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REVIEW ARTICLE

Pimping up Drugs Recovered, Superannuated and Under Exploited Drugs - An Introduction to the Basics of Drug Reprofiling

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Abstract: Drug development has moved along way forward from the days of with doctors peddling cauldrons of herbs and spices, however, the process can still miss opportunities for full exploitation of a drug's potential. Drug reprofiling provides a chance for an established or a forgotten drug to move into a new area of therapy, whether related to the known effects or in a completely new area. In an era of environmental awareness and spiraling costs for traditional drug development, a strategy to squeeze every benefit out of drugs with known safety, tolerability and pharmacological parameters must be a strategically sound desire. We explore examples of success in reprofiling, draw comparisons between techniques, and finally provide two examples from the Valirx plc development pipeline currently undergoing the process.

Keywords: Reprofiling, development, techniques, health economics, risperidone, cancer.

1. INTRODUCTION

Many methods of drug development have passed through fashion, from high-throughput screening [1], to targeted molecular design [2] and natural product selection [3]. A technique that has been re-invented at regular intervals (usually with a new name) is one that ironically also re-invents the drugs in question. Drug re-profiling, (also known as therapeutic switching, repurposing or drug life cycle management) is the re-development of a drug for a use that is an alternative disease or patient population than that for which it was originally developed. For a drug to have a biological effect, it is almost guaranteed to have more biological effects than the developers intend, whether caused by off-target action, whereby the drug hits multiple types of biological sites, which is more common in older drugs; or those side effects that are inevitable due to the action of the drug, such as initial light-headedness being caused by a drug designed to reduce blood pressure. By harnessing either of these classes of serendipitous drug action, a new application for the drug may be developed.

Drug discovery is an expensive process. The cost of bringing a drug from the early discovery stages through to the market currently stands at an estimated average of $2.6 bn [4]. This cost incorporates even more than a simple total of the numbers of patients that go through the multiple phases of clinical trials, the animals that must be tested on during the preclinical stage and the initial screening, design and development stages; they must also include a factor of the number of failures of drug candidates throughout this process. Statistics for failure can range in estimate from 90% to 99+% [5] depending on the source or stage of development considered, with the majority of these being due to toxicity found prior to (and more rarely during) clinical trials or a lack of

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relevant bioavailability found during early clinical trials, where the drug is found to not be absorbed and present in the appropriate body part to treat the disease [6].

In drug reprofiling these risks all but disappear, with drug metabolism and pharmacokinetics already established in a reincarnation of a previously developed drug, and the decision of route of administration and formulation can be made in a much more informed manner. The failure risk of lack of efficacy in the treatment of a disease remains during clinical trials, but leapfrogging the early stages, and minimising these risks highlights the biggest advantages to the technique, demonstrating lower risks, costs and time of development. When you already know the pharmacokinetics, safety, tolerability, contraindications and special populations of a drug under development, half the patient information sheet is already written. If it were all that simple though, surely everyone would be doing it, so let us also consider the challenges, and a few of the solutions with worked examples.

1.1. Off-Label Use

Off-label prescriptions of drugs may be frowned upon by regulators, but impossible to stop by GPs in practice – particularly where the label is geographically constrained, for example Bupropion has an FDA (US) label as a smoking cessation aid and an anti-depressant; yet in the UK has a label only for smoking cessation, leading to temptation by UK physicians to prescribe it off label for depression-related diseases [7]. This act of prescription is not illegal [8], if a physician feels that a patient will benefit from an off-label prescription and a labelled drug is not available to that patient, then this is an acceptable use. It is not, however, allowed for a company to promote the use of their licensed drugs to be used in any disease state or patient population for which it does not have full regulatory approval [9]. This legality of non-promotion of off-label uses of drugs has frequently been enforced, with highly visible lawsuits against companies such as J&J for the actions of their sales representatives in recommending risperidone prescription for geriatric patients [10], but why would a pharmaceutical company carry out the trials to register an alternate use if the drug is already off-patent and available at a fraction of the price through a generics company?

A challenge for the re-development of a drug into a new disease use, therefore, needs a differentiating feature to secure both the intellectual property prescription to allow premium pricing but also to prevent off-label use of the original product which will have limited or no remaining patent coverage. The latter may be achieved simply by using a geographical switch, for example or by using a drug that is no longer in regular use, such as Thalidomide which has moved from being withdrawn an anti-emetic after the teratogenic properties were discovered, to be reborn as first as a treatment of leprosy [11] and later yet again as an anti-cancer treatment of multiple myeloma courtesy of Celgene's re-development program [12]. An even lower risk strategy is demonstrated by the re-licensing of paroxetine from long-standing use as the anti-depressant treatment, Paxil, to be re-launched in 2013 as Brisdelle, a treatment of menopause-related hot flashes – with differentiation provided merely by a decrease in dose from 20 mg to 7.5 mg, below the minimum tablet size previously available, as well as below the level for which side effects were commonly observed [13].

