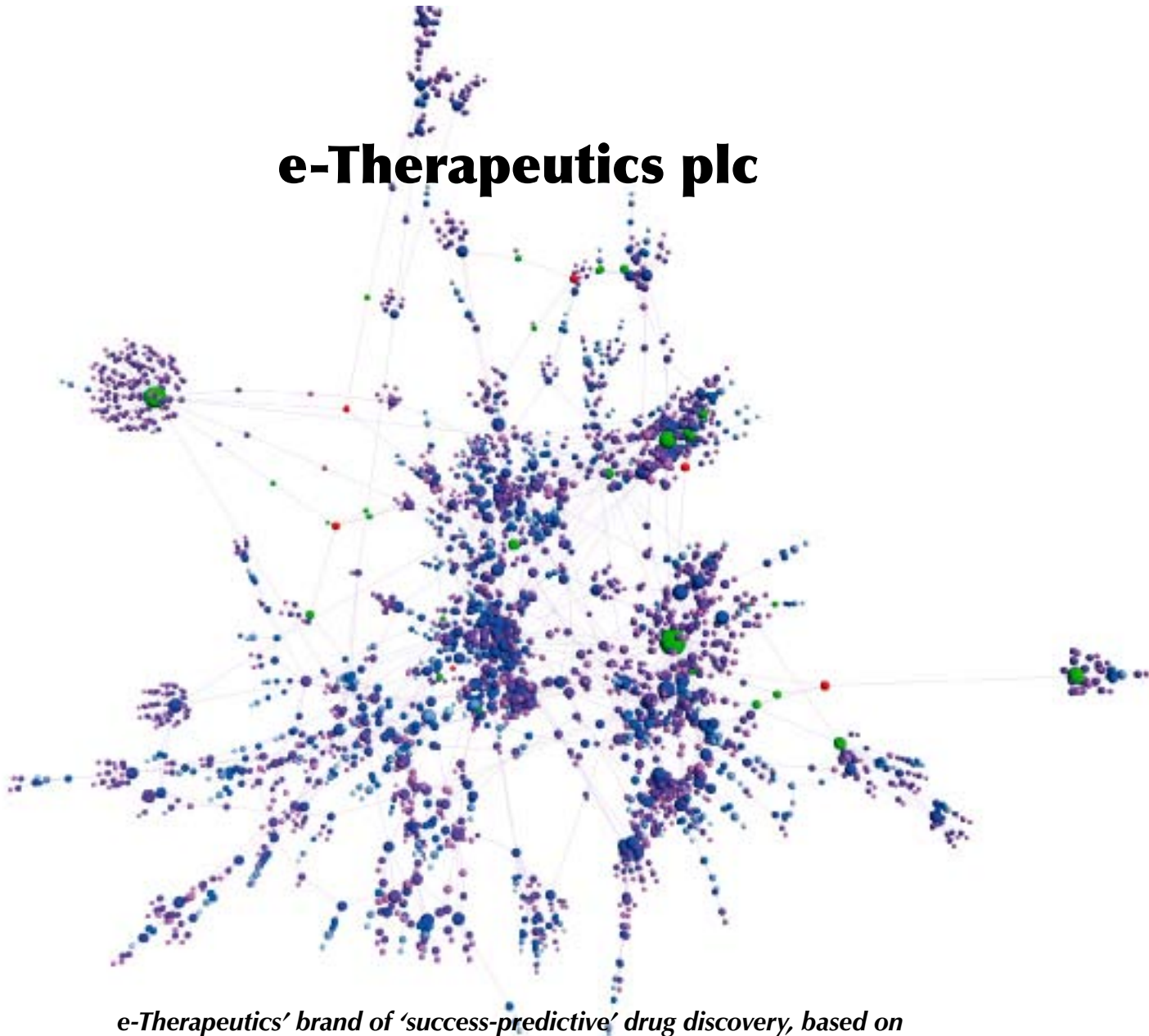


e-Therapeutics plc



e-Therapeutics' brand of 'success-predictive' drug discovery, based on bioinformatics and the analysis of complex biological systems, holds the potential, if clinically validated, to open up entirely new horizons in the treatment of complex, intractable or poorly treated diseases

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I certify that this report represents my own opinions.

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Key Points

18 November 2008

Price: 37.5p

e-Therapeutics' brand of 'success-predictive' drug discovery, based on bioinformatics and the analysis of complex biological systems, holds the potential, if clinically validated, to open up entirely new horizons in the treatment of complex, intractable or poorly treated diseases.

- **If e-Therapeutics has its way, the last frontiers of therapeutic medicine are about to fall** – The treatment of complex, intractable or poorly treated disease remains one of the richest sources of un-mined blockbuster areas of modern therapeutic medicine. e-Therapeutics' predictive drug discovery platform is aimed at providing a solution.
- **Drug development failure rates remain high despite advances in biology** – Only 2-3% of drugs identified as therapeutically relevant eventually make it to market. e-Therapeutics' drug discovery technology is aimed at identifying drugs that circumvent the uncertainties of drug development by identifying drug candidates that offer efficacy and safety.
- **Identification of low-redundancy targets with minimal extraneous interactions are the key** – e-Therapeutics uses powerful computers, integrated databases and sophisticated scientific approaches to overcome the pitfalls of searching for a 'needle in a haystack' in large, complex, 'noisy' data systems. The result is a 'predictive' system that looks for drugs that avoid 'leakiness' in efficacy and tolerance/side-effect interactions with healthy pathways and tissues.
- **The current focus is on re-positioned compounds** – e-Therapeutics has opted to focus first on re-positioning drugs developed for other applications. This represents the 'low hanging fruit' for this technology as it throws up drugs with full regulatory monographs and therefore much shorter development times.
- **Clinical validation and the road to glory** – As with all highly innovative pharma development science, the proof of the pudding remains successful clinical trials that are confirmatory of the predictions of the system. In the end, only clinical outcomes that match the predictions of the system in both efficacy and safety will give this approach the credibility that is needed for e-Therapeutics to become a perceived 'player' in the pharma discovery game.
- **First 'Proof of Principle' trials should give early indications** – The small PoP asthma and depression trials should provide some early insights as to safety and some indication as to whether the predicted efficacy parameters are confirmed. The trials are not statistically powered for efficacy but should give sufficient data to feed into potential licensees.
- **Valuation is indicative and preliminary only** – The valuation work presented here is illustrative in nature. But, should the clinical outcomes match the predictions, what is now highly speculative could rapidly transition into a goldmine of opportunity. Investors, watch this space!

Price chart (p)



Current fair value of equity

Expected value	US\$119.8m
Value per share	US\$2.15 (£1.33)
Optimistic scenario	US\$176.4m
Value per share	US\$3.17 (£1.96)

Company details

Quote

Shares	
- London AIM	ETX
- Berlin	3AQ.BE
Hi-Lo last 12-mos. (p)	70 - 18
Shares issued (m)	55.7
Fully diluted (m)	61.9
Market Cap'n (£m)	22.3
Website:	www.etherapeutics.co.uk

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Overview

e-Therapeutics' black box – a potential disruptive technology

e-Therapeutics plc is a UK-based drug discovery and development company with its head office in Newcastle. Its discovery platform derives from the application of Complex Systems Science, a science that involves the study of interactions within complex biological networks. Massive biological databases containing information about the genes, proteins and metabolites that make up these complex systems are translated into computer-usable information using mathematics and computational algorithms. These data can then be processed via powerful computers, yielding models that can be used to identify important network junctions that have biological relevance in diseased cells and tissues. In turn, these biological 'circuit breakers' can then be used to identify drugs that block them thereby blocking or enhancing a desired biological function.

A pioneer in the application of Network Analysis in Systems Biology

e-Therapeutics is one of several pioneers in the field of Systems Biology as applied to drug discovery and development. The approach it has taken to date has focused on the identification of key network nodes that have the ability to shut down targeted sections of the networks that are active in a particular diseased cell.

Once a data model for a diseased cell has been derived, key system nodes are selected computationally in relation to their ability to shut down the targeted network function and resolve the malfunction that triggered the disease state. e-Therapeutics' analytical system then selects compounds that interact with the key system nodes, but **do not interact** with key nodes in **non-target** cell-types, therefore yielding drug candidates that are **predicted** to be both safe and effective.

A strong pipeline of single and combination compounds tackling major diseases

This approach has yielded a promising pipeline of potential drug candidates in diverse areas such as anti-infectives, anti-depressants and treatments for asthma and cancer. It either yields a single or a combination of compounds depending on whether a single compound has the binding affinities required to effectively and selectively shut down a sub-network.

To start, 'repositioned' is the name of the game.

In its first phase of development, e-Therapeutics has focused on identifying potential drug candidates with clinical regulatory monographs for a particular application that could be repositioned as a treatment for a completely different disease than that originally indicated. These drugs fall into two categories:

- those that have full regulatory safety data that has been validated by a regulator but have failed to show efficacy in either proof of concept or, preferably, in subsequent pivotal trials for a different target indication;
- those already in the market but which are at the end of or beyond their initial composition of matter patent life.

In the field of 'repositioned' drug candidates, the need for intelligent drug formulation and creative patent strategies is a fundamental driver to the business. While in broader terms, Systems Biology offers the potential to identify *new* drug candidates that are 'de-risked' in terms of tolerance and safety, not all elements of de-risking are necessary for re-positioned ones, since their safety profile is already known.

Nevertheless, repositioned drugs bring with them other challenges which include creating new IP that can hold its ground against potential challenge; formulation of the new drug or drug combination to find an optimal dosing regime; and in the case of combination drugs, overcoming any regulatory barriers that creating such a novel entity might entail.

Some early PoC trials with early promising results

e-Therapeutics has risen to the challenge of this novel type of drug discovery/development workflow. Two pipeline candidates have completed their first phase of clinical testing:

- **ETX 9101** is an oral, long-acting anti-asthmatic drug based on the synergistic combination of a repositioned anti-histamine and NSAID¹ both of which are currently marketed and beyond their initial patented life;
- **ETS 6103** is a generic pain medication and is being repositioned for the treatment of depression in SSRI²-refractory MDD³ patients.

The results of the ETX 9101 trial have just been announced which, although of a very preliminary nature, show signs of efficacy and safety that encourage further clinical testing.

The ETS 6103 Phase IIa PoP pilot study (controlled versus amitriptyline) was halted half way through as a significant reduction in depression symptoms was observed.

This drug is intended to be a once daily formulation and is an orally active repositioned compound developed under the hypothesis that in a significant percentage of depressed patients, non-symptomatic pain is involved in the underlying aetiology⁴ of the disease (which is probably why SSRIs do not work in such a large number of depressed patients), so that both mechanisms of central mood and of central pain need to be treated. Hence the development of this drug target was aimed at specific pathways known to be involved in pain and mood. The results of this trial should be announced shortly.

Other candidates all directed at un- or poorly met clinical needs

e-Therapeutics also has:

- a combination drug under development for the treatment of MRSA/VRE/C.difficile⁵ (**ETX 1153**);
- a single agent developed originally for metastatic melanoma (**ETS 2101**) but under investigation as a tumoricidal agent for a wide variety of tumours;
- a combination for the treatment of fibromyalgia⁶ (**ETS 6218**);
- various candidates (**ETS 6107 & ETS 6114**) for the treatment of hypercholesterolaemia but with a view to blocking atherosclerosis⁷ and multiple cardiovascular risk factors as well.

Corporate development activities are in full swing with partnerships in the works

e-Therapeutics is engaged in a wide variety of discussions across the industry to partner the drugs in this pipeline and move them further through clinical development. However, in the near term, the results of its two self-funded Phase IIa trials should provide the evidence needed to validate the company's approach.

¹ Anti-histamines for allergies and NSAID's or non-steroidal anti-inflammatory drugs are used to treat pain and inflammation such as in pre-menstrual syndrome and rheumatoid arthritis amongst many others.

² Selective Serotonin Reuptake Inhibitors of which Prozac was the first and most illustrious member. Patients that are refractory are resistant to treatment.

³ Major Depressive Disorder.

⁴ Aetiology is a medical term from the underlying cause or pathology of a disease. Molecular aetiology would refer to the underlying molecular mechanisms of a disease.

⁵ MRSA or methicillin-resistant *Staphylococcus aureus*, VRE or vancomycin-resistant enterococci and C.difficile or *Clostridium difficile* are all difficult to treat bacterial infections that are associated with very high mortality.

⁶ A chronic musculoskeletal condition involving chronic pain.

⁷ Atherosclerosis is a disease affecting arterial blood vessels. It involves a chronic hardening of the arteries, ultimately leading to the formation of multiple plaques and a narrowing (or stenosis) of the artery.

Valuation

As with most early stage drug development companies, it is easy to get carried away and end up with a great disparity between stock price and valuation. As we have said elsewhere, companies listed on the AIM market are now suffering from a significant change in investor appetite for risk which is reflected in the average 40-60 percent drop in stocks in this sector (and in other similar sectors). In valuing the assets of e-Therapeutics, we have tried to take a very cautious approach to projecting market penetrations in what are very large, and for the most part, established therapeutic markets. As we have discussed further on in this report, we believe that the pricing of drugs will come under increasing scrutiny in the coming years and this has also been reflected in our revenue models.

The current business model of the company is to take compounds through a Proof of Concept or PoC Phase II trial as the basis for inking partnership deals with third parties. We have constructed from our discussions with management and from our own views on the matter, a series of pipeline timelines that drive our model for upfront and milestone payments as well as royalties in our model. As is usual, the set of financial assumptions that underlie our model are depicted in the graphic on the accompanying valuation pages. We have used the standard diMasi probability of success model of the industry with added discounts/premiums wherever appropriate. ETX 9101 and ETS 6103 are estimated to be at Phase II stage with a premium based on the extensive safety data available for these drugs. ETX 6218 and ETS 6103 are not yet in clinical trial but are considered to be a blend of Preclinical and Phase II so end up at a significant premium to preclinical but at a discount to Phase II.

The profile of the drugs being developed, if translated into clinical and regulatory success, would result in the introduction of drugs into the marketplace that could garner significant market shares. Nevertheless, we have refrained from estimating such large penetrations for two reasons:

1. We remain to be convinced that this sort of drug (not generic and not NCE-based proprietary) will trigger partnership deals with the largest pharma companies that have the greatest marketing muscle.
2. These are large highly competitive markets where entrenched positions will put up a vigorous fight to keep new entrants out.

Still, we believe that a clean safety and tolerance profile combined with a highly effective drug could, in the hands of an aggressive regional or specialty pharma company, garner a significant share of each market. We have allowed for two scenarios: one basic, core scenario and the other one more aggressive (primarily in market penetration). In each model, we have taken publicly available data on incidence and prevalence of each disease and calculated the total number of patients that would benefit from these therapies discounted to take into account the precise disease population target. Pricing has been targeted to the market leader or average price of medication and in some cases discounted further to reflect an aim to garner as much market share as possible with a mid-size pharma partner.

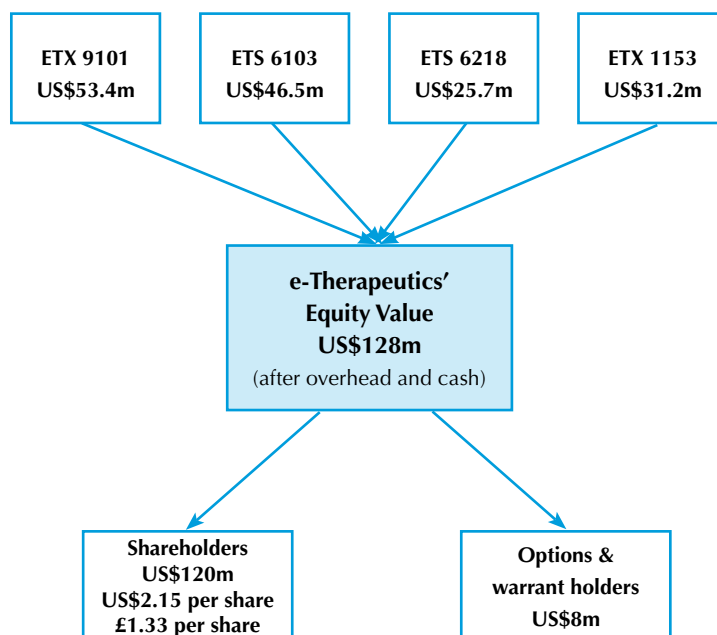
The result is a core valuation of £1.33 and a more optimistic one at £1.96. This is to be compared to a stock price now at 37p, still a long ways away.

Fair value summary (US\$m)

Scenario	Core	Optimistic
Development drugs		
- ETX 9101	53.4	87.3
- ETS 6103	46.5	60.9
- ETS 6218	25.7	27.4
- ETX 1153	31.2	41.7
Less: overhead	32.2	32.2
Expected value of pipeline	124.6	185.1
Add: other assets	0.0	0.0
Add: starting cash + new funds	3.2	3.2
Total current value for firm	127.8	188.2
Less: Bank & other debt	0.0	0.0
Total value to equity claims	127.8	188.2
Less: warrants & options	8.0	11.8
Ordinary equity holders	119.8	176.4
Value per share (US\$)	2.15	3.17
Value per share (£)	1.33	1.96

Components of e-Therapeutics' entity value

If the e-Therapeutics' model works its development portfolio could currently be worth ...



Drug portfolio

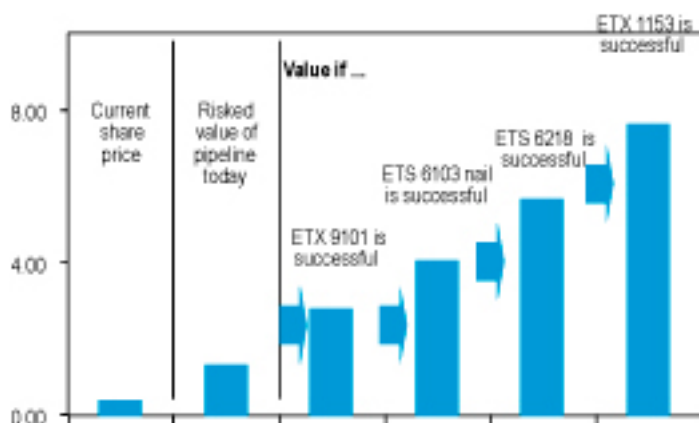
Summary of core drug valuations (US\$m)

Drug	ETX 9101	ETS 6103	ETS 6218	ETX 1153
Royalty revenue				
EV of royalties	271.5	234.5	258.2	316.1
Likelihood of success (PoS)	26%	26%	14%	14%
EMV of royalties	71.7	61.9	35.4	43.3
Add: EMV of upfront payments	2.0	2.0	0.6	0.6
Add: EMV of milestone payments	2.5	2.5	0.8	0.7
less: EMV of dev costs	0.0	0.0	0.1	0.1
EMV	76.3	66.5	36.7	44.5
per share (\$ ps)	1.37	1.19	0.66	0.80
per share (£ ps)	0.85	0.74	0.41	0.49
After tax EMV	53.4	46.5	25.7	31.2
Detailed valuation on page	43	46	49	39

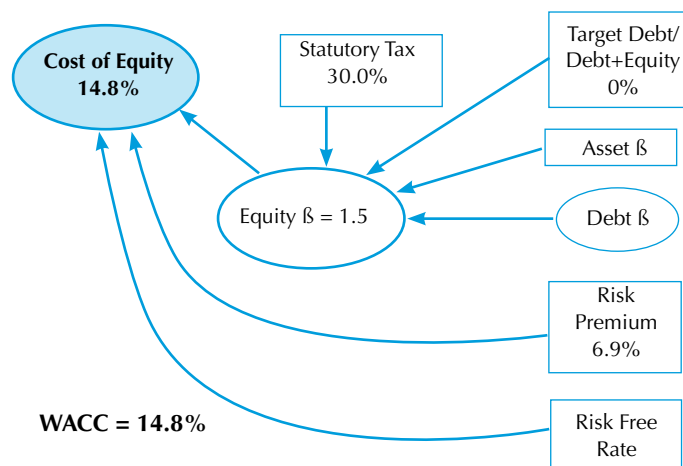
Summary of optimistic drug valuations (US\$m)

Drug	ETX 9101	ETS 6103	ETS 6218	ETX 1153
Royalty revenue				
EV of royalties	454.8	312.0	275.6	425.4
Likelihood of success (PoS)	26%	26%	14%	14%
EMV of royalties	120.1	82.4	37.7	58.3
Add: EMV of upfront payments	2.0	2.0	0.6	0.6
Add: EMV of milestone payments	2.5	2.5	0.8	0.7
less: EMV of dev costs	0.0	0.0	0.1	0.1
EMV	124.7	87.0	39.1	59.5
per share (\$ ps)	2.24	1.56	0.70	1.07
per share (£ ps)	1.39	0.97	0.43	0.66
After tax EMV	87.3	60.9	27.4	41.7
Detailed valuation on page	43	46	49	39

Current EMV and value if pipeline is successful (£ps)



Weighted cost of capital



Key Risks

Inability to deliver clinical outcomes that match the system-predicted safety/efficacy profiles

Validation of the discovery technology rides completely on attaining the predicted safety/efficacy profiles that are the predicted basis for the value of each of the company's pipeline candidates. This is a decisive process which, formulation and regulatory issues aside, will determine the perceptions, both of investors and potential pharma partners, as to the credibility of this approach. The science is plausible and it does deliver candidates; the question that must be answered is whether these candidates pass muster in clinical terms.

