent expiries as over 30 small-molecule drugs come off patent by 2014; and the threat from generics and super-generics, for which revenues may exceed $848 billion by the end of 2010; coupled with failure to exploit new technology and new targets emerging from post-genomic science. These have all conspired to stymie the global pharmaceutical endeavour and biologic therapies, such as vaccines and protein therapeutics, have grown in significance” [1]. While this may have been somewhat overestimated, it nonetheless retains more than a remnant of truth. From 2013 till 2018, patents will expire for drugs with sales in excess of $200 billion. 2012 saw losses from patent expiry totalling $67 billion, while 120 drugs will come off patent in 2013, with losses projected to be $29 billion. Of these, the top 15 are Cymbalta (Eli Lilly’s anxiety and depression drug, which last year grossed $4.9 billion in sales), Avonex, Humalog, Purdue Pharma’s Oxycontin (sales of $2.4 billion in 2011), Rebiif, Aciphere, Xeloda, Neupogen, Zometa, Lidoderm, Temodar, Asacol, Niaspan, and the Novartis anti-osteporosis drug Reclast, generating $612 million.

Pharmaceutical R&D is as notorious for its perceived inefficiency as Corporate Pharma is for its perceived cupidity and ethical ambivalence. It is true that the long development cycles characteristic of drug discovery (10-15 years) and cost structure (R&D invested is typically 18% of sales) is the highest in any industry. Pharma is a business, with all that implies; moreover, drug discovery is just hard: something like 90-95% of projects entering clinical trials fail. Yet the Pharmaceutical Industry remains an essential component of the world economy, while the therapies it discovers are of undisputed societal benefit. In short, it feeds and clothes employees and investors alike, and its products save or improve the lives of millions.

Pharmaceutical R&D is very costly financially and very expensive in other ways, needing considerable investment in resource, time, and ingenuity. A new drug takes up to 15 years to reach market, including 5 years of basic research and preclinical development, followed by 7-10 years for clinical trials. During the late 1990s, the pharmaceutical industry spent a yearly average of US$1.1 billion bringing new drugs to market, doubling to US$2.2 billion in 2009; this equates to a total investment of approximately $1.1 trillion over the last decade. Yet returns on drug investment have dropped from 9% in 1998 to 4% by 2009. Yet, and accepting all that we have said, the Pharmaceutical Industry still remains hugely profitable worldwide. In 2000, total world sales for all human therapies - including small-molecules, therapeutic monoclonal antibodies, vaccines, etc. – exceeded $350 billion, escalating to $850 billion by 2010; with drug sales rising by about 5% a year.

The global market is also highly fragmented: no one dominates the market; even the largest drug company controls only 10% of the market. The structure of the global drug market is also highly biased in terms of target diseases. Over half of marketed drugs target some form of G Protein coupled receptors, including 1 in 4 of the top selling 100 drugs. This equates to sales in excess of $16 billion per year. Many such are so-called blockbuster drugs, earning above $1 billion dollars annually. The biggest sellers have, however, been anti-ulcer drugs, dominating the market for the last quarter century. SmithKline Beecham’s Tagamet, followed in turn by Glaxo’s Zantac and Astra’s Losec, with peak global sales of $6.2 billion. Yet 66% of marketed drugs are said to fail to recoup their development costs.

Drug development costs are driven by the expense of failure, manifest as the so-called attrition rate [2-5]. Only 1 in 12 development drugs reach market. Candidate drugs entering clinical development will typically demonstrate preclinical evidence of efficacy and safety, yet still have more than 90% probability of failing, due to significant side-effects or a lack of clinical efficacy [2-5]. Thus maintaining commercially viable therapeutic pipelines needs a massive enterprise involving many parallel programs, in order to guarantee the survival of a few successful candidates. Attrition, when viewed against ever rising costs and the fact that strengthening regulatory criteria mean fewer drugs that ever actually reach the market, suggests that the whole drug development process desperately needs rethinking.