1.2. Intellectual Property

Intellectual property protection, in the traditional form, of a patent has been clarified in recent years, with the European patent office defining "Second Medical Use" patents as those quoting a known medicament to be used for the treatment of a disease in a sufficiently inventive way [14]. The US patent office allows consideration of "methods of treatment" to cover a comparable, although slightly differently worded coverage of marketing of a drug development program delineated by disease rather than solely by drug structure [15]. Although this does not prevent off-label uses, with astute alterations to either the formulation or dosing level/schedule, this protection is sufficient that the prescription of the new branded treatment will be preferred over the generic. For example, by the use of a delayed release formulation, or an entire switch in the route of administration. An anti-histamine cream to treat an insect bite may be possible to affect with a crushed oral anti-histamine tablet in a plain cream, but why would the prescriber not opt for the pre-formulated, dermal cream.

Reformulation can be explored in much greater detail as a strategy for reprofiling; in fact, it is the answer to many of the criticisms of the entire

paradigm of recycling old drugs for new uses – the true way of adding bling to a development process!

Arguments against reprofiling include the automatic expectation of side effects in the form of the effects of the original use, lack of composition of matter patent protection, off-label prescription risk and overcoming any prejudices or prior reputations of the drug.

1.3. Current Reprofiling Case Studies

Our development program VAL401 provides an example of the combination of reprofiling with reformulation above, and as such we explore the details below to provide an outline of a successful reprofiling process [16].

VAL401 is a formulation of Risperidone in a lipid-filled capsule currently in clinical trials for the treatment of non-small cell lung cancer. Risperidone has a history of clinical use as an anti-psychotic, being developed originally as an oral tablet for use as a once or twice a day treatment, formulations have extended to include oral disintegrating tablets and extended release intramuscular injections [17].

Risperidone has a chequered and very public history. As one of the first of the group known as atypical anti-psychotics, it was first approved for use for the chronic treatment of schizophrenia and bipolar disorder in 1993, revolutionising treatment for many patients, who had received no new treatment options for many years [18]. The licensed uses have expanded across the decades of international clinical use, and it became the first anti-psychotic to be specifically prescribed for adolescent schizophrenia, and is now used also to treat autism-related aggression in children [19].

However, the developers, Janssen, have come under intense scrutiny as they faced accusations of under-reporting some side effects, with gynecomastia in pubescent boys being of particular distress [20]. Off-label use has also been widely evident, with literature reports of Risperidone being used in late stage cancer patients to treat chemotherapy-induced delirium [21] and nausea [22]; and in teenage girls to treat anorexia [23].

In fact, all anti-psychotics (both typical and atypical) carry a black box warning against the treatment of delirium in geriatric patients after a meta-analysis demonstrated an increase in the incidence of death in treated patients [24]. On this matter Janssen have defended a number of lawsuits for off-label marketing, where sales representatives were accused of promoting use in the geriatric population in nursing homes.

In spite of this sometimes negative publicity, Risperidone remained an ideal choice for a reprofiling project. Despite a host of known dopamine and serotonin receptor interactions, the extent of the clinical anti-psychotic effect of Risperidone is not fully explained, by comparison to other antipsychotic drugs [25]. Therefore, when the opportunity presented to look for other biological causes of effect, we were intrigued to discover that Risperidone inhibits an enzyme known as HSD10 (hydroxysteroid dehydrogenase type 10) [26]. This is a redox enzyme, involved in many intracellular reduction and oxidation reactions with substrates including steroids, fatty acids and lipids [27]. In our experiments, Risperidone inhibited both oxidative and reductive actions of HSD10.

Although there is no published evidence that this inhibition contributes to the anti-psychotic properties of the drug, there are many literature references to HSD10 as a putative, but as yet unexploited, target for anti-cancer treatments [28]. It is interesting to note that HSD10 is overexpressed in a number of adenocarcinoma cell lines, and in our experiments VAL401 is selectively effective at targeting these cells [29].

This data provided sufficient evidence to investigate Risperidone as a reprofiling candidate, of an off-target example, however, initial results using the drug directly against relevant cell lines in vitro provided insufficient therapeutic effect. Formulation screening with lipids remedied this lack, and VAL401 was confirmed as a specific reformulation of lipidic Risperidone, with preclinical studies demonstrating safety, pharmacology and anti-cancer efficacy sufficient to build a package of data including the clinical data available on conventional Risperidone.