Formulation of combination drugs

The ability to formulate a single drug with a known pharmacokinetic profile can be difficult enough. Formulating combination drugs where the pharmacokinetic profile in one application (let alone multiple applications) may or may not be transportable to the re-positioned one poses its own challenges. It is unclear at this time (mostly because it is too early to say) whether this will be easily achievable for each of these candidates.

Safety of novel combination drugs

While individually safe with many years of administration, repositioned drugs in combination may or may not display additive safety. The potential for drug/drug interactions will in some cases need to be vetted to satisfy any regulatory concerns. Initial testing of the asthma-directed oral combination underlying ETX 9101 appears to be safe in the preliminary PoP test the company conducted in India. However, there can be no assurances that this will be the case of other current (ETX 1153 as an antimicrobial for example) or future combinations.

Regulatory uncertainties

While there are significant re-positioned drugs that have passed regulatory scrutiny (Rogaine or minoxidil for hair growth and Viagra for erectile dysfunction are most famous for this), the regulatory climate for drug approvals, particularly in complex, chronic and severe conditions, has tightened up considerably (viz. the Vioxx debacle). The safety profiles of the repositioned compounds being pursued by the company, all drug/drug interaction issues aside, are not in doubt. Despite the availability of section 505 (b) (2) in the US for drugs with legacy safety monographs, the regulatory impediments to market for these drugs remain to be tested particularly as they pertain to novel combination drugs. The expectation that drugs derived from this sort of development workflow will lead to shorter development timelines remains to be tested and confirmed.

IP integrity of the pipeline

The patent position for e-Therapeutics' pipeline remains untested at this time. The company's proprietary data search capabilities do put it in a strong position to identify new applications with no prior art. Nevertheless, until these claims are challenged by third parties, uncertainties will remain as to the strength of these patents.

e-Therapeutics emerged in 2003 as a university spin out. It is based on the research of Professor Malcolm Young and colleagues in neuroscience and complex systems science at Oxford and then at Newcastle University. The company was initially financed through a combination of institutional equity and grants from the UK DTI and the EPSRC⁸. The company now consists of a discovery team in Newcastle and a bioinformatics team in Ahmedabad in India. It attained a listing on the LSE's AIM market in November 2007, under the symbol ETX.

The company aims to discover and develop drugs based on the application of a form of Systems Biology called Network Analysis. Systems Biology in general embodies the use and analysis of collected 'omics'⁹ data, which includes data about metabolism, gene function, protein structure, protein interactions, signaling and regulation within the cell. These data are then structured and embodied in a series of databases which facilitate the construction of network models that can be used as a platform for the discovery of new therapeutic modalities.

e-Therapeutics have developed a proprietary IT-based workflow that collects, segregates, curates and collates the massive amounts of data that are generated into an integrated database that can be mined for network structure (including the identification of functional sub-networks) and function.

It can then be used to extract key network junctures (analogous to circuit breakers in an electrical network) that are able to shut down relevant sub-networks which are either known or thought to represent the underlying cause of targeted diseases. Because the information it collects is segregated by cell-type¹⁰, it can also look for blocking drugs that lack undesirable interactions with other tissues or other key 'healthy' functions.

All of this is directed at discovering therapeutic modalities that are highly effective at resolving the underlying cause of diseases, well-tolerated, and are safe from unwanted side-effects. In other words, ***a system designed to de-risk drug development and improve the flow of new, safe and effective therapies for unmet medical needs.***

While the company conducts research projects on behalf of third parties, its main focus is on the development of its own internal drug pipeline. In the latter activity, the focus has been on compounds that already have regulatory monographs and approvals for therapeutic indications, but which could be repositioned, in a proprietary manner, for a totally different one. It is also moving towards a system that can perform the same function in developing NCEs¹¹.

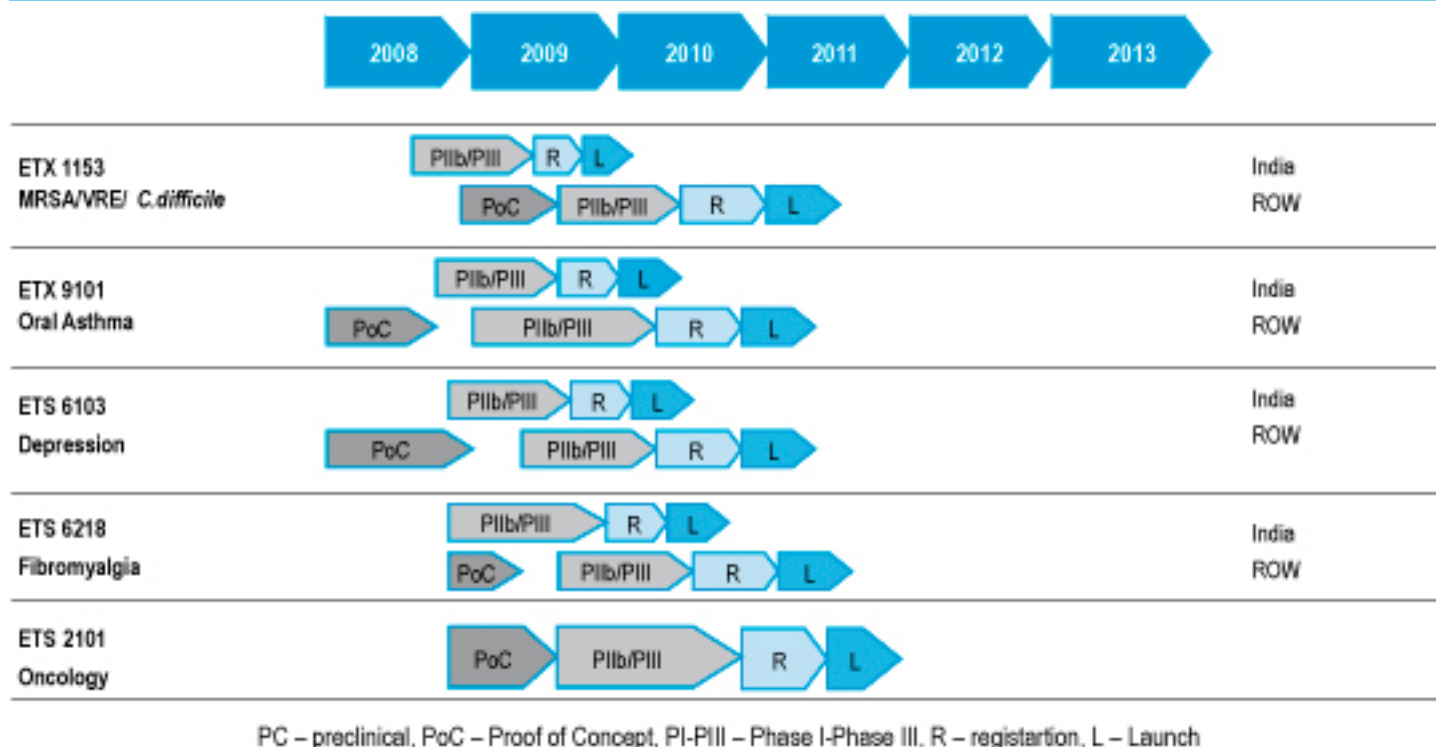
⁸ Department of Trade & Industry and the Engineering and Physical Sciences Research Council.

⁹ 'omics' data are derived from genomics, proteomics, metabolomics and the like.

¹⁰ e.g., blood cells, lung, liver, heart...etc.

¹¹ New Chemical Entities or drugs based on proprietary chemical structures.

e-Therapeutics development pipeline



Source: e-Therapeutics and Objective Capital estimates

As indicated in the accompanying figure the profiles of these pipeline components are diverse indeed. They range from a drug that failed in Phase III clinical trials for neurology being repositioned for cancer; to a combination of off-patent drugs for inflammation and allergies that together are highly effective in significantly reducing the number of attacks in asthma sufferers. Two of these have completed a preliminary PoC Phase IIa clinical trial. The results of the asthma trial (ETX 9101) have just been reported and display preliminary signs of both safety and efficacy which will require further testing. The other trial, in depression (ETS 6103), also showed promising early results which should be announced in the very near future; the rest are in various stages of preclinical development.

Strategically, e-Therapeutics wishes to develop its drugs through to the Proof of Concept or PoC Phase II clinical trials. While for both financial and trial funding reasons, it may ink some early regional deals, the overall strategy is to find partners after a PoC trial has been completed and only a Phase III pivotal trial needs to be conducted. On the back of these data, it will then move to partner these compounds using relatively standard partnership models involving co-development, cost-sharing, upfront, milestone and royalty collection arrangements. All of this forms the basis of current and extensive corporate discussion with potential partners to access funding for the further clinical development of this pipeline.

How e-Therapeutics' 'black box' system works and differentiates itself from other approaches using Systems Biology tools in drug development is a subject fraught with complexity. We have sought ways to reduce this down to a simpler format to the degree possible. Through extensive analysis of the scientific literature, discussions with other scientists in the field and with e-Therapeutics itself, we believe that we have arrived at a view of how the system works (in very broad terms) and how this approach is distinct from what the company views as the mainstream.

While derived from earlier published work in the field of Neurosciences, none of what e-Therapeutics does today is published in the scientific literature. As a result, independent validation of the technology is nigh impossible. The reader will, rightfully, be left with the impression that the only proof of principle that will ultimately hold here is the successful discovery and development of drugs whose system-predicted safety, tolerance and efficacy, translates into clinical and, ultimately, market success.

Glimpses of this sort of success could emerge rapidly with the announcement of the results of the PoC trial in asthma and the upcoming results in depression. We believe some glimpses of success may already be at hand. In some cases, preclinical validation of these concepts has been exceptional but, as anyone familiar with drug development knows, this may or may not hold up through clinical development. In advance of these upcoming developments, we would like to convey an understanding of how the e-Therapeutics 'black box' might be working and, assuming a favourable clinical outcome, the basis for this success.

Complex systems and biology: a primer

Biological systems have had the opportunity over millions of years to perfect the art of dodging the bullet, creating well-honed systems that display all of the functionality required to survive in the environments for which they were selected. The 'robustness'¹² of these systems is remarkable and the conservation of functional molecular mechanisms, from the simplest organism all the way to humans transcends intuitive thought and belief.

The structure and behaviour of complex cellular systems have been found to incorporate some of the same characteristics as human-engineered network systems such as the internet, power and airline grids as well as other natural networks, such as social ones. The common features that link these form the basis of the science of complex networks, derived from mathematics, physics and engineering, applied to the study of biological complexity.

In general, networks consist of connections (interactions) between their constituent nodes (elements). For many years, networks were viewed as a random collection of such connections. Through this randomness it was thought that complex networks could be modeled and explained because the degree of connectivity of each node obeyed an equal, democratic distribution (a bell curve) and had approximately, on average, the same number of links.

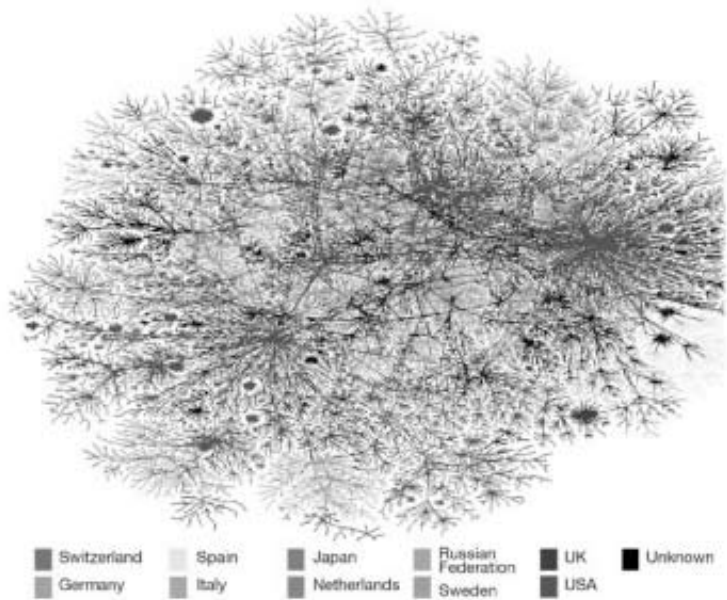
However, this view of networks turned out to be deeply unsatisfactory. An experiment conducted by scientists at Duke University on the structure of the internet which expected to find randomness (everyone's interests combined with the huge number of pages to choose from should have resulted in random patterns) yielded a completely different picture¹³. They found that while most nodes (80%) in the network had only a handful of connections each, there were others that had from hundreds to millions of connections; these so-called 'hubs'¹⁴ were highly connected (viz Google, Yahoo...etc).

¹²This is the ability to withstand attack or inactivation of a portion of the network and survive.

¹³Albert R. et al, *Nature* (1999), **400**; 130-131

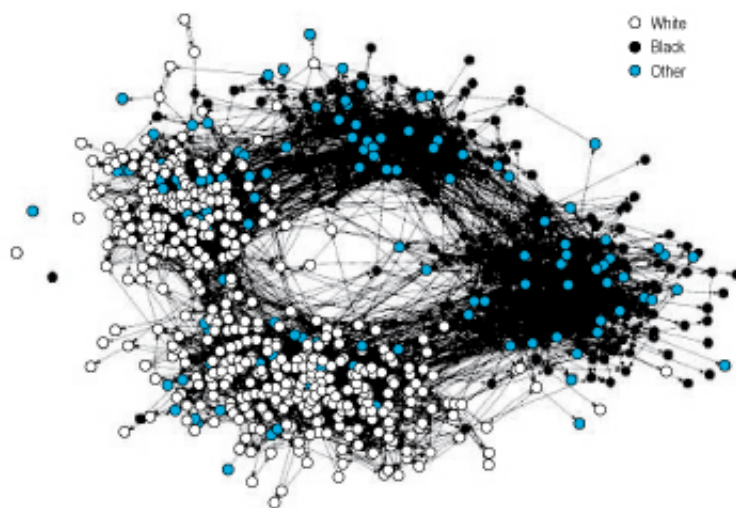
¹⁴Examples of hubs include Yahoo and Google for example or airports like Chicago O'Hare, Heathrow and the like.

Internet



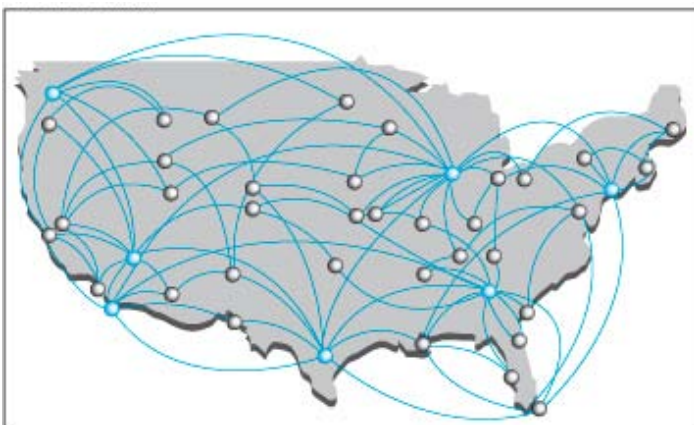
Source: adapted from News and Views, Nature **427**, 27 (1 January 2004)

School network



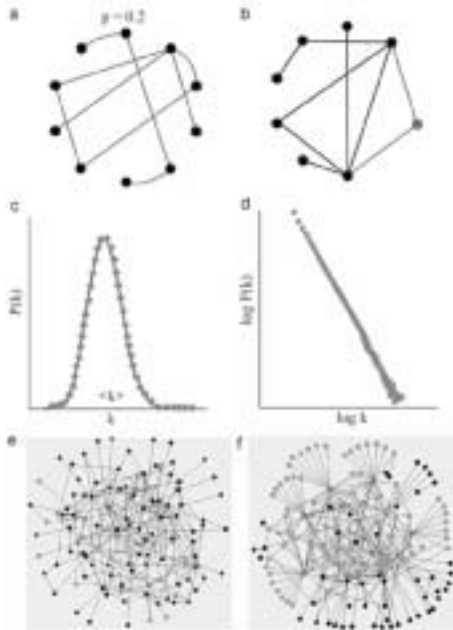
Source: M.E Newman Website, University of Michigan (<http://www-personal.umich.edu/~mejn/>)

Airline network



Source: Barabasi and Bonabeau, May 2003, Scientific American

Random versus scale-free patterns



Source: Barabasi and Bonabeau, May 2003, *Scientific American*

They also found that the distribution of these nodes and hubs did not follow the 'democratic' bell curve distribution but rather obeyed a 'power law'¹⁵.

The importance of this discovery was that in growing networks, the degree of connectivity remains relatively constant.

In a separate experiment¹⁶, the same group conducted a mathematical analysis on the metabolic pathways of 43 organisms across three different domains of life (archaea, which are non-bacterial single cell prokaryotes, bacteria, and eukaryotes) and showed that these exhibit similar topological features to those found in complex non-biological systems. ***This has led to the view that the basic network rules that make the latter robust, tolerant and scale-free seem to apply also to biological networks.***

Given the ability of biological systems to withstand mutation and environmental stress, to adapt and survive, it is not too surprising that nature would have employed principles, evolved through trial and error over millions of years, related to those of today's human-designed networks.

The second important principle discovered was that any node is only a short distance away from any other node in the network. This 'small world' characteristic was popularized in John Guare's play 'Six Degrees of Separation' which derives from an experiment conducted by Stanley Milgram, a Harvard Social Psychologist in 1967 who found that a letter sent from one geographically distant location designed to arrive at a particular individual at another location passed through the hands of, on average, only six individuals.

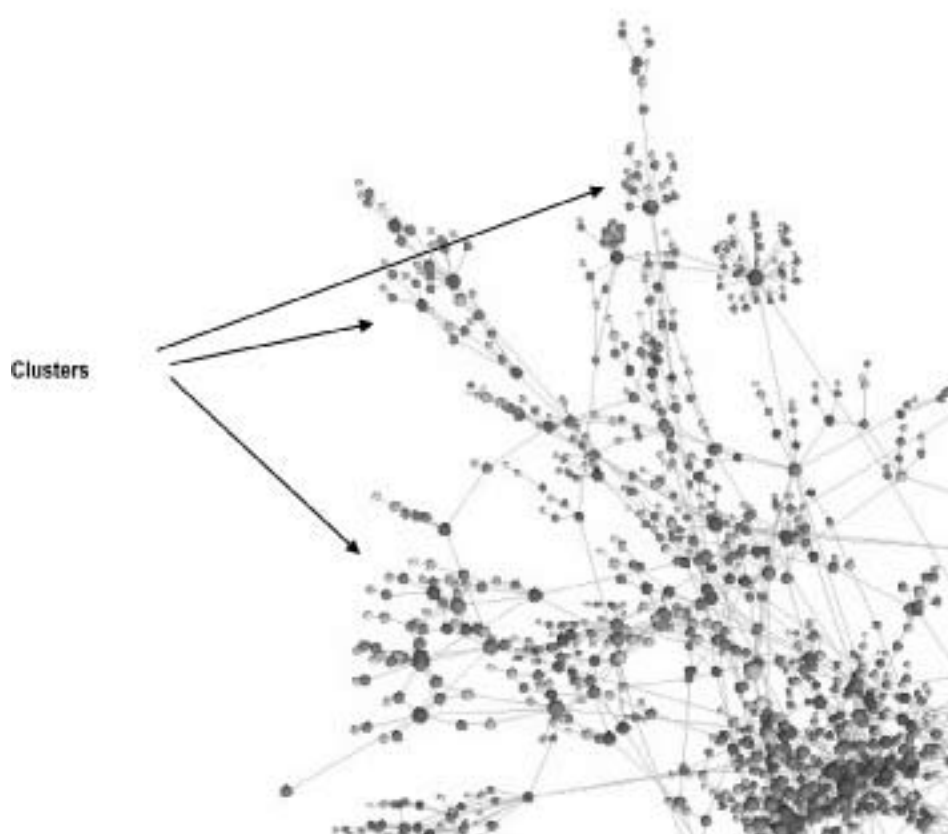
What significance does this have? It turns out that in addition to having highly connected hubs, nodes are also connected in clusters - as in social networks where people of a similar economic status form clusters. This concept is highly significant to what is to come because, in biological networks, these clusters are very often the sub-networks that underlie a particular functionality in cells.

These clusters can be mathematically defined as a topology and are the basis upon which a particular functionality can be identified and targeted in order to shut down an undesirable function. By the same token, a desirable function might also form a cluster/topology of this type.

¹⁵Please refer to *Scientific American* in May 2003 by Albert Barabasi and Eric Bonabeau. A power law means that the probability that any node is connected to k other nodes is proportional to $1/k^n$. The value of n (representing incoming links) was found to be approximately 2 so any node is four times as likely to have just over half the number of incoming links as another.

