

Teaching Old Drugs New Tricks

Drug reprofiling – finding a new indication for a drug – is one way to maximise the potential of a drug. Catherine Brady, Alan Boyd, John Gordon and Nicholas Barnes at Celentyx Ltd highlight the benefits of drug reprofiling as a strategy for drug development



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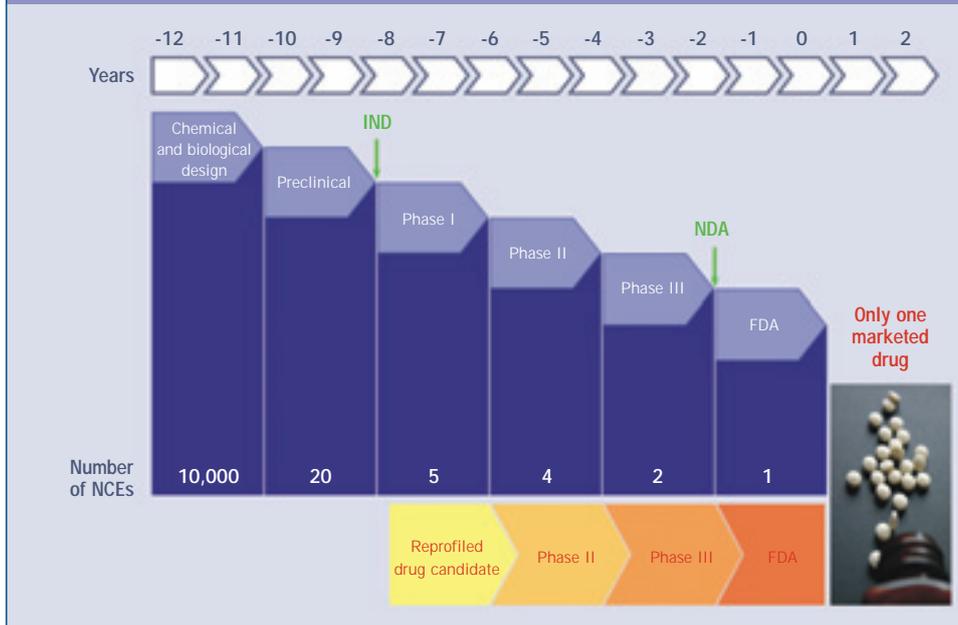
Pharmaceutical research is associated with high costs, both in terms of time and money. In the last year, drugs with a value of over \$20 billion have come off patent, meaning many pharma giants face a crisis in their late-stage product pipeline. This, in addition to the high risks involved in getting a drug to market, encourages maximal exploitation of drugs already proven safe.

It is becoming increasingly difficult for the giant pharmaceutical companies to maintain their success. The delivery of blockbuster drugs to sustain their growth offers enormous challenges, yet is required to nourish the colossal budgets associated with the very risky business of pharmaceutical R&D. The major threats to a drug in

development are twofold; first, that the drug lacks clinical efficacy, and second, that it displays unsuitable characteristics, such as an unacceptable side-effect profile. Although there are a few exceptions (for example, thalidomide, where the side-effects were associated with a distinct population), often little is done with these failed drugs.

Figure 1: Classical drug development versus the reprofiling process

Comparison of the drug development pathway for a novel chemical entity (NCE) and a reprofiled drug. Typically development of a NCE can take over 12 years with less than 1:10,000 reaching the market. Reprofilling 'safe' drugs bypasses the biggest risks to successful drug development and provides a cost and time-efficient delivery of drug candidates for clinical trial. Investigational new drug (IND) (status granted by regulatory authorities); new drug application (NDA) (to an appropriate regulatory authority, such as the Food and Drug Administration (FDA))



To name just one failure in the later stages of clinical development (Phase III), Pfizer's anti-hypercholesterolemia drug, torcetrapib, was terminated due to adverse side-effects – by which time some \$800 million had been spent on the project with little to no chance of return. Worryingly for the pharmaceutical industry, up to two thirds of drugs in clinical development fail due to safety issues. Given this high failure rate of drugs (see Figure 1), maximising the revenue from drugs that are already marketed perhaps offers a new take on the famous mantra of the Nobel Prize-winning pharmacologist, Sir James Black, "The most fruitful basis for the discovery of a new drug is to start with an old drug." This lifecycle management of marketed drugs has essentially two approaches:

1. Extend the exclusivity period of a successful drug by, for example:
 - ◆ Identifying an advantageous reformulation
 - ◆ Broadening the patient population (inclusion of children, for example)
 - ◆ Extending the drug use to related indications (for example, further subtypes of depression)
2. Identify a new indication for the drug

The latter process is given various tags; reprofiling, repositioning, therapeutic or indication switching, repurposing – but the bottom line is that the drug has already navigated the choppy waters of pre-clinical and clinical development, which massively reduces

the risks associated with the further development of the drug.