Faced with the imminent of such a climactic phase, the pharmaceutical industry - as well as industries within the allied sector, including the biotechnology industry, universities, and research institutes - is seeking new and different strategies for drug discovery. Many alternatives to the typical product of the pharmaceutical industry – an orally-bioavailable tableted small-molecule blockbuster drug – have and are being proposed. These include different products and different ways to administer such products. Perhaps the most prominent such saviour is perhaps the biologic drug based on recombinant protein agonists and humanised monoclonal antibody antagonists. Other saviours range inter alia from personalised medicine, through treatments for rare or neglected diseases, antimicrobial agents of...
positive side effects are recognised by online patients’ communities reported data, there is a complementary paradigm, whereby beneficial and characterise, and thus gain proper insight into positive, beneficial 2.0 (bog). This endeavour would aim to identify systematic approach to Drug Repurposing. Some have christened this post-marketing drug surveillance should also allow for a more hospital records, which extend and systematise Pharmacovigilance into litigation. Innovative approaches, such as the statistical data-mining of Pharma companies also monitor case reports involving their own drugs, reporting by patients, pharmacists, and physicians, although most United States. Detection of putative ADRs is reliant on the voluntary reporting by patients, yet does little or nothing to progress the discovery of new drugs [12]. When focussed solely on safety issues, Pharmacovigilance produces information of considerable societal utility to physicians and patients, yet does little or nothing to progress the discovery of new medicines [13]. This is not so much a criticism - for such a purpose this was always the primary historical intention of the discipline - but rather an observation. Hitherto, pharmacovigilance has been largely fixated on delineating ADRs. While this is enormous immediate importance it sells the emerging discipline of pharmacovigilance short. As a discipline, pharmacovigilance can develop further, embracing advanced computational techniques and technology - most notably the internet - as key arbiters and facilitators of its future development. Pharmacovigilance can become as vital a tool for discovering new therapies as it has become in monitoring the safety of extant medicines.

Currently Post-marketing safety monitoring [12] is regulated by the European Medicines Agency in Europe [14,15] and the FDA in the United States. Detection of putative ADRs is reliant on the voluntary reporting by patients, pharmacists, and physicians, although most Pharma companies also monitor case reports involving their own drugs, indicating possible safety issues that might impact sales or worse lead to litigation. Innovative approaches, such as the statistical data-mining of hospital records, which extend and systematise Pharmacovigilance into the proactive sphere, are now being reported [16]. Yet systematising post-marketing drug surveillance should also allow for a more systematic approach to Drug Repurposing. Some have christened this pharmacovigilance 2.0 (bog). This endeavour would aim to identify and characterise, and thus gain proper insight into positive, beneficial effects on both survival and well-being. Alongside pharmacovigilance 2.0, as undertaken by highly-trained scientists or clinicians analysing reported data, there is a complementary paradigm, whereby beneficial positive side effects are recognised by online patients’ communities using techniques culled from the world of social media: a process some liken to “crowd sourcing” [17]. This leverages the motivations and resources inherent in patient groups whose unmet medical need drives the development of novel therapies. This is in addition to the conventional activities of pharmacovigilance: the identification and categorisation of ADRs, as well as the negative and deleterious side-effects, as they manifest themselves during drug use within the wider patient population.

Following primary evaluation, candidates might be fast-tracked for full in vitro and in vivo analysis. Validation through clinical trials will, for novel uses of existing drugs, remain very expensive. In recent years, the Pharmaceutical industry spent over 90% of R&D budgets on Phase III clinical trials; unsurprising given such trials can have as many 20000 enrolled patients with each patient costing over $12000. The Pharmaceutical Industry is reluctant to invest in such undertakings without water-tight patent protection, perhaps necessitating public-private finance initiatives. More straightforward instances might be rationalized using well-studied and well-understood mechanisms of action and disease pathways, and be made available via off-label prescribing.

There are, of course, other approaches to Drug Repositioning, which would act synergistically with Pharmacovigilance as another tool for repurposing drugs. Companies dedicated to Repositioning include: Sea Change (seachangepharma.com), Numedicus (numedicus.co.uk), Ore (orepharma.com), and Biovista (biovista.com). All such companies seem to work via a haphazard, serendipitous discovery process [18,19]. Large pharmaceutical companies, such as Pfizer and Novartis, are also beginning to express a keen interest in DP.