¹⁶Jeong H. et al, *Nature* (2000) **407**; 651-654

Biological Network Clusters/Small World



Source: e-Therapeutics

Knowledge of these so-called ‘topologies’ is at the heart of what can then assist a drug discoverer, in seeking a compound that does not interact with desirable ‘healthy’ networks, while still shutting down the undesirable sub-network.

We must point out here that there is still considerable debate on the scale-free nature of complex biological networks. In some quarters they are held to be scale-rich. However, for the purposes of drug discovery platforms, the ‘scale-free’ approximation is a very useful tool, allowing greater insights into the inner workings of the functional topologies of these networks and, as we shall see, can be combined with other characteristics to enable a **‘predictive’** form of drug discovery; the ultimate application and the goal we are interested in here.

The third important principle necessary in building these models (and one particularly central to e-Therapeutics) comes from the field of **Information Theory** pioneered by Claude Shannon in the mid-20th century. As we shall see, the

massive databases that are mined to collect, curate and collate data for use by e-Therapeutics' system contain data that are subject to error. The quality of these data is uneven, inconsistencies abound, data are missing and there are many false positives (data that should not be there) and, as bad, false negatives (data that should be there but aren't). The accuracy and analysis of a real-life complex system is only as good as the data that is used to construct it – or as the expression goes: garbage in, garbage out.

So how can a network model constructed on the basis of such “noisy” data be reliable as a source of new therapeutic modalities? The answer lies in Information Theory, where it has been shown that the larger the network being analysed, the less the informational weight is attached to knowledge of each node and to the interactions between them in the network.

In smaller networks, all of the value is in the individual interactions, so precise knowledge of these is crucial to understanding the flow of information and the integrity of the network; hence data noise matters. Larger networks are more impervious (i.e., robust) to data noise as it is the overall topology that takes on primary importance. Sufficient information to elucidate the patterns/topology in a network is all that is required to find the circuit breakers that will shut down a particular function while leaving the rest of the network intact.

In summary, e-Therapeutics brand of complex network analysis suggests that complex biological systems may be sufficiently described by their topology so as to provide better models as the basis for drug discovery. When trying to understand the difference between its approach and what others are doing in the field, it is these concepts of topology and robustness to data noise that are most important.

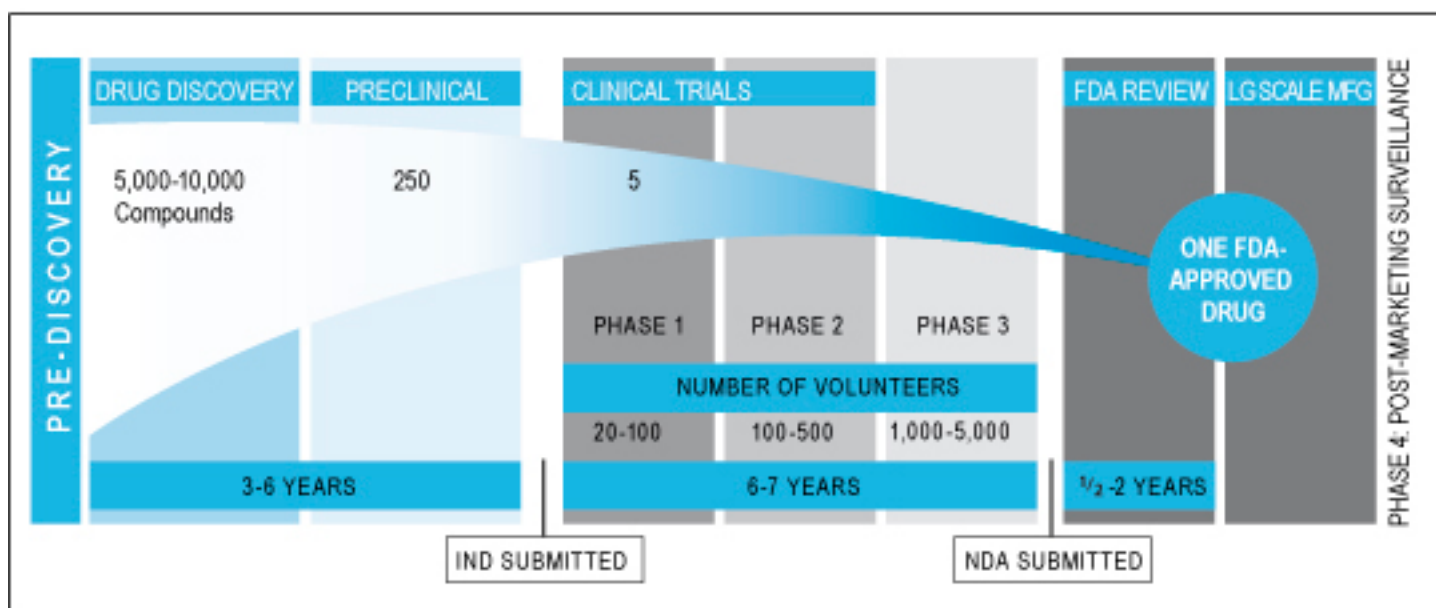
Why do we bother with all of this? What is wrong with drug development today and why do we need this science to move the goalpost of therapeutics forward? At this juncture, it would be useful to review the workflow of drug discovery and development and look at the reasons why a radical change in direction might be called for. This will serve as the context within which the application of Systems Biology to drug development should become clear.

Switching gears: the productivity of the drug development workflow

To understand the context within which drug development using Systems Biology tools is needed, it is very important to understand the dynamics of the industry as they stand today. The Pharma industry is currently a US\$600 billion global behemoth¹⁷. The majority of that consists of proprietary drugs on the one hand and generic drugs, where patent protection has expired and are now marketed at a significantly reduced cost, on the other.

Over the next five years around \$88 billion worth of proprietary drugs, which include blockbusters such as **Fosamax** (for osteoporosis), **Risperdal** (Schizophrenia), **Lipitor** (hypercholesterolaemia), **Seroquel** (for bipolar disorder), **Advair** (asthma) and **Singulair** (Asthma) amongst others, will go off patent and lose an estimated \$26.9 billion in value. In the US, which represents around 45 percent of the global pharmaceutical market will represent the bulk of that drop as it is common for the generics to be priced at a 50-75 percent discount to the branded price and sometimes even more. The flip side to that is that the pharmaceutical industry has been unable to replenish its pipelines with equivalent drugs and the success in conversion of drug discovery into clinical and regulatory approval is woefully low. In its most recent annual industry profile¹⁸ data from the US Pharmaceutical Association (PhRMA) indicates that amongst its members (most of the major pharma companies globally) only five discovery candidates, from some 5-10,000 compounds identified, make it into clinical development and typically yield only one approved drug.

The R&D process: long, complex, and costly

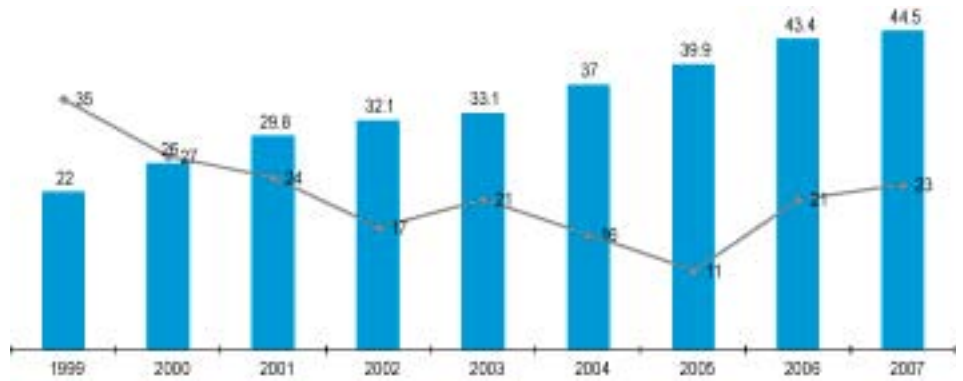


Source: PhRMA, Profile 2008-Pharmaceutical Industry

¹⁷CMR 2006

¹⁸PhRMA, Profile 2008 available on the association's website.

R & D spend vs annual FDA drug approvals



Source: PhRMA data and US FDA

The cost of such an exercise has been estimated to be around US\$1.8 billion although others, using a different methodology have put it closer to US\$500 million¹⁹. Our view from the data presented by both parties indicates that the cost of getting a drug to market is probably somewhere around US\$1 billion for non-niche products. For products that are what we would call 'targeted', the number is most likely considerably lower.

However, the cost of getting drugs to market is not the issue that we need to focus on. The main issue is: why is productivity so low? Drug productivity (i.e., discovery to market) has been progressively declining over the past 45 years. The increasingly critical eye that the FDA and its expert panels are applying to the data that they are receiving from companies is, in our view, partly due to the increased vigilance that the FDA has been applying to new drug approvals after a string of significant post-approval failures (Baycol, Vioxx...etc.). This alone has progressively slowed down the rate of drug approvals over the past five years. As seen in the accompanying diagramme, the rate of drug approvals in the US has considerably slowed from its peak of 35 in 1999 to a current running rate in the 20's (after bottoming at 11 in 2005); this despite a sustained increase in R&D from \$22 billion to \$45 billion over the same period. Whether it is the FDA or not, clearly something is not working here!

¹⁹see di Masi et al (2003) in *J. of Health Economics*, **22**, 151-185 and Licht D.W. (2007) *J. of Health Politics, Policy and Law* **32**:895-913

The very high cost of development pushes companies to submit data to the FDA (and other regulatory agencies around the world) that are not always up to the regulatory standards that have been set in legislation. Also, in many cases, the degree of innovation has been lacking and the panels have been unimpressed with the marginal improvements that these filed drugs offer over existing therapeutic modalities.

However, the real problem, in our view, is the drug discovery/development workflow itself which is depicted in the accompanying diagramme. In today's common workflow, a target biological mechanism underlying a disease is identified. This will usually comprise a series of biochemical reactions involving a series of enzymes (HMG CoA Reductase to affect cholesterol metabolism is an example) but can also involve a transport or other signaling mechanism (SSRI's and serotonin reuptake are an example).

In cancer and autoimmune diseases much of the focus has been on complex signaling mechanisms that trigger inflammation or apoptosis (cell death) or inhibit the growth of new blood vessels that are part of the aetiology of a disease. In all cases, a target protein (enzyme, receptor, signaling agent...etc) is identified and its blockage or potentiating effect is tested in a pre-clinical animal disease model. Once it is deemed to be safe to put into humans, clinical trials are initiated to test the safety and tolerance of the drug in humans first, followed by efficacy testing. In this work flow, it is difficult to predict what side-effects will come up and it is equally difficult to anticipate whether the effect being sought will be durable.

Biological networks are designed to be robust to blockages or problems at any single point within them. Apart from the few highly significant nodes that are essential for life, the rest of the network nodes, on an individual basis, are rather expendable because nature has designed compensatory mechanisms that will rescue the function that has been blocked or eliminated (compare this to taking out a particular node in the internet or a particular node in a power grid).

A recent example is the failure of certain anticancer drugs such as Iressa, SAHA and others to prevent the progression of a cancer in a sustained fashion. Each of these highly molecularly targeted drugs held initial promise but in the end, their efficacy is restricted to a subset of patients with a particular genetic makeup and, for the most part, the effects seen are not lasting.

The inefficacy over time of L-Dopa replacement therapy in Parkinson's is another example. In fact, in serious, progressive degenerative, auto-immune and proliferative diseases, it has been rather common that current therapeutic modalities either do not work in all patients or fail over time in most patients. The rationale for this relates to the genetic make-up of the patient treated, or to the aforementioned network robustness which results in therapeutic effect 'leakage' through alternative pathways.

In other diseases, such as hypercholesterolaemia (for which statins are prescribed), the target itself is only partially effective in slowing the progression of the disease. Altering the ratio of HDL/LDL is only part of the solution. A way must also be found to slow down, arrest or reverse atherosclerosis itself which is a very complex mechanism underlying the deposition and progressive narrowing of plaques in blood vessels which ultimately result in a blockage that can trigger myocardial infarction (or a heart attack).

Hence the world is never as simple as we would like it to be, as goes the old saying! So what can be done to generate drugs that are more effective and avoid the safety pitfalls of the current drug development workflow? Potentially, this is where the tools of Systems Biology, combined with an increasingly better understanding of molecular disease mechanisms, gain their advantage. They represent a potentially powerful means to identify drugs that are targeted to the disease, effective in shutting down the right network to avoid the sort of 'leakage' that the robustness of the latter invariably display, and do not interact with 'healthy' networks and their derived functions, improving tolerability and safety.

In other words ... the holy grail of drug development. What would be the end goal then? If successful, this approach should aim to improve drug development productivity, improve current therapeutic modalities and generate novel therapeutic modalities to tackle remaining unmet medical needs.

Systems Biology and drug development: a path to the future

For the reasons outlined in the previous section, the focus of drug development today is on the improvement of drug discovery/development workflows. These improvements are aimed at a renewed ability to tackle current therapeutic regimens that are based on unsatisfactory modalities, as well as the resolution of diseases that have remained impervious to therapeutic attack.

As an integral part of this effort, Systems Biology and the modern '*omics*' tools that underlie it, now loom large. It is our view, and one obviously shared by companies that use these tools, that a better workflow is required to improve the productivity of drug discovery and development while at the same time providing better therapeutic solutions for poorly or unmet medical needs.

However to achieve this, particularly in complex diseases, it is no longer enough to come up with therapeutic modalities that are an approximation of what they need to be. It is also no longer sufficient to come up with temporary fixes that lead to high levels of relapse or drugs that trigger ‘acceptable’ side-effects in the majority and unacceptable ones in the minority of patients. The profile of a therapeutic agent in the future will need to be viewed within the context of the overall cost to society.

With the ‘baby boom’ generation on the verge of retirement, the transition towards a ‘healthcare-heavy’ future is in full swing. New therapeutic modalities need to achieve a cost/benefit profile that makes their widespread application possible at a cost to society which is fiscally acceptable.

In our view, the era of drugs costing \$80,000 for an average of four extra months of life²⁰ is not sustainable in a healthcare system already bursting at the seams. The recent rejection of GSK’s **Tyverb**[®] (an oral erbB1 & 2, dual inhibitor²¹ for advanced breast cancer) by an NHS committee for cost/benefit reasons (£20,000 per annum with £80,000 in associated costs) is a harbinger of things to come. The pharma development workflow cannot abstract itself from this and needs to address medical needs in a fashion that is ‘cost/benefit’ sustainable to society. We believe that Systems Biology in general and the network analysis-based approach of e-Therapeutics in particular may offer a possible solution to this.

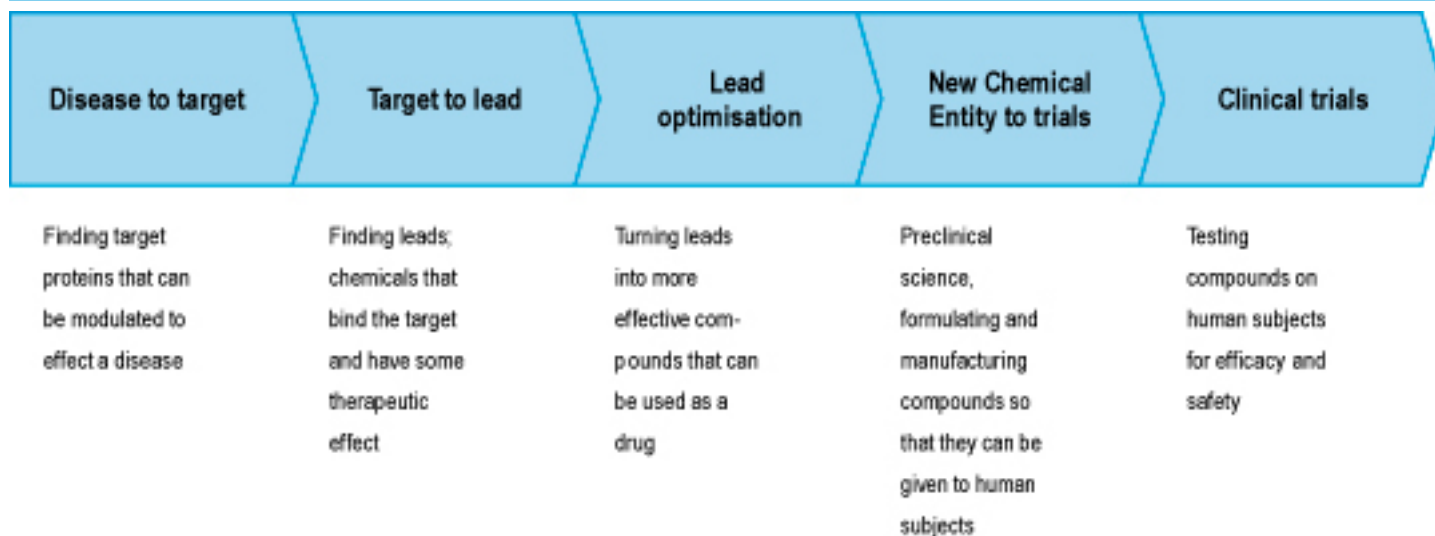
Traditional drug discovery/development workflows

Drug discovery strategies and workflows are as diverse as the companies that practice them. In other words, a simplified common workflow does not exist. Nevertheless, there is an overall theme that is common to most modern workflows followed in today’s pharma and biotech industries. In the past, drugs were derived from the observation of therapeutic practices using natural substances or serendipitous observations (e.g., Alexander Fleming and antibiotics) and a subsequent effort to mimic these drugs through the synthesis and testing of massive libraries of chemical compounds. Today’s drug discovery pathways are much more focused on specific biological mechanisms that have been identified as putative underlying causes of disease and hence become targets for pharmaceutical intervention. **This workflow can be summarised as depicted in the accompanying diagramme.**

²⁰Erbix (Bristol-Myers) for advanced colon cancer is a particularly salient example of this.

²¹It inhibits the important signaling mechanism driven by the enzyme Tyrosine Kinase, a component of these receptors in breast cancer patients that express the Her2 gene and is approved in combination with the cytotoxic drug capecitabine having shown a median to progression of 28 weeks in patients who have failed Herceptin therapy.

Standard drug discovery workflow



Source: *e-Therapeutics as adapted by Objective Capital*

Once a molecular mechanism of disease has been uncovered, a 'bioassay' (or several assays) incorporating this mechanism can then be devised to test for the activity of a chemical compound against this target. In the past twenty years, robotics-based technologies have been deployed to enable large quantities of compounds to be tested using such assay systems.

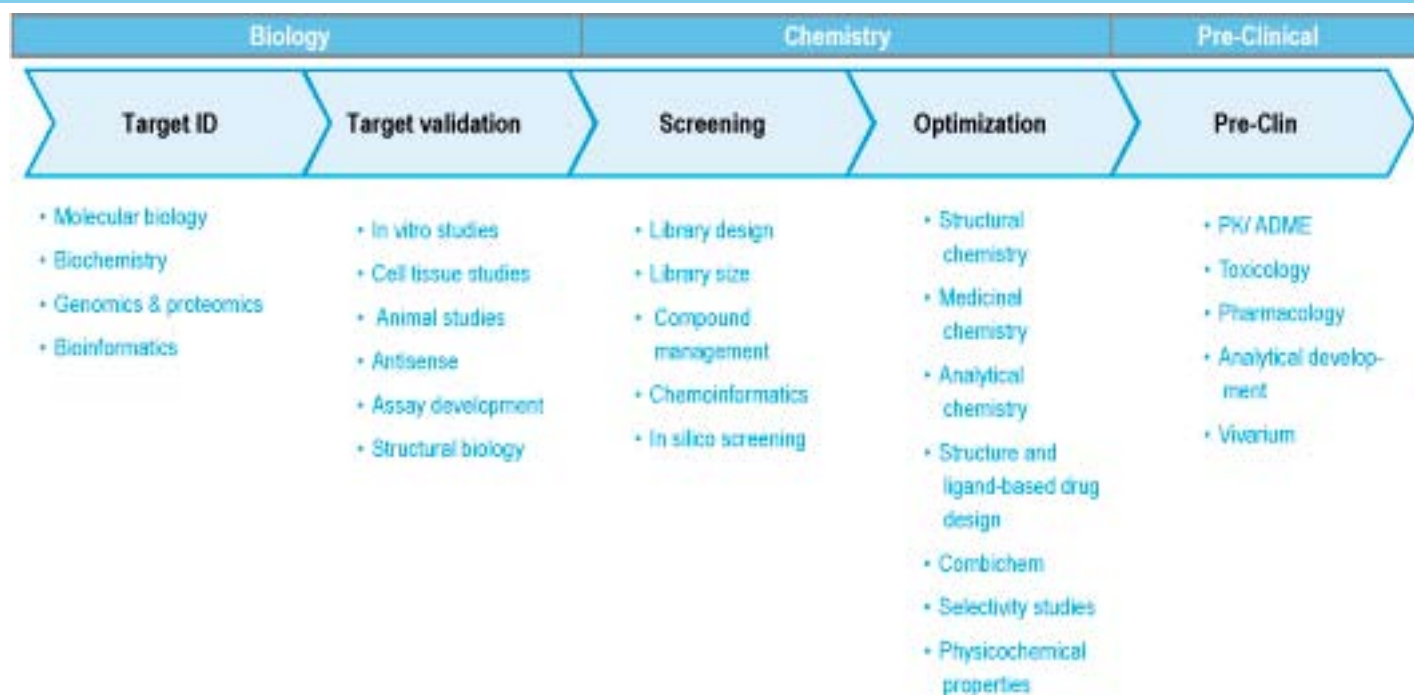
High throughput screening, or HTS, technologies are commonly used in the pharmaceutical industry where very large libraries of compounds are screened for activity in these assays. This will generate a series of candidates that will then go through a process of what is called 'Lead Identification' which attempts to extract out of this group of candidates, the most active ones.