The clear challenge to successful drug reprofiling is the identification of suitable new indications. Often by definition the patent life on the drug (as novel matter) will be relatively short – indeed if not already expired – and hence a 'medical-use patent' for the new indication is required to offer protection within the sector. However, it still remains a potential problem that generics can be prescribed 'off-label', although reformulation and altered dosing strategies for the new indication can provide significant barriers. Furthermore, for rarer indications, the benefit of a drug receiving 'orphan status' from regulatory authorities offers additional

shielding as well as other incentives; particularly relevant for small- to medium-sized pharmaceutical companies that have less need to develop blockbuster drugs.

The importance of a granted 'use patent' to safeguard the company's interest may, however, prevent obvious new indications from being pursued due to 'prior art' considerations damaging the likelihood of patent approval. Hence a number of companies have developed a technology platform that identifies the all-important inventive step in the identification of a potential new use for a drug (for example, Arachnova's CANDI®, Gene Logic's DRS™ and NeuroCure's repurposing programme). One further such strategy was developed by Celentyx Ltd. The

Figure 2: Example of a proprietary technology process to facilitate drug selection for reprofiling

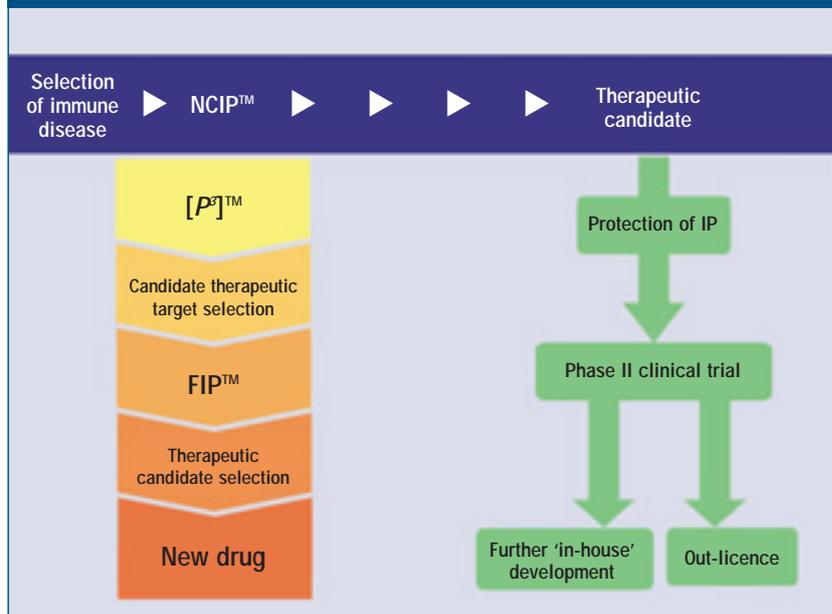


Table 1: Example companies that reprofile drugs

Company	Reprofiling approach	Therapeutic focus	Source
Arachnova	Public info and company insight	Multiple	www.arachnova.com
Aspreva	Proprietary screening programme	Rare diseases	www.aspreva.com
BTG	Public info and company insight, collaborative research projects	Multiple	www.btgplc.com
Celentyx	Novel research using NCIP™	Immune system disorders	www.celentyx.com
CombinatoRX	Public info and company insight	Inflammation and cancer	www.combinatorx.com
Curidium	Novel research using Homomatrix®	CNS	www.curidium.com
Cypress Biosciences	Public info and company insight	CNS and fibromyalgia	www.cypressbio.com
Daniolabs	Novel research using zebrafish	CNS and ophthalmological diseases	www.daniolabs.com
Dynogen	Public info and company insight	Gastrointestinal and genitourinary diseases	www.dynogen.com
GeneLogic	Novel research using Drug Repositioning and Selection™ Programme	Multiple	www.genelogic.com
KineMed	Novel research using KineMarkers™	Multiple	www.kinemed.com
Melior	Discovery, impact of drug on biology	IBS, diabetes and obesity	www.meliordiscovery.com
Somaxon	Public info and company insight	CNS	www.somaxon.com
Sosei	Drug reprofiling platform®	Cancer, pain, respiratory disease, nocturnal enuresis	www.sosei.com
Syntopix	Novel research (bacteria)	Acne and S aureaus infections	www.syntopix.com
Vastox	Novel research using fruitflies and zebrafish	Multiple	www.vastox.com