In contrast to the opportunistic approach of most in the Drug Repositioning field, a few have even sought more systematic and possible more sensible experimental or computational approaches to Drug Repositioning. Some have sought experimental methods, such as Iorio et al. [20] who compared measured gene expression profiles using network analysis [20]. They constructed a network comprising 1,302 drugs and 4,047 similarities between drug pairs and used it to correctly predict Mechanisms-of-action for nine anticancer compounds. They also discovered that a Rho-kinase inhibitor could be repositioned as a cellular autophagy enhancer.

Others have used computational approaches [18]. Most in silico methods are based on the analysis of chemical structures, transcriptional responses following treatment, and the mining of text and database annotations [21-23]. Notable such examples include Keiser et al. [24] who used chemical similarity between 3,663 licensed or investigational drugs and the known ligands of hundreds of target proteins to identify thousands of unanticipated potential associations [24]. Thirty were tested experimentally, and one confirmed in a mouse knock-out model. Campillos et al. [25] used recorded side-effect similarities to identify drugs with the same target. Applied to 746 marketed drugs, a network of 1,018 drug-drug relations was seen [25]; 261 of these comprised chemically dissimilar drugs with distinct therapeutic indications. 20 of the drug-drug relations were tested experimentally. 13 of which were validated using in vitro binding assays; 11 had inhibition constants less than 10 micromolar. Schneider et al. used so-called self-organizing maps to identify compounds to be repurposed [26].

Pharmacovigilance aside, the most obvious tools for drug repurposing are high-throughput screening (HTS) and its computational twin: virtual screening (VS). In either case we can envisage subjecting the so-called druggable genome to screening either.
experimental or computational. The case of HTS has been made before. Virtual Screening can also identify real, high-affinity ligands with unmatched cost-effectiveness and efficiency [27]. Three-dimensional or structure-based virtual screening (SB-VS), which utilises automated protein docking (APD), is an efficient and effective way to identify ligands with unmatched rapidity [28-30]. APD-based SB-VS docks enormous numbers of ligand molecules into a defined binding site [27]. SB-VS is usually logistically efficient, saving significant labour and resource. Months of robotically-mediated experimentation are replaced by days or - at most - weeks of computational analysis, complemented by a handful of reliable, hand-crafted assays. Only a small selection of highly prioritised molecules need ever be tested [27]. This handful is put through a hierarchical cascade of highly specific and informative assays in vitro, with actives then tested for their whole system properties in vivo.

Above all, VS represents a systematic approach to Drug Discovery. Whatever anyone might say, traditional approaches to drug discovery is decidedly unsystematic, indeed as it is deployed, it is almost anti-systematic, with companies generally chasing the same small cadre of proven drug targets and financially-remunerative diseases. Rare diseases and diseases prevalent in underdeveloped nations were hitherto given short shrift. Driven by the prospect of patent expiry this attitude is changing. Had the enormous effort expended over the decades by Big Pharma instead been directed into a coordinated and well-orchestrated systematic drug discovery then we might have hundreds more medicines combating dozens of major disease groups. Of course, with such a venture comes the bureaucratic nightmare and incipient complacency that tend to characterise and bedevil such public undertakings, yet has the achievement of the profit-driven competition model of private industry been so great that it justifies the wastage of duplicated effort. Would a globally financed United Nations drug discovery effort not have been more successful? Drug repositioning propelled by pharmacovigilance and virtual screening may in some way redress the balance, squeezing every last scintilla of medical pragmatism from the decades of impossibly-expensive clinical trials.

If the auspices hold, Drug repositioning should prove to be a low risk, low cost, innovative, yet financially-viable strategy for the development of drugs. Discovering new indications and applications for extant drugs and safety-evaluated, late-phase drop-outs possesses enormous potential for improving the health of patients and identifying additional new revenue for cash-strapped pharmaceutical companies. While efforts in universities, research institutes, and the pharmaceutical industry are continuing to increase, obstacles remain before repositioning can become a steady source of new medications. Nonetheless, Drug repositioning seems to have a promising future, if we can combine the PharmacoVigilance with other techniques, such as HTS and VS, should - in the medium-term - become a standard of process of resource utilization within drug discovery.

References