This then goes on to 'Lead optimisation' where the most active compounds are further tweaked synthetically or simply used to fish out other compounds that would be predicted to be even more potent.

All of this is aimed at generating a small group of lead compounds that are highly active for the target and can then be taken into proper preclinical testing through a process called ADME-T or Absorption, Distribution and Metabolism, Excretion/ Elimination, Toxicology. From this a lead compound will be selected to enter human clinical trials.

The oversimplification here is blatant as omissions abound. The advent of gene technology, DNA and protein microarray technology, increasing amounts of automation, increasingly sophisticated tools such as the ability to produce genetic knockout animals, block selected gene activity using RNA interference, not to forget increasingly sophisticated antibody, fluorescence and chemiluminescence detection tools have all contributed to amplifying, accelerating and improving the workflow described above.

Enhanced traditional discovery and preclinical workflow



Source: e-Therapeutics

However, all of this is based on the reductionist view of drug development which ignores the complexity of biological systems and has resulted in a costly and relatively unproductive development process, itself being used as the underlying rationale for high pharmaceutical prices.

Systems Biology: the road to predictive drug discovery/development

The advent of Systems Biology has added a new dimension to this workflow. Today, most companies involved in drug discovery and development have recognised the need to look at what is going on at the 'System' level as an integral part of generating drugs that are not only safe and effective, but will also stand a better chance of making it to market!

This recognition has resulted in the construct of pharma and biotech-based 'Systems Biology' groups and has spawned an industry of 'tools' companies that support these efforts. Hence today, Systems Biology is almost part of the syntax of the Drug Discovery process but it still has a long way to go to become the 'predictive' tool that it needs to be to have the desired impact on discovery workflow, drug development costs and productivity.

In today's workflow, Systems Biology tools play, for the most part, an 'adjunct role' to the mainstream workflow. The confidence in its predictive power is simply not there and for good reasons.

Without going into the technical reasons for this, suffice it to say that the mathematical approximations that are used to produce the simulation models used by pharma companies' systems biologists are insufficient for the task. The various systems that are used with a putative predictive ability are not viewed as sufficiently robust to be trusted. They are perceived as requiring more standard confirmatory testing in order to trigger further development.

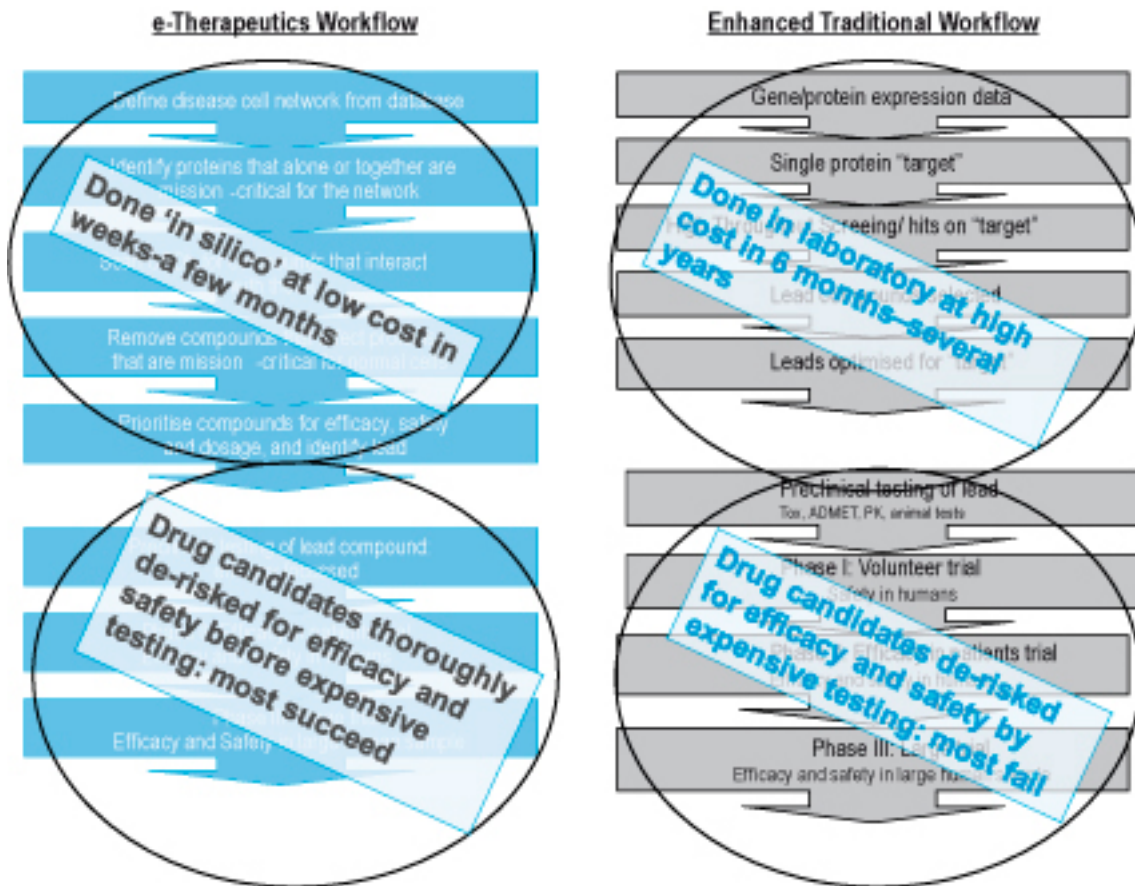
Such systems are making small incremental contributions to the workflow and helping to identify undesired characteristics for new therapeutic modalities which were impossible to detect before. There are very useful approaches being developed by smaller companies involving combinatorial chemical approaches within a 'Systems' framework, Cellular-based Modeling, and Disease Models all with some contribution to make. None of these, on their own, seem to stand out as truly predictive drug discovery tools.

The reader should keep in mind that the end objective here is to turn the workflow on its head and carve a pathway for a more predictive form of drug discovery which would avoid the pitfalls of traditional development, reduce its overall cost and improve its productivity and success.

The Network Analysis approach developed by Professor Malcolm Young and his team has the makings of a predictive approach. It generates a drug discovery workflow that looks rather different although, to be fair, the primary focus of this workflow at present is to seek and find drugs that can be repositioned for a purpose they were not originally developed for. So, in pure workflow terms, once a compound (or combination of compounds) has been identified by the system, the path forward is focused less on proving the safety of the drug but rather on its efficacy.

Depicted in the accompanying diagramme is a side by side comparison of the more traditional workflow and the one devised by e-Therapeutics. As seen in this diagramme, the discovery part of the workflow is done in silico and sets the stage for de-risking whatever makes it into the next phase. This phase is relatively less costly and yields, in the case of re-positioned compounds, leads that already have regulatory monographs and are ready for limited preclinical testing (when needed) but can mostly go directly into man in a proof of concept trial. On the other hand, expensive laboratory screening and testing needs to be carried out to get to a preclinical and clinical phase, where significant unknowns remain about how the drug will behave in vivo. This can be somewhat mitigated by Systems Biology tools and the probabilities appropriately enhanced, but the de-risking is only partial.

Workflow diagrammes



Source: e-Therapeutics

In the e-Therapeutics workflow, where two compounds are involved, some degree of safety testing in both animals and humans is required to check whether the combination has any unforeseen effects and to determine what the optimum dosage and dosage form will be.

If e-Therapeutics were to begin applying its brand of Network Analysis to NCEs the workflow would most likely need to reproduce the same degree of preclinical testing as with any other NCE. However, it is likely that the nature of such a 'predictively' generated NCE would enable the human trials to be more streamlined and focused, and more likely to end in success.

Network Analysis: a differentiated System Biology approach?

The key question that investors need to ask themselves is whether this approach exhibits the sort of differentiation which might make it unique and thus allow IP rights to be secured. Preceding that of course are the more pragmatic questions of whether the approach works, will it generate viable candidates that are consistent with the predictions that led to their choice in the first place, and, last but not least, does this result in a streamlined drug development pathway?

Off the bat, we can say that we are unable to answer these questions conclusively until we have more conclusive clinical data. What we can do is to convey what we think are the points that differentiate this approach from others that we have seen. Our analysis has uncovered a number of intriguing areas where differentiation is a distinct possibility but, lacking a peer-reviewed analysis of this, we are unable to deliver a definitive view.

Pathway-driven System Biology vs. Network Analysis

Much of Systems Biology-driven drug discovery today has taken on an adjunctive role in the workflow and this is driven by the perception that current System Biology approaches tend to lack robustness (particularly in the data that underlies them) and predictive power.

Why is this so? The reasons for this tend to lie in the nature of the approach that is taken which starts from the bottom up and attempts to construct a network around the particular pathway of interest. However, this approach has significant limitations as the complexity required to get meaningful information for drug-discovery purposes is orders of magnitude greater.

More recently, others have modeled these systems by taking existing data and inferring the missing links from these. The limitations here are many, not least of which are that the relatively small size of these networks precludes an approach that is inclusive of broader system interactions which might reduce the longevity of the effect (the aforementioned system 'leakage') or trigger other systems that underlie unwanted system effects.

The main problem is that the static properties of each node or hub in a network (the degree of connectivity, essentiality, distance from all nodes, its membership of a community of nodes that relate to a particular characteristic of the network...etc.) are inadequate to truly comprehend the dynamics of a network and the rules that allow it to perform its various functions. The underlying data is incomplete or inconsistent and resides, for the most part, in disparate databases which are often hard to mine let alone to integrate.

So in a world of such noisy data, is it really possible to gain a reliable understanding of how these complex networks function and translate that into a valuable platform for drug discovery? Much is being done to address this issue and perhaps solutions are in the pipeline in various academic centres. From a practical point of view, e-Therapeutics appears to have found a solution which, as we described earlier, resides in the application of concepts derived from Complex System Science, and particularly from the use of elements from Information Theory.

To understand the true dynamics of a system in functional terms in a smaller network (and therefore confer a predictive power to it in drug discovery terms) requires a degree of information about each node that is realistically unattainable at this time. Various approaches have been developed and, in recent years, some groups have developed what is called inference modeling which attempts to infer structure from missing data.

Inference modeling creates a dynamic model based upon a series of assumptions. The model can then be tested iteratively in an attempt to validate the assumptions. The difficulty with this has been that the number of assumptions makes this validation process difficult to achieve and calls into question the predictive power of the model itself.

More recently, work at Imperial College and elsewhere, has attempted to overcome these inadequacies using network-testing methodologies (derived from engineering) combined with innovative mathematical treatments and massive computing power.

e-Therapeutics has taken an entirely different approach to this derived from the observations of Professor Young and his teams at Oxford and then at Newcastle while working on the elucidation of complex visual cortex networks in the brain. It can be characterised as combining a bottom-up and a top-down approach. It employs a massive integrated database to mine for sub-networks that relate to a target disease. Data mining proceeds by recognising patterns in the data that can constitute testable network topologies that are either related or unrelated to the target function.

A computer-based methodology then searches for what are called 'low redundancy nodes' (essential network nodes that are mission critical) without which the sub-network in question would be unable to function. These network nodes are very different from the highly connected hubs that are truly mission-critical for life. The latter hubs cannot be shut down without risking the viability of the organism itself. These hubs tend to be highly conserved from an evolutionary standpoint, critical across tissues/cell types and so tend not to be useful druggable targets. The low-redundancy nodes however are not highly connected but have the 'right' kind of connection in the target sub-network.

To summarise, the difference in approach is fundamental. One approach tends to be 'pathway-centric' looking to build as much of a network around a pathway and then "mine" as many related functions as possible. This results in the construction of a network where any missing nodes (related to missing data) are inferred, and assumptions made as to how the network might be operating (absent a lot of non-static, dynamic data about the interactions within the system).

A mathematical model is then built and the dynamics are tested iteratively until a 'real world'-type network behaviour can be ascertained. The flaws in this have tended to be around the validity of the assumptions and the approximation of network structure derived from inferences. The perception is that while this may yield interesting adjunctive information, its prospective/predictive use is not perceived to be sufficiently robust.

e-Therapeutics on the other hand is addressing the 'noisy data' issue by utilising the Information Theory relationship of the diminishing information value of individual nodes in an increasingly large network. It claims that by seeking related and unrelated network topologies, the individual informational value of the nodes is not that important and it can extract highly valuable information about critical network vulnerabilities from its overall topology without knowing everything about each individual node.

We have not found much traction as well as considerable skepticism for this concept when we approached mainstream people in the academic community. The e-Therapeutics approach is based on earlier peer-reviewed work by Professor Young and colleagues, in, for example *Philosophical Transactions of the Royal Society* (1995), but this work seems not to have been noticed by mainstream systems biology people. However, when a group in the US, working in a very similar field, was queried about the plausibility of this approach, we received a "thumbs-up" on that account. In the end, talk is cheap and the proof will lie in the clinical outcomes of drugs discovered in this way.

The pharmaceutical and biotechnology industry is structured into two main areas: a proprietary pharmaceutical and biotechnology industry and a generic drug industry.

Over the past three years, as more and more blockbuster drugs have come to the end of their useful patent life, the generic drug industry has rapidly flooded the market with bioequivalent drugs at a fraction of their original cost.

The biotechnology industry with its complex protein-based drugs has, to date, mostly escaped this. Interferon, which has been off-patent for many years, sells at a price that is greater than its original cost upon launch; no streamlined regulatory process exists here biosimilars.

Many drugs aimed at a particular indication, fail in clinical trials or while on the market. One concept that has begun to emerge over the past ten years is the idea that some of those could be repositioned as a safe and effective treatment for another illness.

There are many instances where, based mostly on serendipity, it was found that a drug developed for a particular purpose found a much more lucrative market when applied to another. Probably the best example is minoxidil, a minor cardiovascular vasodilator which was found, completely by accident, to be an effective trigger for hair growth. Now the basis of **Rogaine**, it has become a popular treatment for certain forms of hair loss. Sildenafil, a drug originally developed for the treatment of angina, failed to have an effect in the latter but seemed to trigger marked penile erections! The resulting drug **Viagra** has gone on to create an entirely new field of pharmaceutical endeavour within what is now called 'lifestyle' drugs that have generated billions of dollars of revenues for large pharma.

The nature of e-Therapeutics' system makes the search for re-purposed drugs a natural fit; it is the main development strategy being pursued at this time and its current pipeline derives from this strategic thrust.

e-Therapeutics system: a novel discovery platform

The e-Therapeutics approach centers around two massive databases. One is an integrated, curated²², interactive database which collects Protein-Protein interactions (we will refer to this as the **PPIDB**). It takes data from 50-60 public or commercially available sources and contains information related to 160 pathogens and 400 human cell types.

The other database (the Chemo-Proteomic or **CPdB**) contains a large number of chemical compounds (~15 million) and descriptions of their interactions with 2.6 million proteins.

²²Curation in database terms is a form of verification of the data which focuses on eliminating data that is contradictory with other validated data, irreproducible...etc

It is the interplay between these two databases that is the core motor of the e-Therapeutics process. The workflow, in very broad terms, works as follows:

PPiDB workflow

- disease information (target biological pathway, tissue/cell type...etc.) is the starting point of any project; initiation processes focus on:
 - a set of macromolecular identities;
 - the cell-types where these are expressed;
 - interaction data in these and other cell-types.
- the user inputs instructions to the PPiDB which then begins the process of seeking the 'low-redundancy' network nodes (i.e., proteins) that are critical to the integrity of the target function;
- while this process is ongoing, the system is collecting information at different levels. It is looking at these nodes within the context of the overall network in which is located. Simultaneously it is looking at the node in its local environment and finally it is also looking at the ways in which the node is reached and how it reaches others;
- all of this is translated into information flow data and the data set generated is scanned for patterns. It is these patterns which form the so-called network topologies. These topologies are sets of related or unrelated functions which will be crucial for subsequent efficacy and safety discovery work;
- while all of this data is being collected, the system is constantly looking at the impact of taking out nodes on the integrity of the system. This is in fact the way in which the relative importance (or rank order) of nodes is discovered;
- from network analysis of these data, a 'Desired Protein Spectrum' is generated which contains a collection of all of the possible targets for small molecules that are critical for target sub-network function. The results can be single or multiple protein targets.

CPdB workflow

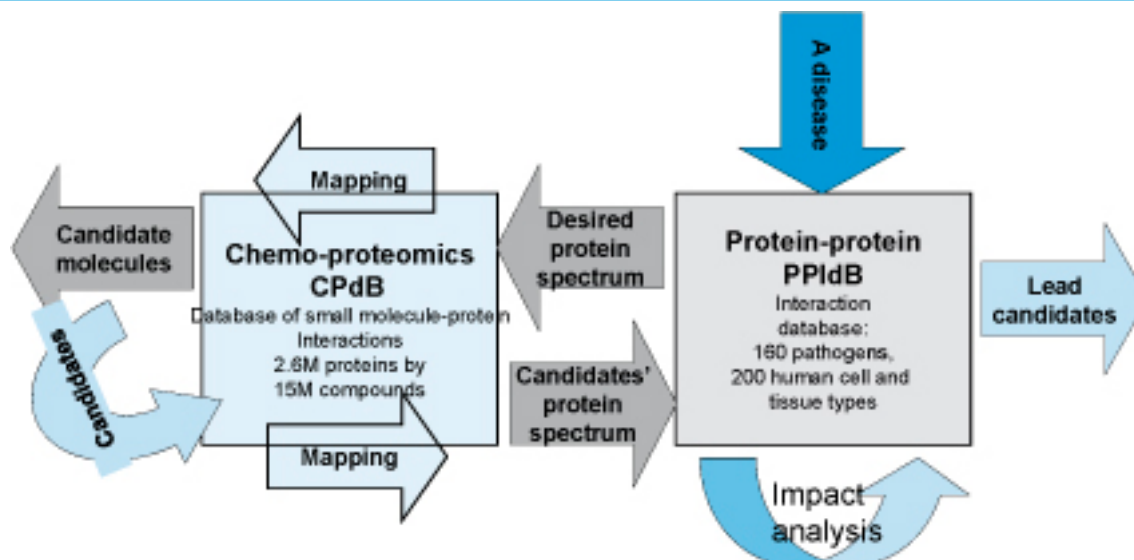
- the 'Desired Protein Spectrum (DPS)' generated by the PPiDB is then fed into the Chemo-Proteomic database where it can be mapped to the overall spectrum of proteins versus small molecules;
- the relevant data subset is then generated and the compounds that are generated are the initial drug candidates;
- this creates a 'Candidate Protein Spectrum (CPS)' targeted to the disease in question and containing all known compounds that would interact with the target sub-network. This CPS can then be fed back into the PPiDB for further analysis.

The process is iterative, i.e. the first generated CPS is fed back into the PPiDB which, effectively, refines it into a second DPS. That in turn is fed into the CPdB for a second time to generate a second CPS. That is re-entered into the PPiDB and the process is repeated.

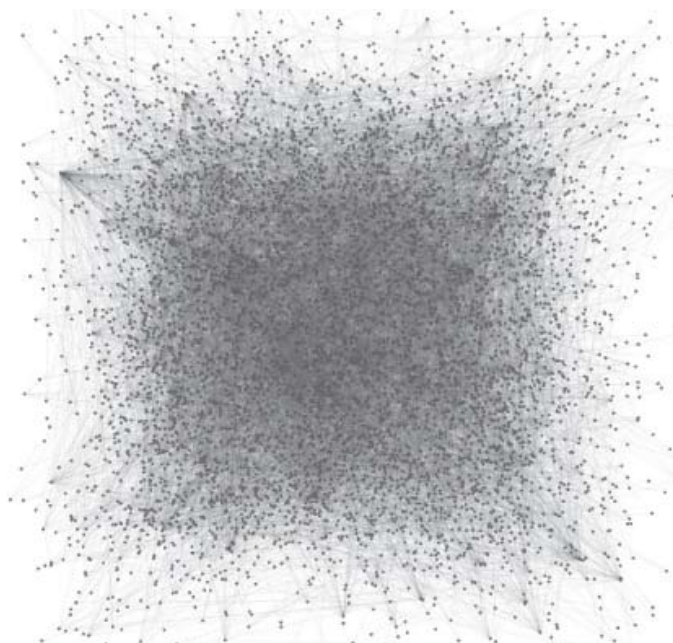
This iterative process continues until it has generated an optimal, lead, set of candidates. Those candidates will, by definition, have been selected for their effectiveness at shutting down a disease-related 'defective' function without interacting with non-diseased pathways.