process uses proprietary novel clinical indication profiling™ (NCIP™) (see Figure 2, page 101) to hunt for druggable targets on pathological or dysregulated human immune cells termed Pharmaceutical Proteome Profiling™ ([P²]). The understanding of a cell's 'pharmaceutical proteome' then directs potential therapeutic target selection in the knowledge that a suitable drug is already available to engage the identified target. Subsequent

proof of concept research on the target human cells, Functional Immuno Profiling™ (FIP™) allows an early (and hence cost effective) go/no-go decision to perform Phase II clinical trials, aided by the availability of the 'safe' drug.

Due to the obvious appeal, the reprofiling market is becoming increasingly competitive, and so the growing number of companies adopting this approach often try to carve their own niche, be it a particular therapeutic area or the proprietary technology platform that underpins project identification (see Table 1). Many of these companies are relatively small, which further allows efficiency in the earlier stages of drug development, although if the drug remains in-house, the



Table 2: Examples of reprofiled drugs that are marketed or in the late stages of development

Drug	Original indication	Reprofiled indication	Brand name
Apomorphine	Parkinson's disease	Erectile dysfunction	Uprima*
Bupropion	Depression	Smoking cessation (1)	Zyban*
Duloxetine	Depression	Stress urinary incontinence	Cymbalta*
Finasteride	Prostate hyperplasia	Male-pattern baldness	Propecia*
Imidapril	Hypertension	Cachexia (2)	Vitor*
Mycophenolate mofetil	Transplanted organ rejection,	Lupus nephritis (3) Pemphigus vulgaris (4)	CellCept*
Ropinirole	Hypertension	Parkinson's disease, primary restless legs syndrome	Requip*
Sildenafil	Hypertension, angina	Erectile dysfunction	Viagra*
Thalidomide	Emesis	Erythema nodosum leprosum (5) Multiple myeloma (6)	Thalomid*
Retinoic acid	Acne	Acute promyelocytic leukaemia	Vesanoid*

1. Potentially also obesity and sexual dysfunction
2. Weight loss associated with cancer
3. Renal symptoms associated with lupus erythematosus
4. Blistering skin condition
5. Skin condition associated with leprosy
6. Potentially other cancers and inflammatory diseases

latter stages of project development towards reaching the market may necessitate partnering – however, the option to out-license the project is often attractive, particularly for these smaller companies. The proliferation of reprofiling companies also reflects the availability of venture capital funding chasing the potentially lucrative de-risked drug-to-market reprofiling strategy. The increased speed by which significant milestones in

the drug development process are reached, at least in the early stages (up to Phase II), rapidly adds value to promising projects, offering attractive timelines for investor exit.

An alternative avenue to part-finance emerging drug reprofiling companies is to offer the proprietary drug reprofiling strategy to other pharmaceutical companies on a service or partnering basis (such as Arachnova, Celentyx, GeneLogic, Vastox). Pharmaceutical companies are well aware how difficult and expensive it is to take a new chemical entity (NCE) to market, and increasingly see the benefit of leveraging further value from their own products, without the huge risks associated by developing a NCE. A number of such associations have been reported (Gene Logic's deal with Pfizer, for example), which is likely to add momentum to this approach.

A focussed approach to drug reprofiling is fast becoming a recognised arm of pharmaceutical R&D, and the upward trend is likely to continue. This attractive strategy delivers drug champions at a fraction of the cost, with the added benefit to patients of a drug less likely to cause side-effects. ♦

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There are a number of positives and negatives associated specifically with the reprofiling approach to drug discovery and development:

Positives

- ◆ Clinical pharmacology already well understood aiding selection of lead compound
- ◆ Early proof-of-concept in clinical trial offering early go/no-go decision
- ◆ Reduced likelihood of failure due to safety
- ◆ Known manufacturing process of active pharmaceutical ingredient

Negatives

- ◆ Requirement of inventive step to support patent protection
- ◆ Availability of suitable drug and associated data package (particularly if drug still patent protected)
- ◆ Reformulation/different route of administration may not work or introduce problems
- ◆ Competition from generics and off-label prescribing