VAL401 is now entering the clinical stage of development by moving straight to a Phase 2 clinical trial for the treatment of end stage non-

small cell lung adenocarcinoma patients, entering with the dose level and schedule intended in the eventual market label. The pre-knowledge of side effects, contraindications, tolerability and special indications allowed an exemption from Phase 1 trials to be effected, and the ready availability, as well as pre-knowledge of formulation and stability parameters allowed an accelerated CMC program.

The conversion of this active ingredient from anti-psychotic use to use in terminally ill cancer patients, allows an acceptance of the side effect profile. As a general rule, the more severe the disease, the greater side effect burden can be tolerated; but in this case the argument is even greater. The greatest side effect from chronic Risperidone use is reported as being an increase in appetite leading to a significant gain in weight in the patients, as late stage lung cancer patients are usually suffering from the wasting of cachexia, this 'side effect' is seen as an advantage; while the primary pharmacology is not perceived as being an additional hurdle, as the modulation of dopamine and serotonin levels is expected to provide an amelioration of potential instability in the patients. The pubescent male gynecomastia is of course completely irrelevant in this patient population, as the late stage lung adenocarcinoma population includes very few if any pubescent boys. This provides an example whereby the side effects and original desired effects are either acceptable in the patient population, or in fact irrelevant to the patient [30].

At the beginning of this reprofiling project, consideration was also given to the patent landscape surrounding Risperidone. As the drug was only just coming off patent for the original composition of matter patent, this was judged ideal, as the active ingredient was available as a generic, but the development was recent enough to ensure that development was carried out to modern standards. The reformulation required to achieve the anti-cancer activity of Risperidone provided opportunity for patent protection of the formulation and process surrounding this, as well as for the method of treatment utility patents. In fact we have been granted US patent protection on both these elements, and international protection is pending, demonstrating the strength of the program strategy [16, 31].

Our other current clinical program (VAL201) is a good demonstration of how a drug life cycle management can be built in from the very beginning of the program. In this example it is a function of the mechanism of action, the inhibition of the docking of estragon and androgen receptors to the SH3 domain of SRC kinase [32]. This inhibition is believe to be the primary mode of action for the use of VAL201 in the treatment of prostate cancer, for which it is currently in clinical trials as a sub-cutaneous injection; but even before this trial is complete, investigations are underway to reformulate VAL201 API into a newly designated drug product (IMP) VAL301 into an implantable device or an oral formulation for use in the treatment of endometriosis.

In this case we will be able to project the safety and tolerability data from the men in the prostate cancer clinical trial to short-cut the Phase 1 Clinical trial, and use the pharmacokinetic data to provide an indication of the level of dosing needed in the women enrolled in the endometriosis trial. This package of information will allow a fast-tracked discovery process to design a trial that co-ordinates the level of drug being release from the implant into the patient's bloodstream with a measure of disease modifying effect – such as a reduction in pain or lowering of endometrial lesions.

This therapeutic switch from prostate cancer to endometriosis provides a life cycle management that will extend the patent protection over VAL201, include an element of reformulation to produce the implant, which may also ultimately be also used in cancer patients, and potentially provide an accelerated solution to a very much unmet medical need. By developing both disease indications nearly in parallel, in this case we are able to assist both programs by transfer of real-time information about patient responses, formulations and opportunities.

CONCLUSION

Therefore, in summary, we present reprofiling as an economic and environmentally friendly alternative to traditional drug development. There is the recycling of out dated solutions of the problems into the shiny new tools in the

physician's toolkit. Although frequently out of fashion, this process of checking the fundamental science beyond compounds should be included in the to-do list of any company, when looking forward to expand the clinical pipelines.

Too often reprofiling is used only in an emergency to shift a candidate that has failed efficacy trials in a cancer indication to an alternative cancerous body-part; whereas we believe an understanding of the overall biological action of a drug can allow access to entirely new opportunities for use. With ever increasing understanding of genomics, epi-genetics and network pharmacology we have confidence that the ability to harness the power of old compounds will become ever more valuable.

The two examples described above within the Valirx portfolio are ideal examples of the strategy in practice, and demonstrate how a forward-thinking company can maximize opportunities from a basic science understanding; it is the authors' opinion that the acceptability of this approach will continue to increase in trend.

LIST OF ABBREVIATIONS

API = Active Pharmaceutical ingredient
CMC = Clinical Manufacturing and Composition
FDA = Food and Drugs Administration
IMP = Investigational Medicinal Product
USA = United States of America

CONFLICT OF INTEREST

SJD and GSM are employed by Valirx plc and its subsidiaries and have been involved in the direct project management of the VAL201, VAL301 and VAL401 programs discussed herein.

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