As the above process is carried out through a technique called 'combinatorial impact analysis' where the iteration doubles as a process of elimination, the impact of each molecule is evaluated against its relevant protein targets. If the interaction is within the desired cell-type it is efficacy related, if not then it is safety related. In this way, it is possible to generate a set of compounds that combine 'predicted' features of high efficacy and safety, all in one go.

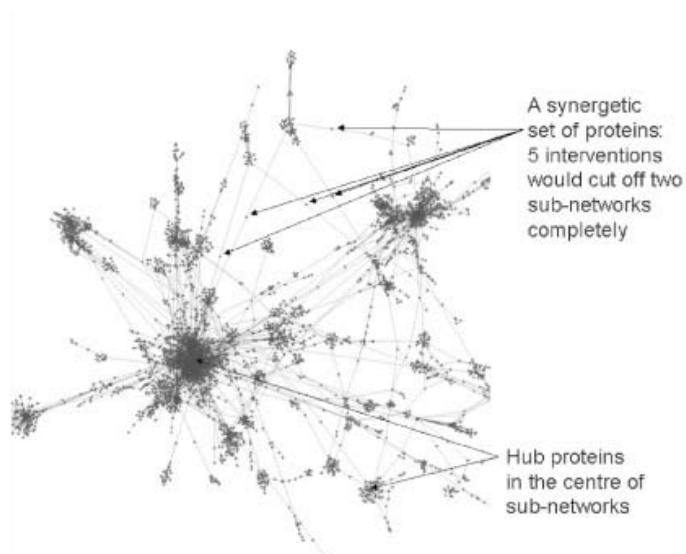
To illustrate how the system identifies the appropriate nodes, the accompanying diagrammes depict what is going on. Depicted are the sum total of data from the PPiDB for *Staphylococcus Aureus* displayed as a random graphic. Visually, not much structure can really be seen from this. However, the computer, using the data contained within the databases, sees this much differently. In the second representation, we depict a visualisation for illustrative purposes of what the system is able to compute. As seen, crucial, very busy hubs are identified and indicated on the graphic. However, importantly, the system has also identified five mission critical nodes (which the company calls 'synergetic') which, if taken out, individually or in various combinations would surely undermine the viability of the organism. Any compound that shuts most or all of these down would impact the viability of the organism resulting in its certain death. It is then the role of the CPdB to identify those compounds which it does by scanning through structural data to identify potential fits.



Random representation of *Staphylococcus aureus* network



Computed representation of *Staphylococcus aureus* network



Graphically, this can be depicted as seen in the above graphic. The system scans through the database and attempts to identify within a compound/protein spectrum, where these particular nodes are situated. It then pulls out the most likely candidates that would interact and runs them through the PPIdb to further refine the list.

e-Therapeutics' discovery and development strategy

At the core of e-Therapeutics' corporate strategy is the use of its drug discovery platform to uncover drugs that are either on the market or have failed to make it to market, that can be repositioned quickly as safe and effective therapeutic agents addressing poorly or unmet medical needs.

Its drug discovery platform contains all published information about any drug that has ever been developed. Any such drug will also have a full regulatory package in existence which can potentially reduce significantly its development costs and time-frame. The toxicology and human safety data are already part of an extensive regulatory filing so, for the most part, the only mountain to climb is one of efficacy.

The other advantage to re-positioned drugs is that they do not need to be priced at egregious levels even if their new application has a significant cost benefit advantage. Their cost to market is relative modest and their production efficiency has already been extensively worked out. As with generics, it is likely to be rather low in most cases. Sounds simple enough but what are the drawbacks to this?

Business strategy

The business strategy is two-pronged: internal pipeline development in selected therapeutic categories and consultative/development projects for third parties.

e-Therapeutics' internal pipeline, has targeted areas where the company has uncovered a specific knowledge angle which it can use to approach a particular disease area with the expectation of significantly improving on current therapeutic modalities or addressing unmet medical needs.

The focus of its near-term efforts is on using its network-analysis approach to uncover drugs that are used in unrelated applications but are predicted to be safe and effective for a novel target application that the company has selected. In the longer term, the company is looking to validate its approach for new chemical entities or NCE's.

On the repositioned side, its approach in depression is probably the best example of how this works. Depression is thought by many scientists often to be associated with pain. Much work has been carried out to elucidate the CNS and PNS²³ pathways and interactions involved in both pain and depression. Depression medications are often used in the treatment of pain (tricyclic antidepressants such as Amitriptyline in particular) and chronic pain is known to have a frequent co-morbidity with depression.

²³CNS is the Central Nervous System and PNS the peripheral nervous system.

e-Therapeutics' approach was to target medication-refractory²⁴ depressed patients to see whether a known, but atypical, anti-pain medication would have an effect on depression. The early results have been quite remarkable.

Strategically, e-Therapeutics will take each pipeline candidate, either itself or in partnership with a third party (in a particular country/region), into a proof of principle (PoP) trial to verify the safety of its approach (particularly where a combination is involved) and to collect early evidence of efficacy or effect. It then intends to conduct a pivotal, registration-orientated Phase IIb/Phase III trial and use the data emanating from this to license its drugs in a geographically broader fashion.

In the US, the company has learnt that the type of drugs that it is currently developing will fall under section 505(b)(2) of the Food and Drug Act regulated by the US FDA. Under this section of the law, the FDA is mandated to evaluate drugs under the following conditions:

Section 505 of the Act describes three types of new drug applications:

(1) an application that contains full reports of investigations of safety and effectiveness (section 505(b)(1));

(2) an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2)); and

(3) an application that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product (section 505(j))²⁵

Hence, there exists a specific procedure coupled with specific exclusivity in the Waxman Hatch Act²⁶ specifically designed for the type of drug that e-Therapeutics is developing. There will remain regulatory hoops to jump through on the safety side, particularly with respect to dosing and safety for a novel application or a novel combination of compounds.

²⁴Refractory refers to treatment resistant.

²⁵Guidance for Industry Draft Guidance Applications Covered by Section 505(b)(2), U.S. Department of Health and Human Services FDA, Center for Drug Evaluation and Research (CDER), October 1999

²⁶Waxman Hatch is the main amendment to the original Food, Drug and Cosmetics law that established the regulatory powers of the FDA. It pertains mostly to generics and has various amendments related to orphan drugs and drugs with historical safety/efficacy data to encourage the development of these types of drugs.

On the consulting/third party development side of the business, the company will take on projects that enable it to generate cashflow but also to throw up knowledge which could lead it to develop new pipeline candidates for its own account.

What are the partnership targets and where does e-Therapeutics fit within the industry? Re-positioned drugs are a bit of a novelty although the concept has been around now for some years. Successes such as Rogaine and Viagra have triggered some interest and, as we shall see, a number of companies are specialising in the discovery of new applications for old drugs. Hence the field is gaining traction despite the fact that it is situated between the generic industry on one side and the NCE-driven proprietary drug field on the other.

e-Therapeutics has, to date, been unable to forge a lasting relationship with big pharma. We believe that the lack of such relationships may have something to do with the profile of the pipeline that e-Therapeutics has generated, based on old drugs and combinations thereof, which, in our view, have yet to resonate with these companies. To be sure, there is an inherent bias in large pharma away from this sort of drug, despite evidence of historical commercial success. With clinical data on the way, it is possible that this situation might change dramatically in a very short period of time.

IP strategy

The platform's IP had been carefully crafted to create a 'pathway' blockage to their methodology. The inherent mechanisms used today in their platform are not revealed, but anyone taking the route to their methodology would, in principle, be blocked from doing so. This has the effect of enabling the company not to reveal its fundamental methodology while disclosing an application that, in itself, is novel and can be reduced to practice. How this would be enforceable and how this will hold up in the end can not be ascertained at this time. We are of the view, that by the time this IP strategy fails, if it were to do so, the barriers to entry afforded by what they have achieved will probably give them a 3-5 year head start anyway. We are in no doubt that if the company's 'predictive' system works, other will try to emulate it. Keeping the core of its technology under wraps will act to delay entrants sufficiently so as to allow it to achieve a very solid position.

With respect to product IP, there are a number of challenges associated with re-positioned drugs. In order to create a proprietary position, it is crucial to know whether the discovery that you are going after has been pre-empted in any way in the medical/scientific literature before any patent application is submitted. Hence the barriers to a proprietary application in repositioned compounds are high and may be more difficult to achieve than for NCEs, although chemical structure patents are also highly complex and difficult to navigate.

Second, application patents are notoriously hard to enforce so these must be augmented by formulation and manufacturing IP in order to be able to carve out a relatively solid position. In Europe, there is automatically a 10-year exclusivity that comes with the registration of a novel application of any drug (proprietary or not). However that is not considered a sufficiently long commercial life for most pharmaceutical companies and the development costs, despite being lower versus NCEs, still may be high for generics companies.

However there are potential ways around these issues.

- for one, a clinically relevant novel formulation that provides significant advantages over a standard formulation can be of some help;
- the use of combination drugs, if safe, tolerable and offering therapeutic advantages can gain composition of matter-type IP protection. In this case, one must be careful to include the drugs and any derivatives to be as comprehensive as possible.

For each of the drugs that e-Therapeutics has discovered so far, it has been able to construct an IP position which it believes will stand up to challenge. However, it is only upon patent issuance (and upon challenge) that we will know how effective this strategy will be. In any case, at the very least, the ten year protection offered by the EU and between 3-8 years protection offered under Waxman Hatch will confer some exclusivity. In the US, an approval (under Section 505 (b)(2)) involving clinical studies triggers three years exclusivity and if the drug is an NCE, an additional 5 years (which is what a combination of two drugs effectively is).

Clearly, where a combination is involved, an IP position is more likely to hold up unless such a combination has been described in the literature for the application in question or any other related application. One of e-Therapeutics' strengths is its ability to use its system to scan the scientific and medical literature for even an iota of mention of a compound/application combination. In this regard, it is better positioned than many patent attorneys!

In its early development plan e-Therapeutics has targeted anti-infectives (intractable nosocomial²⁷ infections), asthma, depression, fibromyalgia and cancer. In each case, a well-characterised disease mechanism was derived by the system in a process that in all cases has yielded multiple points of attack to achieve the desired effect. What follows is a detailed review of each pipeline component.

Anti-infectives

The advent of antimicrobial resistance in serious bacterial infections is a serious public health problem. Although consistent data are hard to come by, in the US alone, the rate of hospital-based MRSA²⁸ infections more than doubled from 127,000 to 278,000 between 1999 and 2005. Mortality in this group of patients escalated from 11,000 to 17,000 over the same timeframe²⁹.

A more recent study³⁰ from the CDC, based on 2005 data, found that the incidence of serious invasive MRSA infections was 94,340 with an in-hospital mortality of around 18,000. A further study by the US AHRQ³¹ estimated that in 2005 there were 368,000 hospital stays for MRSA or triple those found in 1999.

These infections cost on average around US\$14,000 per stay at an estimated cost of around US\$5 billion to the US healthcare system (other estimates put this at between US\$3.2 and US\$4.2 billion. It has been estimated that the global cost of MRSA infections, at around US\$36bn, is larger than the antibiotic market as a whole, now pegged at around \$32 billion.

The e-Therapeutics' system has produced ETX1153 as its response to these hospital-borne infections, which tend to involve organisms such as MRSA, VRE (Vancomycin-Resistant Enterococci) and *Clostridium difficile*. The company started out by looking at the bacteria themselves to see if it could find multiple low-redundancy network points where blockage would result in an effective shut down of the organism while preventing the potential for mutation of the organism to create therapeutic resistance. To make this treatment impervious to resistance, multiple points of attack needed to be generated and a way to avoid 'leakage' through functional rescue defined.

This development project is as good a way as any to illustrate the power of the company's discovery workflow. The sum total of knowledge about these bacteria (one in particular) is illustrated in the random network depicted in the accompanying graphic. Using its computational power, the computer organizes this network in a very different fashion. This is illustrated in the second graphic shown and highlights what the computer is actually seeing computationally. It depicts a series of clusters that are very highly connected (they contain the hubs

²⁷These are hospital-acquired infections

²⁸Methicillin-Resistant Staphylococcus Aureus

²⁹Klein E et al (2007). *Emerg Infect Dis* 13 (12): 1840–6

³⁰Klevens M. et al., *JAMA* (2007), **298** (15), 1763-1771

³¹Agency for Healthcare Research and Quality (in H.CUP Statistical Brief #365, July 2007)

as indicated) surrounded by a large number of nodes that are connected to it and interconnected in other ways. What it also depicts are another set of nodes that are outside of these busy clusters but seem to be connected to several of them. This is an illustration of the low-redundancy nodes (circled) we have talked about. These are mission-critical and if blocked or closed down, have a devastating effect on the survival of the organism. In this example, the computer has selected five nodes that would constitute an irreparable shut down mechanism for these particular bacteria.

e-Therapeutics' CPdB then proceeds to identify groups of compounds that would interact with this set of nodes as the basis for selecting one or a combination of compounds to test clinically.

ETX 1153 Revenue model													
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Total Number of Nosocomial Infections													
US	2	2.0	2.1	2.1	2.2	2.2	2.3	2.3	2.3	2.4	2.4	2.5	2.5
Japan	0.936	1.0	1.0	1.0	1.0	1.0	1.1	1.1	1.1	1.1	1.1	1.2	1.2
Europe (5 major countries)	2	2.0	2.1	2.1	2.2	2.2	2.3	2.3	2.3	2.4	2.4	2.5	2.5
RoW	4	4.1	4.2	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1
Total	8.9	9.1	9.3	9.5	9.7	9.9	10.1	10.3	10.5	10.7	10.9	11.1	11.3
Average drug cost per day(*)	80	80	80	80	80	80	80	80	80	80	80	80	80
Average number of days of treatment(**)	7	7	7	7	7	7	7	7	7	7	7	7	7
Total Average cost per treatment	560	560	560	560	560	560	560	560	560	560	560	560	560
Estimated discount to current treatment costs	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
Estimated Price for ETX 1153	504	514	524	535	546	556	568	579	591	602	614	627	639
Total Therapeutic Market potential for ETX 1153	\$4,504	\$4,686	\$4,875	\$5,072	\$5,277	\$5,490	\$5,712	\$5,943	\$6,183	\$6,432	\$6,692	\$6,963	\$7,244
ETX 1153 Revenue Estimate													
Prophylactic uses (in millions)													
High Risk Surgical Procedures (***)	14	14.3	14.6	14.9	15.2	15.5	15.8	16.1	16.4	16.7	17.1	17.4	17.8
ICU visits	14	14.3	14.6	14.9	15.2	15.5	15.8	16.1	16.4	16.7	17.1	17.4	17.8
Dialysis patients (***)	1.6	1.7	1.8	1.9	1.9	2.0	2.1	2.3	2.4	2.5	2.6	2.7	2.9
Total number of high risk patients	30	30	31	32	32	33	34	34	35	36	37	38	38
Number of topical applications at insertion or surgical sites													
High Risk Surgical Procedures (***)	14.0	14.3	14.6	14.9	15.2	15.5	15.8	16.1	16.4	16.7	17.1	17.4	17.8
ICU visits (assumes average 5 day/2 applications)	28.0	28.6	29.1	29.7	30.3	30.9	31.5	32.2	32.8	33.5	34.1	34.8	35.5
Dialysis patients (1x monthly)	19.2	20.2	21.2	22.2	23.3	24.5	25.7	27.0	28.4	29.8	31.3	32.8	34.5
Total Applications	61.2	63.0	64.9	66.8	68.8	70.9	73.0	75.3	77.6	80.0	82.5	85.1	87.7
Estimated penetration for prophylactic use	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%	30%
Estimated Total Available market	18.4	18.9	19.5	20.0	20.6	21.3	21.9	22.6	23.3	24.0	24.7	25.5	26.3
Estimated Price per applications (in US\$)	150	150	150	150	150	150	150	150	150	150	150	150	150
Estimated total Prophylactic topical market	\$2,754	\$2,835	\$2,919	\$3,006	\$3,096	\$3,189	\$3,286	\$3,387	\$3,491	\$3,599	\$3,711	\$3,828	\$3,949
Estimated Total Market	\$7,258	\$7,521	\$7,794	\$8,078	\$8,373	\$8,679	\$8,998	\$9,329	\$9,674	\$10,032	\$10,404	\$10,790	\$11,193
Core Model													
Estimated Market penetration				0.1%	0.2%	4.0%	5.0%	6.0%	6.5%	7.0%	7.3%	7.5%	7.7%
Estimated Sales (in US\$ millions)				\$8	\$16	\$335	\$434	\$540	\$606	\$677	\$732	\$780	\$831
Optimistic Model													
Estimated Market penetration				0.2%	0.4%	5.0%	7.0%	8.0%	9.0%	9.5%	9.7%	10.0%	10.3%
Estimated Sales (in US\$ millions)				\$16	\$32	\$419	\$608	\$720	\$840	\$919	\$973	\$1,040	\$1,111

(*) Daily antimicrobial costs range from around US\$60-US\$100 per day

(**) Treatment ranges from 5-10 days on average (SSSi=5 days and Nosocomial Pneumonia and Septicaemis=10 days)

(***) OC estimates from Grassman A. et al, *Nephrol Dial Transplant* (2005) 20: 2587-2593

Source: literature data and Objective Capital estimates

ETX 1153 is based on a known antifungal and a known antiviral agent which, when combined, appears to shut down these types of pathways in these organisms in a way which leads to their death and clearance. In vitro data confirms that this is the case, and the applications for this are both systemic (IV delivery) as well as topical (particularly for wounds, catheter insertion sites, surgical sites...etc as a preventive measure).

We have estimated the size of the global market for this application to the best of our ability (precise data tends to be lacking) to be around US\$6.7 billion for therapeutics and an additional US\$3.7 billion for prophylactic uses. We believe that these numbers are conservative both in magnitude and in growth rate. We are estimating that a drug with the profile of ETX 1153 could achieve a ten percent market share in 2017 equating to about a US\$1 billion drug.

Expected value of ETX 1153 (pre-corporate tax)

Summary of valuation (pre corp tax)		
Scenario (\$m)	Core	Optimistic
EV of royalties*	316.1	425.4
Likelihood of success (PoS)	14%	14%
EMV of royalties	43.3	58.3
Add: EMV of upfront payments	0.6	0.6
Add: EMV of milestone payments	0.7	0.7
less: EMV of development costs	0.1	0.1
EMV of ETX 1153	44.5	59.5
per share (\$ps)	0.80	1.07

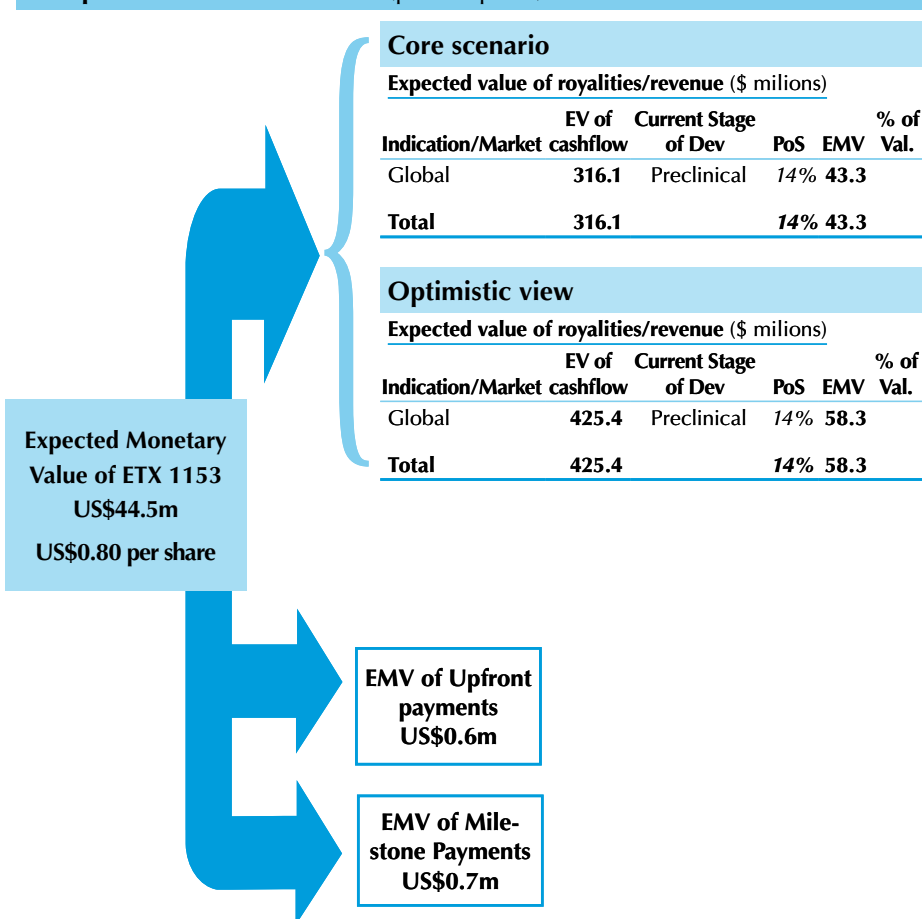
Key market & licence assumptions

Indication/Market	Route to Market	Royalty Rate/Effective Margin	Impact of Generics	
			Approx Date	Price Impact
Global	Licensed	12%	2022	-75%

Sensitivity to change in ...

Impact of generics (+ % price decline)					
	-20.0%	-10.0%	+0.0%	+10.0%	+20.0%
Value (\$m)	47.9	46.2	44.5	42.8	41.1
Change in Value	8%	4%	0%	-4%	-8%
Increase in royalty/margin (+%)					
	-10%	-5%	0%	5%	10%
Value (\$m)	8.5	26.5	44.5	62.6	80.6
Change in Value	-81%	-41%	0%	41%	81%

Components of core valuation (pre-corp tax)



* The value of royalties has been calculated assuming our explicit revenue forecasts, a period of further growth until generics enter the market, and a period of further market growth and decline as competing products enter the market.

Anti-infectives: market constraints

The competitive environment for drugs to treat these infections is rather intense at this time. There are 6 drugs slated to enter the market over the next 2 years of which three, Pfizer's dalbavancin (note: additional studies required by the FDA and setback) and Theravance/Astell's telavancin and Basilea/J&J's ceftobiprole (ceftobiprole has poor or no efficacy against *C. difficile*) are slated to hit the market by the end of 2008. The three others have completed Phase III and should be on the market within the next 18-24 months. While all of these drugs have strengths and weaknesses, we see no evidence at this time to suggest that any one of these drugs have broad enough characteristics to tackle this problem in a cost-effective way. In this regard, the e-Therapeutics drug profile does stand out as somewhat unique. Nevertheless, clinical proof of this concept is yet to be completed at this time.

First it is important to note that the serious infections that we are focused on here are nosocomial infections (as opposed to community-acquired infections). These infections are primarily endemic to hospitals and other healthcare facilities and tend to be the result of cross infection due to physical transmission (usually based on careless hygiene). Three organisms stand out as culprits in these infections: MRSA, Vancomycin-resistant Enterococci and *Clostridium difficile*, all gram positive bacteria. As evidenced by the degree of press coverage on the issue, strains of antibiotic-resistant bacteria constitute a serious public health risk. Significant efforts are being expended to find novel antibiotic classes to enable clinicians to cope with these intractable infections.

Asthma/COPD

Asthma and COPD are chronic inflammatory diseases of the lung that result in the narrowing of pulmonary pathways and various degrees of chest tightness and respiratory difficulties. COPD³² (which includes chronic bronchitis and emphysema), is a progressive, irreversible disease usually triggered by smoking although in a small number of cases, hereditary factors may be involved. While irreversible, it is treatable with similar medications to those used in asthma.

The mainstays of asthma treatment are beta-agonists³³ and glucocorticosteroid treatment (called ICS or inhaled corticosteroid), usually given by an inhaler but in serious cases as oral medication. Beta-agonist treatment (short-acting ones, or SABA's, are aimed at a rapid opening up the alveolar passages of the lung) is used for acute conditions such as in asthma attack. Longer acting ones, or LABA's, are also on the market.

³²Chronic Obstructive Pulmonary Disease

³³Beta2-adrenoreceptors are smooth muscle receptors whose stimulation (by beta2 agonists) will act to relax bronchial passageways

Steroids tend to be longer acting aimed at treating the underlying inflammation. In mild to moderate asthma, these drugs tend to be used in time of need (post exercise, during hay fever season or when allergies are present). For moderate to severe persistent asthmatics, there is a need to manage their condition on an ongoing basis. Again the beta-agonists are used during acute attacks and the steroid inhalers are used to prevent these attacks. In more recent times, combinations of LABA's and ICS are marketed (e.g., Glaxo's Advair and AZN's Symbicort) have taken over significant shares of the market.

In addition, a new class of drugs called anti-leukotrienes has also emerged. Singulair is an oral anti-leukotriene marketed by Merck. Leukotrienes are active in a number of cell types that are implicated in inflammation: monocytes in particular are involved in both acute and chronic inflammation. They help to maintain the inflammatory response so their blockage should be useful in the treatment of asthma.

Singulair, supported by the marketing power of Merck, has carved a significant share of the asthma market and generates some US\$4bn of annual revenues. While it is not superior to the ICS drugs, its clean side-effect profile and once-a-day oral formulation makes it particularly suitable for the geriatric and pediatric patients. It has also found use in the same population with co-morbid Allergic Rhinitis and associated asthma.

To be a true market winner, Singulair would have had to demonstrate its ability to reduce the intake of inhaled products, which it has failed to do. However, its US\$4 billion in annual revenues demonstrates that there is a significant market for a safe, convenient dosage oral form drug that can reduce the subsequent intake of inhaled drugs.

Enter ETX 9101, a combination product which includes a common anti-inflammatory agent with some prior evidence of efficacy in asthma and an anti-histamine (allergy medication) also showing some effect in asthma. Both products are generic and obviously have full safety monographs with regulatory agencies worldwide. This combination has been subjected to a preliminary, randomised open label, PoP clinical trial in moderate to severe asthmatics. The primary aim of this trial was to double check safety and to see whether there was any evidence of reduction in both daily and nighttime usage of inhaled medication (both ICS and SABA).

e-Therapeutics has just announced the results of this trial but the results presented, while encouraging, present for the most part only non-statistical clinical data. The trial, which contained an arm with patients treated with their normal course of therapy, was not meant to be statistically powered, and hence not

expected to show any statistically significant effects. Some interesting tidbits of information emanating from the data are intriguing and will be investigated in a subsequent trial:

- respectively, 42% versus 16% of patients in the ETX 9101-treated versus the untreated group were independent of inhaler at week 12;
- no patients treated with ETX9101 in response to signs that would lead to an attack went on to experience asthma exacerbation, whereas in the control group, similar patients went on to have an attack, with one incident leading to hospitalisation
- they found a statistically significant effect between the first and fourth visit in nighttime asthma score (patients' self-evaluation of symptoms).

e-Therapeutics are mainly looking for indications of efficacy sufficient to induce a potential partner to take the product into a pivotal, registration orientated Phase IIb/Phase III trial. Also, to compete with Singulair, the product still needs to be formulated in a once-a-day format.

ETX 9101 Revenue model

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Total Number of Asthma sufferers													
US	23	23.7	24.4	25.1	25.9	26.7	27.5	28.3	29.1	30.0	30.9	31.8	32.8
Japan	5	5.2	5.3	5.5	5.6	5.8	6.0	6.1	6.3	6.5	6.7	6.9	7.1
Europe (5 major countries)	17	17.5	18.0	18.6	19.1	19.7	20.3	20.9	21.5	22.2	22.8	23.5	24.2
RoW	15	15.5	15.9	16.4	16.9	17.4	17.9	18.4	19.0	19.6	20.2	20.8	21.4
Total	60.0	61.8	63.7	65.6	67.5	69.6	71.6	73.8	76.0	78.3	80.6	83.1	85.5
Total Persistent Moderate to Severe													
US	9.2	9.5	9.8	10.1	10.4	10.7	11.0	11.3	11.7	12.0	12.4	12.7	13.1
Japan	2.0	2.1	2.1	2.2	2.3	2.3	2.4	2.5	2.5	2.6	2.7	2.8	2.9
Europe (5 major countries)	6.8	7.0	7.2	7.4	7.7	7.9	8.1	8.4	8.6	8.9	9.1	9.4	9.7
RoW	6.0	6.2	6.4	6.6	6.8	7.0	7.2	7.4	7.6	7.8	8.1	8.3	8.6
Total	24.0	24.7	25.5	26.2	27.0	27.8	28.7	29.5	30.4	31.3	32.3	33.2	34.2
Average Singulair cost per annum*(in \$US)	400	400	400	400	400	400	400	400	400	400	400	400	400
Estimated discount to Singulair	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
Estimated Price for ETX 9101(in \$US)	340	340	340	357	375	394	413	434	456	478	502	527	554
Total Market potential for ETX 9101	\$9,600	\$9,888	\$10,185	\$10,490	\$10,805	\$11,129	\$11,463	\$11,807	\$12,161	\$12,526	\$12,902	\$13,289	\$13,687

ETX 9101 Revenue Estimate

Core Model

Estimated Market penetration	0.1%	0.2%	1.5%	3.0%	4.0%	4.5%	5.0%	5.2%	5.4%	5.6%
Estimated Sales (in US\$ millions)	\$10	\$22	\$167	\$344	\$472	\$547	\$626	\$671	\$718	\$766

Optimistic Model

Estimated Market penetration	0.2%	0.4%	3.0%	5.0%	7.0%	7.5%	8.0%	8.5%	8.7%	8.9%
Estimated Sales (in US\$ millions)	\$21	\$43	\$334	\$573	\$826	\$912	\$1,002	\$1,097	\$1,156	\$1,218

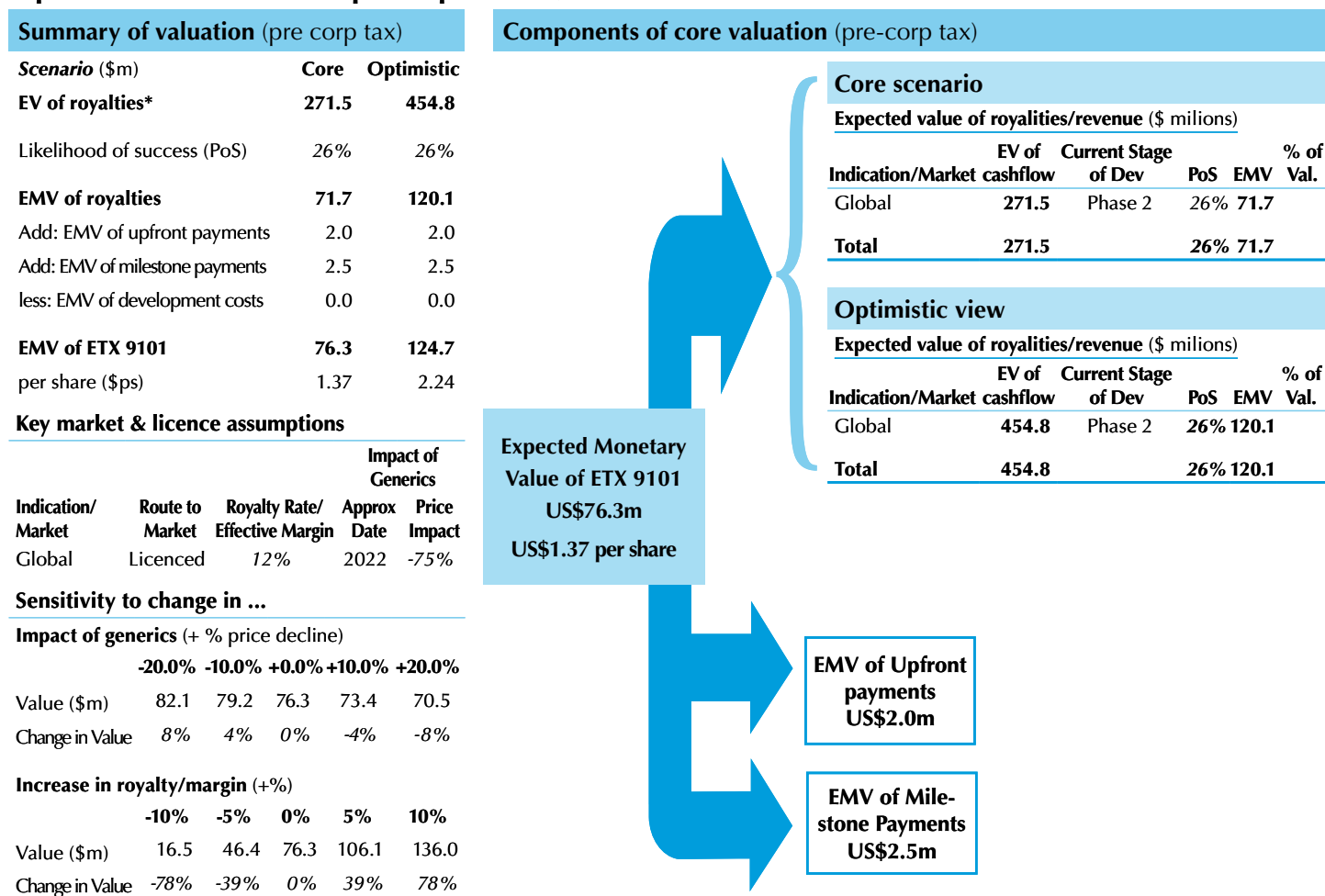
(*)Singulair goes ex-patent in 2013

Source: company documents based on market and literature data, Objective Capital estimates

We have focused our estimate of the potential for this drug on the moderate to severe persistent market as this is the one where Singulair is most applicable. We estimate that this segment of the market, based on an average annual Singulair cost of around US\$400 where the segment represents about forty percent of the total, is worth just under US\$10 billion or less than a third in value of the total market of just under US\$30 billion globally.

In this market, we are estimating that it is reasonable for a product with this profile to achieve around US\$1 billion in revenues. We believe that this is a conservative estimate and takes into consideration the fact that only four companies dominate the market. Unless one of these takes this product up, the competitive thrust will not be easy. Second, we think that an effective longer acting once-a-day oral drug could also make in-roads into the persistent mild to moderate market and, as demonstrated by Singulair (with a current revenue take of around US\$4.5 billion) into the paediatric and geriatric markets. Our more aggressive estimate reflects that at just under \$2 billion.

Expected value of ETX 9101 (pre-corporate tax)



* The value of royalties has been calculated assuming our explicit revenue forecasts, a period of further growth until generics enter the market, and a period of further market growth and decline as competing products enter the market.

Anti-Depressants

Depression and pain have been known for some time to occur in many patients as simultaneous morbid conditions. An extensive literature review conducted a number of years ago concluded that 'on average, 65 percent of patients with depression experience one or more pain complaints' and that 'the presence of pain negatively affects the recognition and treatment of depression'. The flip side to this is that, depending on the treatment setting, depression appears to be present in a significant number of patients with pain symptoms³⁴.

The biological basis for this is that the mood and pain pathways have in common the neurotransmitters Serotonin and Dopamine. One dominant theory of depression holds that it is an imbalance in these substances that is the underlying molecular aetiology of this disease. The fact that serotonin reuptake inhibitors such as fluoxetine (the base ingredient in Prozac and a selective serotonin reuptake inhibitor of SSRI) replenish levels of serotonin and act to alleviate symptoms of depression is certainly an indication that this may be a valid theory.

However, as many as 25-40 percent of patients that take SSRI's fail to benefit which leads one to believe that this is not the entire answer. SSRI's having been tested (and are often prescribed) as anti-pain medication but exert only a modest, if any, effect over placebo. The well known fact that pain and depression are co-morbid in many patients would imply that depression is a complex disease with multiple pathways involved, and that resolving underlying pain pathways might be needed to resolve depression.

The most effective drugs for the treatment of depression and pain are those that seem to modulate both of the neurotransmitter systems. Drugs such as the Tricyclic Antidepressants (TCA), venlafaxine, mirtapazine and monoamine oxidase (MAO) inhibitors all beat SSRI's in inducing higher rates of remission³⁵.

Venlafaxine (Efflexor; Wyeth) is a dual serotonin-norepinephrine reuptake inhibitor or SSNRI which, when given at doses of 150 mg/day or higher, has been seen (through a meta-analysis of many trials) to be associated with higher remission rates than SSRI's (45% versus 35% respectively)³⁶. However, these drugs carry side-effect and dependence issues and, whether with SSRI's or SSNRI's, the number of patients that fail these therapies remains very high.

This begs the question as to whether something else is not at work here. Is it the case that much of the depression seen derives from multiple malfunctions in central mood and pain systems? Many think so, including Malcolm Young and his group at e-Therapeutics. This is the underlying rationale that led the company

³⁴Bair, M.J. et al, (2003), *Arch. Intern. Med.* **163**; 2433-2445

³⁵Remission is defined as a Hamilton Depression Scale rating of less than 8.

³⁶Thase ME et al (2001) *Br. J. Psychiatry*; **178**;234-241

to search for and develop ETS 6103. The objective was to find a drug that would affect both the central mood and pain pathways which, although separate, are interconnected by the use of common neurotransmitters and other mechanisms. ETS 6103 was selected out of a group of fourteen candidate compounds and is aimed, initially, at patients that fail SSRI therapy. Longer term though, the aim is to see whether a drug of this kind might be useful as a broad spectrum antidepressant drug.

Our initial model of this drug focuses on its use in SSRI-refractive patients. In our model, we estimate that about twenty percent of patients today are treated on SSRI's based on the current sales of this class of drug as a percentage of the total market of about US\$17 billion globally or just under US\$4.5 billion (many SSRIs are generic today).

ETS 6103 Revenue model													
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Total Number of Depression patients													
US	20	20.4	20.8	21.2	21.6	22.1	22.5	23.0	23.4	23.9	24.4	24.9	25.4
Japan	4	4.1	4.2	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1
Europe (5 major countries)	20	20.4	20.8	21.2	21.6	22.1	22.5	23.0	23.4	23.9	24.4	24.9	25.4
RoW	26	26.5	27.1	27.6	28.1	28.7	29.3	29.9	30.5	31.1	31.7	32.3	33.0
Total	70.0	71.4	72.8	74.3	75.8	77.3	78.8	80.4	82.0	83.7	85.3	87.0	88.8
Total Depression on SSRI's (circa 20% of the market)													
US	8.0	8.2	8.3	8.5	8.7	8.8	9.0	9.2	9.4	9.6	9.8	9.9	10.1
Japan	1.6	1.6	1.7	1.7	1.7	1.8	1.8	1.8	1.9	1.9	2.0	2.0	2.0
Europe (5 major countries)	8.0	8.2	8.3	8.5	8.7	8.8	9.0	9.2	9.4	9.6	9.8	9.9	10.1
RoW	10.4	10.6	10.8	11.0	11.3	11.5	11.7	11.9	12.2	12.4	12.7	12.9	13.2
Total	28.0	28.6	29.1	29.7	30.3	30.9	31.5	32.2	32.8	33.5	34.1	34.8	35.5
Total SSRI resistant patients													
US	2.4	2.4	2.5	2.5	2.6	2.6	2.7	2.8	2.8	2.9	2.9	3.0	3.0
Japan	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.6	0.6
Europe (5 major countries)	2.4	2.4	2.5	2.5	2.6	2.6	2.7	2.8	2.8	2.9	2.9	3.0	3.0
RoW	3.1	3.2	3.2	3.3	3.4	3.4	3.5	3.6	3.7	3.7	3.8	3.9	4.0
Total	8.4	8.6	8.7	8.9	9.1	9.3	9.5	9.6	9.8	10.0	10.2	10.4	10.7
Average SSRI cost per month (All in US\$)	85	85	85	85	85	85	85	85	85	85	85	85	85
Estimated discount to SSRI	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
Estimated Price for ETS 6103	81	81	81	85	89	93	98	103	108	114	119	125	132
Estimated Annual cost of the drug (6 months in US\$)	485	485	485	509	534	561	589	618	649	682	716	752	789
Total Market potential for ETS 6103	\$4,070	\$4,151	\$4,234	\$4,535	\$4,857	\$5,202	\$5,571	\$5,967	\$6,390	\$6,844	\$7,330	\$7,850	\$8,408
ETS 6103 Revenue Estimate													
Core Model													
Estimated Market penetration					0.1%	3.0%	5.0%	7.0%	7.2%	7.5%	7.6%	7.7%	7.8%
Estimated Sales (in US\$ millions)					\$5	\$156	\$279	\$418	\$460	\$513	\$557	\$604	\$656
Optimistic Model													
Estimated Market penetration					0.2%	5.0%	7.0%	9.0%	9.5%	9.7%	10.0%	10.2%	10.4%
Estimated Sales (in US\$ millions)					\$10	\$260	\$390	\$537	\$607	\$664	\$733	\$801	\$874

Source: various literature estimates, WHO, US CDC data and Objective Capital estimates

On that basis, we believe that the potential market for such drugs is potentially as large as the current SSRI market, growing to about US\$7.4bn in 2017. We also believe that in this market, a broad-spectrum drug with a benign side-effect profile that is capable of inducing remission in these patients could garner a significant chunk of the market which we have pegged at around 18-20 percent in our core model leading to projected revenues of around US\$1.3 billion. With such a profile, all of this could prove to be conservative.

The clinical status is that a controlled study of ETS6103 and amytryptilline in forty very seriously depressed patients has been conducted but was halted as recruitment hit the half-stage. The company has indicated, on a preliminary basis, that the effects of ETS6103 on depression were dramatic. The final results of this trial will be available in the next few months and discussions are ongoing with potential partners for further development of the drug.

Expected value of ETS 6103

Summary of valuation (pre corp tax)		
Scenario (\$m)	Core	Optimistic
EV of royalties*	234.5	312.0
Likelihood of success (PoS)	26%	26%
EMV of royalties	61.9	82.4
Add: EMV of upfront payments	2.0	2.0
Add: EMV of milestone payments	2.5	2.5
less: EMV of development costs	0.0	0.0
EMV of ETS 6103	66.5	87.0
per share (\$ps)	1.19	1.56

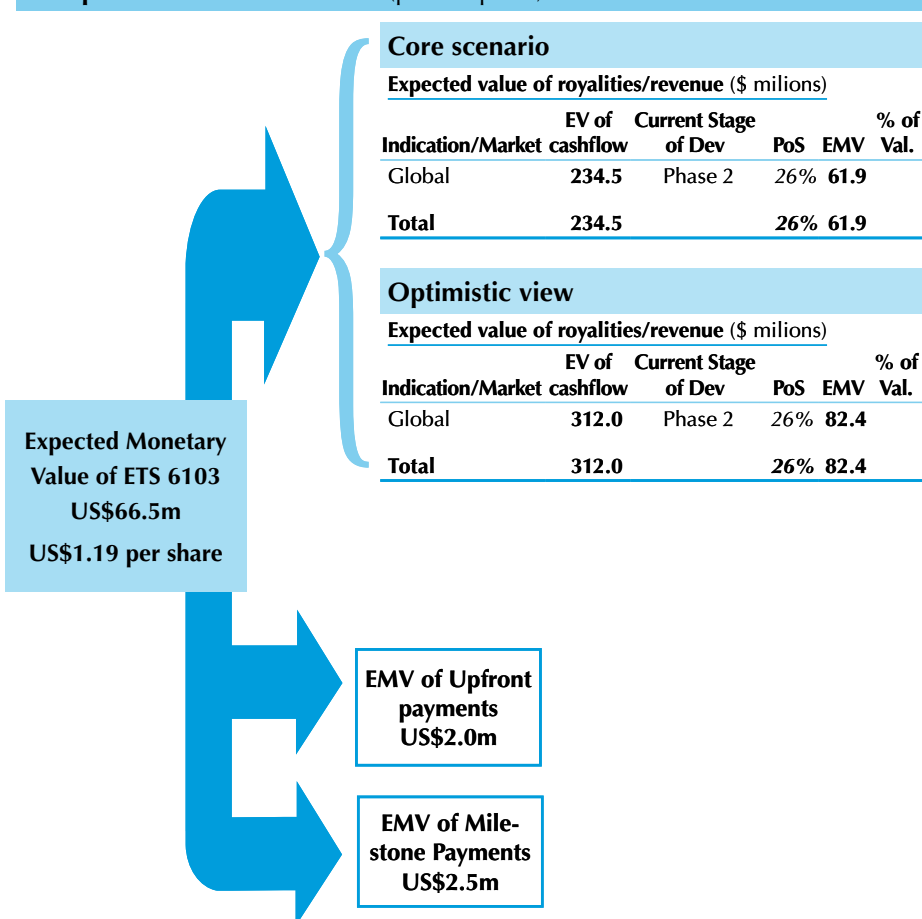
Key market & licence assumptions

Indication/Market	Route to Market	Royalty Rate/Effective Margin	Approx Date	Price Impact	Impact of Generics
Global	Licensed	12%	2022	-75%	

Sensitivity to change in ...

Impact of generics (+ % price decline)					
	-20.0%	-10.0%	+0.0%	+10.0%	+20.0%
Value (\$m)	71.7	69.1	66.5	63.9	61.3
Change in Value	8%	4%	0%	-4%	-8%
Increase in royalty/margin (+%)					
	-10%	-5%	0%	5%	10%
Value (\$m)	14.9	40.7	66.5	92.3	118.1
Change in Value	-78%	-39%	0%	39%	78%

Components of core valuation (pre-corp tax)



* The value of royalties has been calculated assuming our explicit revenue forecasts, a period of further growth until generics enter the market, and a period of further market growth and decline as competing products enter the market.

Fibromyalgia

Fibromyalgia, also referred to as fibromyalgia syndrome or FMS, is an umbrella disease that encompasses a range of symptoms primarily involving pain and tenderness to light touch (also known as allodynia). Other symptoms of the disease include fatigue, muscle aches and spasms, limb weakness, depression, nerve pain (also known as neuralgia), bowel and sleep disturbances. There are many other potential symptoms in this disease which also makes its diagnosis rather controversial.

Nevertheless, in 1990, the American College of Rheumatology elaborated a set of criteria for both research and clinical purposes to enable the diagnosis of this disease. This entails a history of three months or greater in all parts of the body. There are also eighteen pre-defined points on the body to which pressure is applied, if eleven of those display pain, a diagnosis of FMS is confirmed.

The treatment of the disease is carried out with a wide variety of medications to greater, lesser, or no effect. The most prominent of these is the recently approved pregabalin analgesic marketed by Pfizer as Lyrica. In a recent trial, the drug triggered a statistically significant reduction in pain of fifty percent in the great majority of the patients treated in a large placebo-controlled trial³⁷.

The disease is often associated with other co-morbidities such as depression. The disease affects about two percent of the US population with similar prevalence rates elsewhere except in Germany and Italy where it appears to be around three percent. On this basis, we have constructed a patient model which is incorporated into our revenue model for ETS 6218, e-Therapeutics' candidate for this market.

The origin of this project is interesting in and of itself. e-Therapeutics conducted a due diligence project on behalf of a third party related to a drug it wished to license. As part of this exercise, e-Therapeutics conducted an exhaustive review of the drugs used for the disease.

As per usual in its dealings with third parties on such projects, the company retained the right to develop other drugs for its own account on the basis of the information that it derived. It constructed a profile of fibromyalgia mechanisms derived from a spectrum of targets weighted by their relative therapeutic success across the many drugs prescribed for fibromyalgia. Then, using its chemoproteomic database tools, e-Therapeutics undertook to search for compounds that ideally matched this profile.

³⁷ Crofford LJ, Rowbotham MC, Mease PJ, et al (2005), *Arthritis Rheum.* **52** (4): 1264–73.

Given the complexity of multi-target nature of the disease, it felt that a multivalent approach was the most likely to succeed in this case. The result was the combination of an anti-viral drug and an anti-histamine neither of which are obvious candidates to resolve such a disease.

The clinical development of this product will likely be part of a partnership with the conduct of a PoP Phase I/IIa trial to test both safety and indications of efficacy in a small number of patients to be followed by a full-blown Phase IIb/III trial to ready the product for registration if successful.

As can be seen in the accompanying market and revenue model, the current market for fibromyalgia products is just north of US\$1 billion today based on a very low penetration of what we see as a US\$25 billion market worldwide. The advent of increasingly effective drugs (the latest being Lyrica) should drive an increasing penetration of this market which should see it grow to close to US\$3 billion by 2015. We believe, that an effective drug in this area should be able to garner a significant chunk of this market which is why we have allowed the potential for ETS6218 to penetrate around one fifth of the market. This translates into a drug which could reach the half a billion dollar mark by 2015.

ETS 6218 Revenue model

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Total Number of fibromyalgia patients													
US	6	6.2	6.4	6.6	6.8	7.0	7.2	7.4	7.6	7.8	8.1	8.3	8.6
Japan	2.6	2.7	2.8	2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.7
Europe (5 major countries)	7.2	7.4	7.6	7.9	8.1	8.3	8.6	8.9	9.1	9.4	9.7	10.0	10.3
RoW	6	6.2	6.4	6.6	6.8	7.0	7.2	7.4	7.6	7.8	8.1	8.3	8.6
Total	21.8	22.5	23.1	23.8	24.5	25.3	26.0	26.8	27.6	28.4	29.3	30.2	31.1
Average cost per annum(*) (in US\$)	1,200	1,200	1,200	1,200	1,200	1,200	1,200	1,200	1,200	1,200	1,200	1,200	1,200
Estimated discount to Current Treatment	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
Estimated Price for ETS 6218	1,140	1,140	1,140	1,197	1,257	1,320	1,386	1,455	1,528	1,604	1,684	1,769	1,857
Total Market potential for ETS 6218	\$24,852	\$25,598	\$26,365	\$28,514	\$30,838	\$33,351	\$36,070	\$39,009	\$42,189	\$45,627	\$49,346	\$53,367	\$57,717
Current market penetration	4%	5%	5%	6%	6%	7%	7%	7%	7%	7%	7%	7%	7%
Addressable Market (in US\$ millions)	\$994	\$1,152	\$1,318	\$1,568	\$1,850	\$2,168	\$2,525	\$2,731	\$2,953	\$3,194	\$3,454	\$3,736	\$4,040

ETS 6218 Revenue Estimate

Core Model

Estimated Market penetration	1.0%	2.0%	10.0%	15.0%	17.0%	17.2%	17.3%	17.4%	17.5%	17.6%
Estimated Sales (in US\$ millions)	\$16	\$37	\$217	\$379	\$464	\$508	\$553	\$601	\$654	\$711

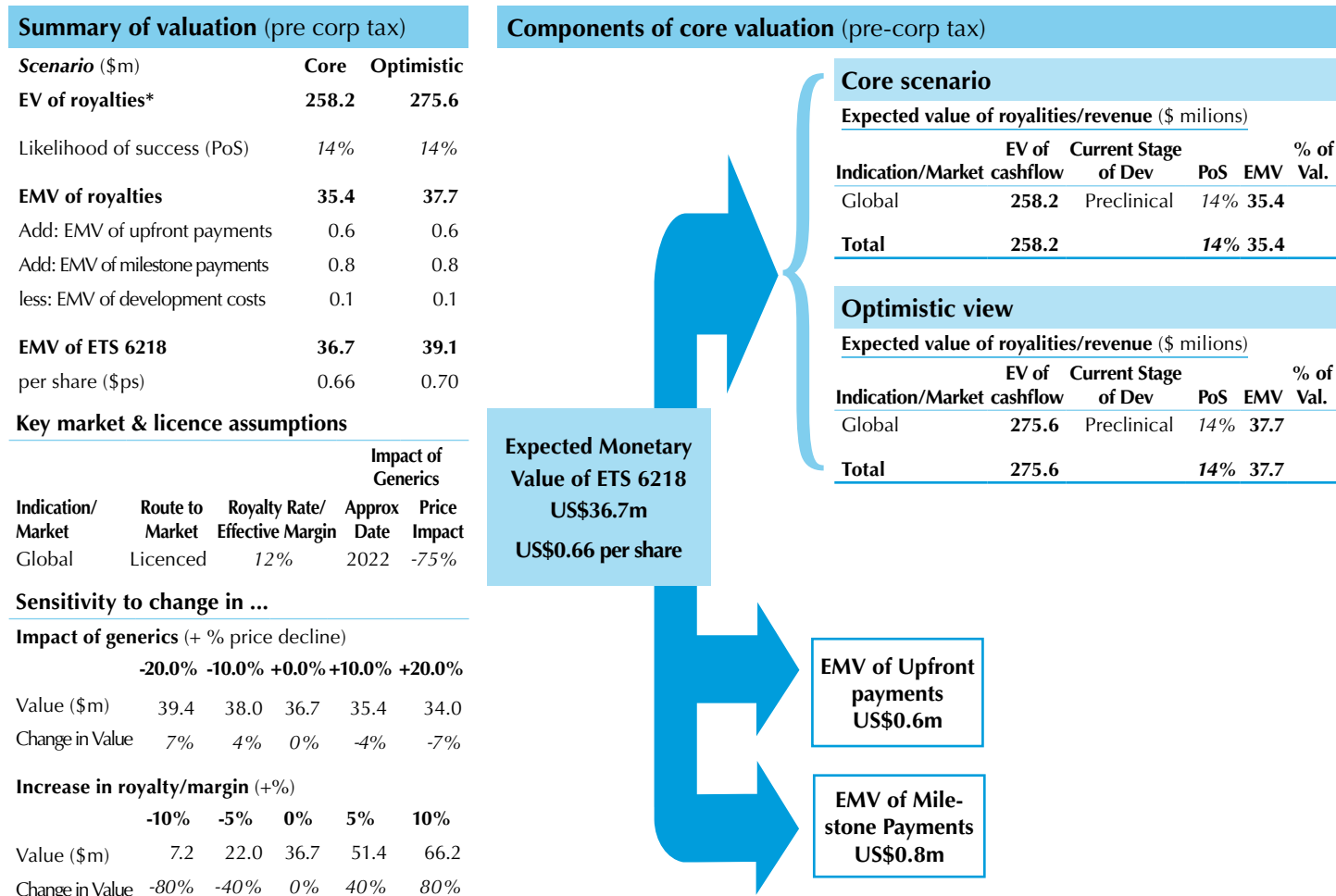
Optimistic Model

Estimated Market penetration	1.5%	2.5%	12.0%	17.0%	19.0%	20.0%	21.0%	21.5%	21.7%	21.9%
Estimated Sales (in US\$ millions)	\$24	\$46	\$260	\$429	\$519	\$591	\$671	\$743	\$811	\$885

(*)based on Cymbalta (LLY) and Lyrica (PFE) average estimated costs per month

Source: company documents based on market and literature data, Datamonitor and Objective Capital estimates

Expected value of ETS 6218 (pre-corporate tax)



* The value of royalties has been calculated assuming our explicit revenue forecasts, a period of further growth until generics enter the market, and a period of further market growth and decline as competing products enter the market.

Cancer

The company's oncology programme was initially designed to target metastatic melanoma, because the intractable and deadly nature of the disease made it a pressing priority. In the US alone, the incidence rate is around 40 per 100,000 population growing at around four percent per annum.

The lifetime risk of developing melanoma has been estimated at 1 in 75 and the disease, which affects around 60,000 patients per annum kills around 8,000 every year in the US. While the prognosis for early stage melanoma (Stage I and II) is rather good (usually surgical treatment suffices), late stage metastatic melanoma's (Stage III and IV) have a very poor prognosis. Survival rates for Stage III are less than five years and for Stage IV less than one year.

It is the 7th most common cancer in the US. Datamonitor estimates that there are around 100,000 patients per annum with melanoma in the seven major markets (US, Japan, UK, Germany, France, Italy and Spain) which translates currently into a therapeutic market of around US\$750 million annually. The mainstay therapies are cytotoxic drugs (dacarbazine, temozolomide, cisplatin, vinblastine and others) and biologicals such as Interleukin-2 and Interferon-alpha. Many combinations of these drugs are used, but the response rates vary from a low eleven percent all the way to 40-60 percent but with the poor survival statistics mentioned earlier.

Hence, metastatic melanoma seemed like a good target for e-Therapeutics to demonstrate the power of its technology. The approach taken was to collect data on all of the different protein-protein interactions reported for this disease and to look at the mechanism of action of all known drugs.

However, in this case, there is a considerable amount of data of up- and down-regulated proteins in these cells which e-Therapeutics could mine in its databases.

This led to the profile of a 'typical' melanoma cell, and a large number of 'local area network' or LANs which could be mined for targets. The Chemoproteomic database was then mined for candidates that might shut down these networks, further de-risked by looking for compounds that had a full regulatory monograph. It is in this way that ETS2101 was identified. The drug was originally developed for a neurological indication for which a full Phase III trial was conducted but, while the compound showed good safety, it failed to demonstrate any efficacy in its original indication.

This compound, which has been tested by Cancer Research UK among others, has been tested extensively in vitro, on a wide variety of cancer cells. It displays highly effective pro-apoptotic activity³⁸ not only in metastatic melanoma cells but also in many other cancer cell types.

As this project is still at a rather early stage, we have chosen not to include it in our valuation at this time. The reason for this relates to the unknown range of target cancers against which it will be developed. We have however estimated what its value for metastatic melanoma alone would be which is presented in the accompanying table. We have estimated that for metastatic melanoma (one of the smaller but deadlier markets in cancer) alone, based on a therapeutic regimen involving Interferon alpha and cytotoxic chemotherapy, the cost of therapy is some

³⁸Apoptosis is an inherent cellular mechanism that results in cell death.

where around \$35,000. We believe that the adjunctive use of a drug such as ETS 2101 could cost as little as 25 percent of that number. Based on our population estimates we calculate a total market of around \$2 billion of which an effective drug could capture around 25 percent of the market translating into a revenue potential of between \$500-600 million. Of course, efficacy in any other cancer would see this number multiplied appropriately.

If the *in-vitro* profile carries over to in-vivo animal studies, we believe that the drug will be subjected initially to an 'all comer/all advanced cancer' Phase I/IIa-type exploratory trial to see where the drug is most active. We also believe that the drug will be tested on its own but also in combination with standard chemotherapeutic regimens. Often, pro-apoptotic drugs are 'leaky' in that cancer cells find ways to outsmart these drugs by turning on pro-survival pathways. It remains to be seen how effective this drug will be at shutting down such 'leakiness', although it was particularly effective at killing cells that were resistant to cisplatin.

The beauty of this project is that is quintessentially a network analysis approach which has dug out a drug developed for a completely unrelated condition and repositioned it for this application. It will be, along with ETS 6218 for fibromyalgia, a show case for this technology. As ever, the proof will lie in clinical validation of the concept.

ETS 2101 Revenue model													
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Skin Cancer (# patients in mills)	3.20	3.26	3.33	3.40	3.46	3.53	3.60	3.68	3.75	3.82	3.90	3.98	4.06
Metastatic Melanoma incidence at 10%	0.32	0.33	0.35	0.36	0.37	0.39	0.40	0.42	0.44	0.46	0.47	0.49	0.51
Addressable market (50%) in Millions	0.16	0.17	0.17	0.18	0.19	0.19	0.20	0.21	0.22	0.23	0.24	0.25	0.26
Therapy Cost Est. per annum (US\$)	35,000	35,000	35,000	35,000	35,000	35,000	35,000	35,000	35,000	35,000	35,000	35,000	35,000
Estimated Market Size (in US\$ millions)	5,600	5,824	6,057	6,299	6,551	6,813	7,086	7,369	7,664	7,971	8,289	8,621	8,966
Est. Price at ~50% of total therapy cost (in US\$)	8,750	8,750	8,750	8,750	8,750	8,750	8,750	8,750	8,750	8,750	8,750	8,750	8,750
Total Market potential for ETS 2101 (in \$ millions)	\$1,400	\$1,456	\$1,514	\$1,575	\$1,638	\$1,703	\$1,771	\$1,842	\$1,916	\$1,993	\$2,072	\$2,155	\$2,241
ETS 2101 Revenue Estimate													
Core Model													
Estimated Market penetration					0.1%	1.0%	5.0%	10.0%	15.0%	20.0%	22.0%	23.0%	23.5%
Estimated Sales (in US\$ millions)					\$0.8	\$17	\$89	\$184	\$287	\$399	\$456	\$496	\$527
Optimistic Model													
Estimated Market penetration					0.2%	2.0%	7.0%	14.0%	18.0%	22.0%	24.0%	25.0%	25.5%
Estimated Sales (in US\$ millions)					\$3	\$34	\$124	\$258	\$345	\$438	\$497	\$539	\$572

⁽¹⁾ R.E. Coleman, *Cancer Research Rev.* (2001);27;165-176

⁽²⁾ Cancer Population Estimates from a combination of GLOBOCAN 2002 and SEER 2006 Prevalence Estimates

Source: company documents based on market and literature data, Objective Capital estimates

How does the competition stack up? It comes in two forms:

- better medications from traditional biotech and pharma;
- other Systems Biology companies involved in repositioning drugs.

As the therapeutic areas reflected in e-Therapeutics' pipeline are very diverse and the stage of development of each candidate quite early, a comprehensive review of competitive drugs seems rather premature. Nevertheless, it is possible to make some general competitive comments about what the competitive environment is for each therapeutic area.

In anti-infectives

There is a considerable pipeline of drugs from novel drug classes that is making its way through the various stages of clinical development of which 6 are at a very advanced stage. e-Therapeutics' entrant has the distinction of being the only one that is simultaneously effective against VRSA, MRSA and C.Difficile, three highly prevalent nosocomial infections.

Infections of this kind tend to have multiple organisms involved which is the reason why they are so difficult to treat, resistance issues aside. Broader spectrum drugs able to resolve a number of these at the same time are sorely needed in the anti-microbial armamentarium making the e-Therapeutics entrant a useful addition if its safety and efficacy can be verified in the clinical setting.

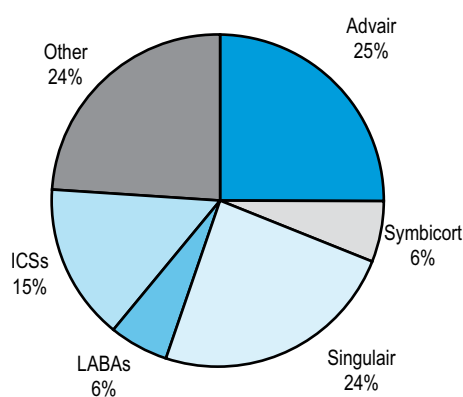
Resistant nosocomial infections late-stage pipeline

Drug name	Company		Admin Route	Indications	Stage	Comments
Zeven	Pfizer	dalbavancin	IV	cSSTI	pre-Reg/PIII	Additional PIII trial needed/not active against gram- bacteria and VRE
Telavancin	Theravance/ Astellas	telavancin	IV	cSSSI HAP/VAP	Pre-Registration PIII	Nov 08 FDA Advisory Committee/not active against gram-negative bacteria/ renal and cardiac toxicity
	Basilea/Jnj	ceftobiprole	IV	cSSSI HAP/VAP CAP	Pre-Registration PIII PIII	no C.difficile activity
Arpida		iclaprim	IV/Oral	cSSSI/HAP/VAP		Possible cardiac toxicity, some gram- activity early data on cSSSI
Intermune/ Targanta		oritavancin	IV	cSSSI Catheter Bacteraemia	PIII PIII	May have broad activity against MRSA, VRE and C.difficile (oral trials in progress). FDA action date in December
	Takeda/ Forest Labs	ceftaroline	IV	cSSSI HAP/VAP	PIII PIII	PIII just completed Filing in 2009/10 with HAP data

Source: data from company documents

2006 Global asthma market

% of sales - total US\$15 billion



Source: e-Therapeutics

In asthma/COPD

As indicated earlier, the ability to deliver a once a day, oral, anti-asthmatic in a convenient dosage form has been proven by Merck's LTA Singulair to fill a market need. Despite its lack of superiority over combination inhaled treatments, it has still managed to garner a significant chunk of the market aided, no doubt, by the marketing prowess of Merck, but also by the fact that these convenient dosage forms are very useful for pediatric and geriatric patients. An oral, once a day, convenient dosage form that is effective and can be shown to reduce the need for inhaled therapy could make very significant inroads into what is today almost a US\$30 billion market and growing. It is too early to tell whether e-Therapeutics' potential entrant stands a chance in this market but if its profile matches market needs, it is sure to be picked up by a major pharma with a stake in the market.

In anti-depressants

According to the WHO, depression will rank only second to ischaemic heart disease as a disability by 2020. Its co-morbidity with pain and the overall cost to healthcare systems and the overall economy worldwide is of major significance. The current generation of treatments have come some way towards alleviating the burden of MDD (Major Depression Disorder) with a more benign side-effect profile than the previous generation of TCA's. Nevertheless, much remains to be achieved. We have indicated earlier that as many as forty percent of patients fail these therapies and only 35-45 percent of those treated actually achieve remission. Those patients that present with depression tend to have the underlying physical pain symptoms untreated and vice versa, the depression of patients with primary pain symptoms tends to be under treated for the latter. There is a massive pipeline of drugs targeting multiple potential targets including:

- specific serotonergic receptor agonists;
- Noradrenaline receptor inhibitors of NARI;
- SSNRI's but also other mixed multiple RI's;
- Neurokinin-1 receptor antagonists;
- CRF-1 receptor antagonists;
- BDNF agonists.

Each of these strategies holds the potential for incremental advantages but also have potential weakness. All in all, the field is still open to novel approaches and the market is large enough for a potential entrant, with the right profile, to thrive. Hence, should the early profile of ETS 6103 hold up, we see no reason that it could not play a significant role in this market segment.

In Fibromyalgia

As indicated above, this therapeutic category remains somewhat undefined and controversial in nature. Nevertheless, its symptoms are real and the distress and morbidity that it causes requires serious consideration, diagnosis and treatment. The approval of Pfizer's Lyrica and, more recently, Lilly's Cymbalta for Fibromyalgia, has given this therapeutic category significant visibility and may very well act as a catalyst to further interest and entrants. In our view, this is a very young, underserved market which, as our market model indicates, is relatively poorly penetrated at this time. Hence the opportunities for a safe and effective treatment will find great acceptance amongst treating physicians and particularly patients who suffer from this condition.

As an indication of the complexity of this disease, Lyrica (pregabalin) is an anti-convulsant approved as an anti-epileptic agent and Cymbalta is a SNRI for the treatment of anxiety and depressive disorder in addition to pain. As we noted earlier, pain is a co-morbidity of depression but it is also interconnected with different pathways involving different neurotransmitters. Lyrica mimics a neurotransmitter called GABA (or gamma amino butyric acid), a neurotransmitter that acts to inhibit receptors that are active in nociceptive³⁹ pain pathways. Again, this market needs more effective medication and its penetration (below US\$1 billion) is an indication, given the patient potential, that there is a long way to go before competitive issues might act as a block to an effective treatment that is also safe.

In cancer

It goes without saying that this is a very complex and crowded market. The complexity of the market is a function of the heterogeneity of the disease itself. We have focused only on the malignant metastatic melanoma segment here for which there are many pipeline candidates in testing. It is unlikely that there will be one winner here so a drug with the potential profile (pro-apoptotic) of ETS 2101 if, as suspected, not limited to metastatic melanoma, could have a very large potential indeed. The market has been searching for generalised mechanisms across various cancers (cell cycle modulators are an example) for some time. It is too early to tell whether this drug fits the bill but we do not see any particular competitive impediment to the development of its full potential.

³⁹Nociceptive pain is a form of pain with the potential to cause tissue damage.

In drug-repositioning

The repositioning of drugs as a market segment means different things to different people. One common thread though is that most of the companies that we see in this market segment are taking a retrospective approach in searching for viable candidates. Whether it is **Ore Pharmaceuticals** (the former **GeneLogic**) looking for failed Phase II drugs where they can use a combination of imaging and various biological techniques to pinpoint a novel use, or **CombinatoRx** who test combinations of known drugs to find ‘patterns of activity’, the game is to look retrospectively at drugs that are deemed safe, to see whether a novel use can be found so that the product can be repositioned and licensed on. This is very different from the ‘prospective’ approach that e-Therapeutics has taken which consists of identifying a therapeutic/disease profile and mining massive databases to find network topologies that would be highly effective in turning off (or potentiating) a desired biological function. It then identifies the best compounds to do the job.

On the Systems Biology front, again, this means something different to different people. There are a number of public and private companies that classify themselves as Systems Biology companies. Closest to home are two companies that exemplify the general type of companies that are present in this market segment.

Entelos, a California-based company listed on AIM in the UK, has developed a system for modeling the behaviour of selected organ systems *in silico*⁴⁰, down to individual protein interactions. In its product *PhysioLabs*, it can create a series of ‘virtual patients’ to directly test phenotypic and genotypic variability as it relates to drug response. This in turn alerts and informs as to the construct of clinical trials for a drug and is aimed at speeding up the rate of clinical development and reducing failure rate. Entelos has used this system to simulate disease models for customers such as Roche, Pfizer, Merck, Bristol Myers and Astra Zeneca. However, this work is not aimed at the prospective discovery of novel therapeutic targets that would yield optimized therapeutic agents. It is rather a service to optimize the drug development process.

Physiomics is an Oxford-based System Biology tool and service company providing systems based pharmacokinetic and pharmacodynamic modeling as part of both the drug discovery and drug development phases for clients with a specific focus in oncology. It has also developed a ‘virtual tumour’ for studying the behaviour of drugs and drug combinations in various tumours and other simulation approaches.

⁴⁰*in silico* simulations are those that are conducted using bioinformatics tools based on computers and databases rather than in vivo or in vitro testing.

There are many other so-called 'Systems Biology' companies but all are a variation on the theme of either '*in silico*' modeling of one type or another, pathway analysis and simulation or database provision. e-Therapeutics' brand of network analysis is truly unique as far as we can tell. Apart from some academic laboratories that are beginning to go in the direction that the company has taken, we do not see anyone going in this direction at this time.

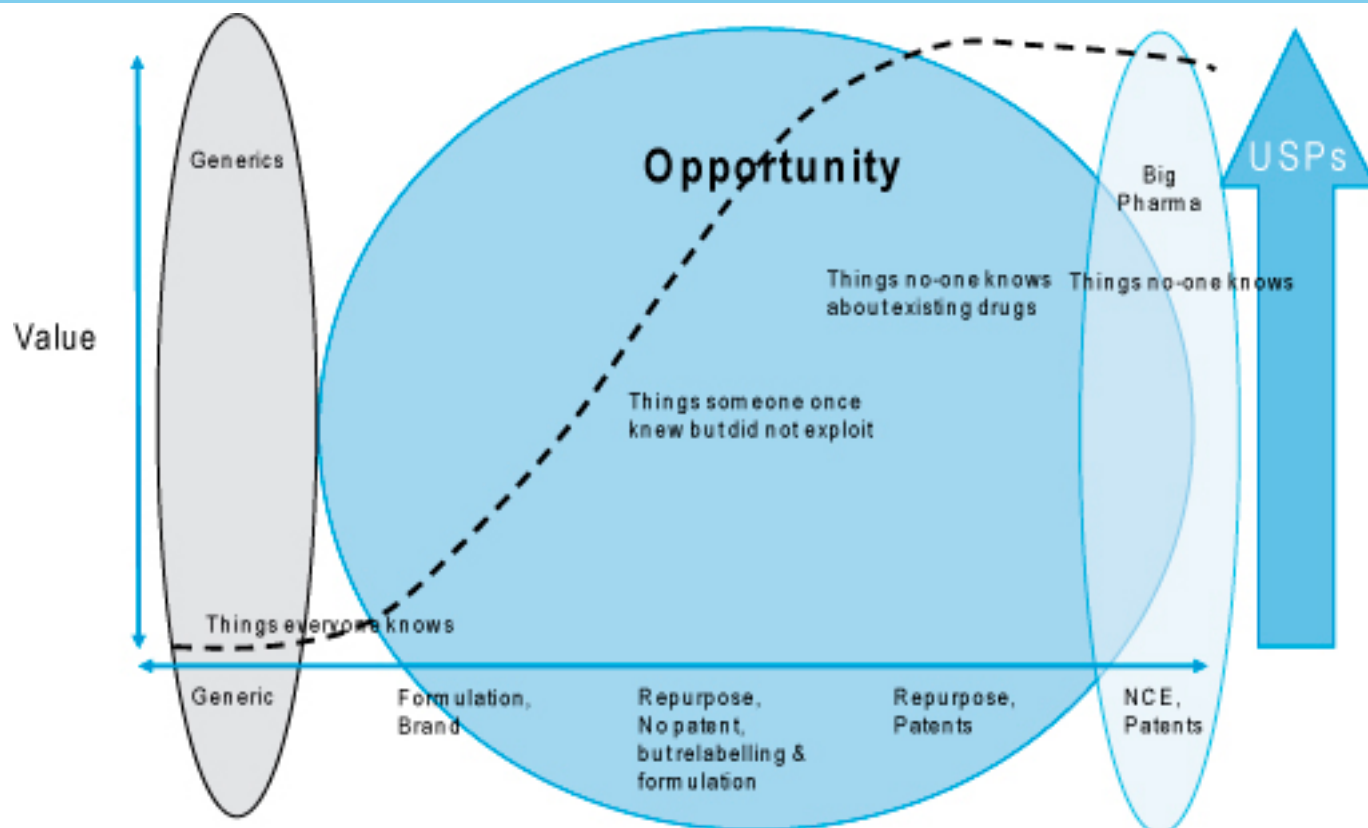
The company's 'do not publish' policy has translated into a significant lack of visibility both in the commercial as well as in the academic arena. Hence uniqueness without clinical validation means very little in the end.

Business strategy

e-Therapeutics has a distinctive discovery platform, and so might be thought to belong to the category of 'platform discovery' companies. So-called 'platform' companies were all the rage with venture capitalists in the 90s, but this model has fallen into significant disrepute with the financial community. The emphasis is now on products, partnerships, licensing upfronts, and milestones and, in the final phase, royalties. Some companies have taken on mixed models of generating cash through third party service contracts and using this cashflow and outside financing to build a pipeline of candidates. Third party research on the basis of a technology platform is as old as the biotechnology industry and has spawned biotech giants such as Genentech, Amgen, Biogen and others. e-Therapeutics' model is still evolving, but it started out with a mixture of outside projects and internal development with a heavy emphasis on the latter. It has astutely used its outside projects to leverage the knowledge gained into developing its own pipeline candidates: its fibromyalgia project is a good example of this.

e-Therapeutics is a company with constrained resources, and a full pipeline of projects which require proof of principle trials to validate its system. Its immediate strategy is to ink deals with companies that are able to assist in funding the trials required for full-blown partnerships, while not giving too much away. The second part of this strategy is to find collaboration partners who can assist it with complementary technologies, to better model diseases, and strengthen its discovery capabilities. Its recently announced deal with Nanjing Keygen Biotech in China is an example of this.

We believe that lack of validated clinical data and industry biases have contributed to a dearth of big pharma partnerships. We are not concerned because we see the company initially inking deals with regional/speciality players which, in many ways, may be preferable partners. We believe that the first set of transactions for the portfolio will be focused on a narrow geographical area while providing full support for the funding of both PoC and local pivotal (Phase III) registration clinical trials. These initial transactions are unlikely to involve much in the way of upfronts and milestones. However, as the company has a very low burn rate, getting these clinical trials funded is an absolute priority.



Source: e-Therapeutics

e-Therapeutics is operating in a new, intermediate market situated between the generic industry and the proprietary drug industry. As can be seen on the above diagramme, generic drugs imply a significantly lower value than the highest value offered by the NCE-driven proprietary arena. In the middle, repositioned drugs offer a range of values depending on the end market and application, and the degree to which a cost/benefit analysis favours a higher or lower value. With healthcare cost issues a major political and social issue – and only increasing in importance – the ability to generate drugs with a attractive cost/benefit profile is essential. The strategy that e-Therapeutics (and others) has evolved plays to this trend and should stand it in good stead should it achieve success in its clinical programmes.

Profit & Loss

Year ending Jan (£000's)	2007A	2008A	2009E	2010E	2011E
Revenues					
Projects for third parties	—	64	137	110	88
Upront payments	—	—	—	4,849	32,326
Milestone payments	—	—	—	—	—
Licensing/royalty revenues	—	—	—	4,076	9,555
Net revenues	—	64	137	9,035	41,969
Development costs					
Development costs	—	—	—	323	—
Other development costs	—	—	—	—	300
Other cost of sales	—	24	99	227	700
Gross profits	—	40	38	8,808	41,269
Gross margins	<i>NM</i>	63%	28%	97%	98%
Other operating income	—	82	—	—	—
Administrative expenses	1,158	2,399	2,024	2,205	2,324
Depreciation	27	31	91	148	149
Amortisation	—	—	—	—	—
Wages and staff costs	827	1,020	1,071	1,178	1,296
Share-based payments	125	8	9	9	10
AIM flotation costs	—	472	—	—	—
Other costs	179	868	853	870	870
Profit from operations	(1,158)	(2,277)	(1,986)	6,603	38,945
Interest income	10	52	20	195	929
Interest expenses	(1.00)	—	—	—	—
Pretax income	(1,149)	(2,225)	(1,966)	6,798	39,874
Net tax	—	(259)	(485)	(120)	11,842
Net income	(1,149)	(1,966)	(1,481)	6,918	28,032
Ending shares outstanding (000's)	1,530	55,710	55,710	55,710	55,710
Average Shares Outstanding (000's)	1,530	55,710	55,710	55,710	55,710
EPS (p)	(75.1)	(3.5)	(2.7)	12.4	50.3

Balance Sheet

Year ending Jan (£000's)	2007A	2008A	2009E	2010E	2011E
Non-current assets					
Property plant & equipment	78	56	165	267	268
Goodwill	—	—	—	—	—
Other intangible assets	51	72	122	172	222
Total	129	128	287	439	490
Current assets					
Trade and other receivables	143	613	100	200	300
Cash & equivalents	150	1,977	745	7,432	35,320
Total	293	2,590	845	7,632	35,620
Total assets	422	2,718	1,132	8,071	36,111
Current liabilities					
Other trade payables	98	154	51	50	50
Other payables	—	75	65	79	79
Total	98	229	116	129	129
Net assets	324	2,489	1,016	7,942	35,982
Shareholders' equity	324	2,489	1,016	7,942	35,982

Cashflow					
Year ending Jan (£000's)	2007A	2008A	2009E	2010E	2011E
Operating loss	(1,158)	(2,277)	(1,986)	6,603	38,945
Depreciation and amortisation charges	27	31	91	148	149
Loss on sale of PPE	—	80	—	—	—
Share-based payments expenses	125	8	8	8	8
Income tax/credit	—	259	485	120	(11,842)
Net cash from operations	(1,006)	(1,899)	(1,402)	6,879	27,259
(Increase)/Decrease in trade and other receivables	(99)	(470)	513	(100)	(100)
(Decrease)/Increase in trade and other payables	52	131	(113)	13	—
Net cashflow from operations	(1,053)	(2,238)	(1,002)	6,792	27,159
Cashflow from investing					
Property plant & equipment sales	—	66	—	—	—
Property plant & equipment purchases	(47)	(155)	(200)	(250)	(150)
Purchase of intangible fixed assets	(5)	(21)	(50)	(50)	(50)
Net interest received	10	52	20	195	929
Net cash from investing activities	(42)	(58)	(230)	(105)	729
Cashflow from financing activities					
Issue of ordinary shares	1,100	4,123	—	—	—
Interest paid	(1)	—	—	—	—
Net cash from financing	1,099	4,123	—	—	—
Net increase (decrease) in cashflow	(4)	1,827	(1,232)	6,687	27,888
Opening cash equivalents	154	150	1,977	745	7,432
Closing cash equivalents	150	1,977	745	7,432	35,320

Source: Objective Capital

Professor Malcolm Young

Chief Executive

Malcolm is a scientist by background. He has recently been Director of the Complex Systems Group, Director of the Institute for Neuroscience, Provost of the Faculty of Science, Agriculture and Engineering, and Pro-Vice Chancellor for Strategic Development at Newcastle University, after having been a Royal Society Research Fellow at the RIKEN Institute in Japan, and at Oxford University. His research expertise lies in complex systems analysis and informatics, and recent outputs of his group include six publications in Nature and Science and twelve in Proceedings and Philosophical Transactions of the Royal Society. The main goals of his research have been to understand how biological function arises from structural aspects of complex biological systems. His recent research funding exceeds £11 million, and includes programme and project grants for research on complex systems from the Wellcome Trust (the world's largest medical research charity), EU Framework programmes, the Human Frontiers Science Programme Organisation, DEFRA, BBSRC, EPSRC and DTI e-Science. He is one of eighteen scientists worldwide nominated by the Sunday Times as the "Brains behind the 21st Century". All this scientific experience and expertise is now dedicated to delivering safe and effective new medicines through e-Therapeutics. Professor Young founded e-Therapeutics, and has led its development since.

Dr Royston Drucker

Chief Medical Officer

Royston is a medical doctor, with a great deal of experience of the pharmaceutical industry. He originally joined the European R&D organisation of Sterling Drug Inc. as a medical adviser, and was promoted to be responsible for clinical pharmacology, drug metabolism and bioanalysis in Europe. In 1986, he moved to the Upjohn company, subsequently Pharmacia & Upjohn, Inc, where he held a range of international responsibilities. His positions there included Director, Marketing with responsibility for worldwide marketing of cardiovascular products; Executive Director, European Community Affairs and Business Systems; and Vice-President, Drug Development, with global responsibility, in multiple therapeutic areas, for clinical drug development. A graduate of the Harvard Business School Advanced Management Program and Member of the Securities Institute, Roy managed Technomark Consulting Services, including a corporate finance operating unit, BioCorp Securities, which is the European leader in crossborder transactions in the pharmaceutical contract research industry, before joining e-Therapeutics.

Johnny Cordiner

Finance & Commercial Director

Johnny is an experienced investment banker who specialised in life sciences. Johnny is a graduate chemist, a member of the Institute of Chartered Accountants for Scotland, and a member of the Securities Institute. He gained 15 years' business experience in a number of financial roles, including working in industry, management consulting and offshore banking before entering investment banking. Johnny has been instrumental in the commercialisation of e-Therapeutics, having worked with Malcolm and Royston for more than three years to place the company in a sound financial and strategic position for rapid development.

Professor Oliver James

Non-executive Chairman

Oliver has been a non-executive director of BUPA since 1999 and was a non-executive director of Goldsborough Health Care plc from when it floated on the main market in 1995 until it was acquired by BUPA in 1997. He has also been a non-executive director of the Newcastle upon Tyne Hospitals NHS Foundation Trust since 2006. Oliver qualified as a physician in 1975 and practised until 2004 when he became head of the medical faculty at Newcastle University. He was senior vice president of the Royal College of Physicians from 1997 to 1999 and has also been a member of a number of national and governmental medical-related boards and committees. Oliver joined the company as a non-executive director in November 2007.

We are pleased to bring you this report on **e-Therapeutics plc**.



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As always, I welcome your comments and feedback on our research!

Gabriel Didham, CFA
Objective Capital

Steven Zimmer, M. Sc. (Molecular Biology)

Steven has more than 25 years experience in analysis, corporate finance and as a portfolio manager in biotech and pharma including working for DLJ, CSFB and Robert Fleming in London, NY and Switzerland.

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