ELSEVIER

Learning lessons from drugs that have recently entered the market

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Which projects in the drug discovery field are most likely to be successful? In this article, I provide guidelines for answering this question by examining recent drug market entrants in detail, in particular their route of administration, trial design, novelty, therapeutic target and toxicities. I identify targets, trials and organizations as the key issues that are currently leading to the poor productivity in the pharmaceutical industry. Here, I outline some solutions and reasons for optimism, and suggest that the key determinants for success in drug discovery can be defined by studying recently launched drugs.

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Introduction

'We know nothing of what will happen in future, but by the analogy of experience'. (Abraham Lincoln)

Which drug discovery projects are most likely to lead to a launched drug? Many medicinal chemists will have posed this question as they survey the project portfolio of a company. It is an important question to ask, given that no amount of clever design will rectify pursuing the wrong project. In this article, I delineate some guiding principles, by examining those drugs that entered the market during 2006–2008. Such an exercise is useful because better decisions are likely to be made by drawing analogies from successful experiences. Failure can also be instructive, but it is assumed that there are more ways to fail than to succeed. An authoritative survey of new chemical entities (NCEs) introduced to the market each year can be found in *Annual Reports in Medicinal Chemistry* [1]. This survey is sponsored by the American Chemical Society through the Division of Medicinal Chemistry. With its audience of medicinal chemists, the focus is on new drugs that have entered their first market that year. Macromolecular drugs, such as peptides, oligonucleotides, proteins and antibodies, are included, whereas launches of new combinations, new applications of existing drugs and vaccines are excluded.

The number of non-oral drugs is high and that of macromolecular entrants limited

A total of 71 NCEs entered their first market during 2006–2008 (A table of these containing USAN, year to market, molecule type, route of administration, trade name, company at launch, therapy

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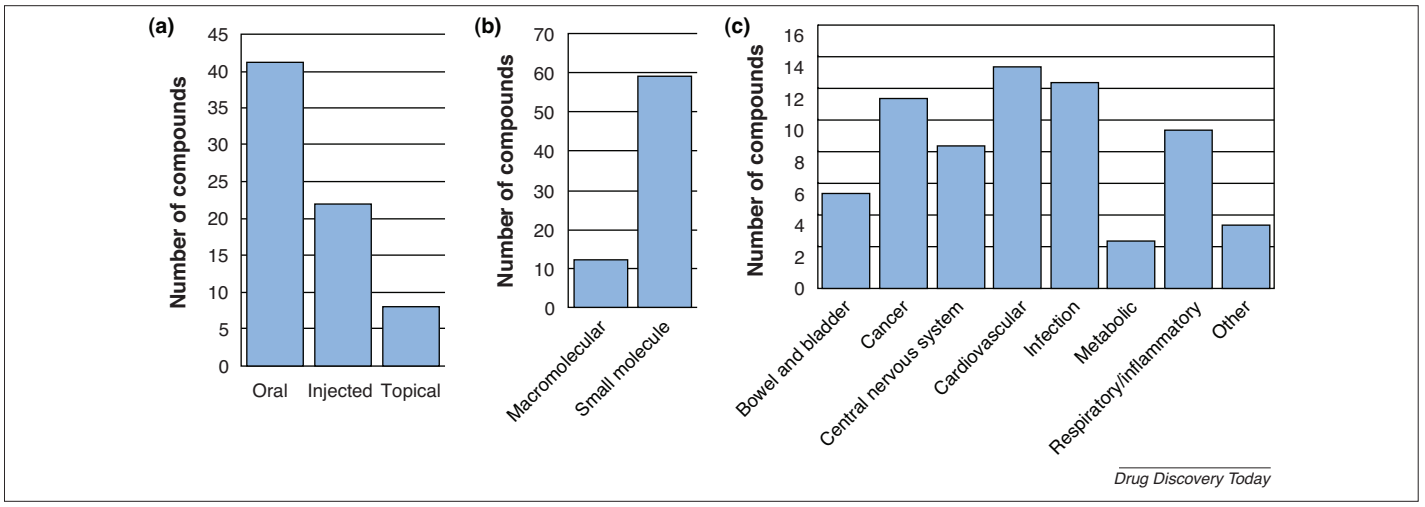

FIGURE 1

Details for drugs entering the market between 2006–2008. **(a)** Route of administration. **(b)** The number of macromolecular and small molecule entrants (cut-off ~1500 Da) during 2006–2008. **(c)** Drugs entering the market in each therapy area.

area, indication and receptor is included in the Supplementary material online). A breakdown by route of administration, molecule type and therapy area is shown in Fig. 1.

Despite the focus on oral drugs in most companies, the number of drugs administered by injection or topically is still high. In a hospital setting, the increased compliance associated with oral administration is less crucial. Injection is also acceptable when the duration of action of the drug is long, as is the case with antibodies. The desirability of oral administration can sometimes be overstated. Where there are few options, a great need and an effective treatment, subcutaneous administration is still acceptable, as illustrated by the millions of patients using injected insulin and the commercial failure of the inhaled alternatives. Insulin by inhalation (Exubera®) was withdrawn, whereas insulin glargine (Lantus®) and insulin aspart (NovoLog®) are predicted to be in the top ten selling drugs worldwide by 2014 [2]. Delivery using techniques such as extended release formulations, depot injection and transdermal patches offers advantages in certain patient populations, such as the forgetful elderly, mentally ill or patients who are unconscious or fitting. When both an oral agent and an injected agent are available, oral therapies are often preferred even in a hospital setting, because the same therapy can be continued after discharge. Topical administration is expected to have the advantage of reducing toxicity. Devices, such as inhalers, also offer the possibility of device patents and so reduce generic competition, as a result of the additional cost imposed by manufacture and by that of proving bio-equivalence during use.

Macromolecular drugs (i.e. peptides, proteins, oligonucleotides, oligosaccharides and antibodies) still represent a small proportion of market entrants. They fall into two broad classes. The first are hormones, such as insulin, growth hormone and erythropoietin (EPO). The second are antibodies, many of which titrate out unwanted proteins, such as tumor necrosis factor (TNF), or recognize a cell surface receptor, such as anti-*epidermal growth factor receptor* (*EGFR*). Some antibodies address therapeutic targets that are unsuitable for intervention using small molecules. The sales growth of these agents, their safety profiles and the lack of a clear pathway for generic competition have made them attractive to pharmaceutical companies in recent years. However, extrapolation of future growth, based on that of the past, might be unreliable. The need for most hormones is largely satisfied. Some surveys even fail to distinguish between novel interventions and cases in which hormones were already used in the clinic, but their production was improved through biotechnology. Examples include insulin, growth hormone and Factor VIII. The success of antibodies is concentrated in a few therapeutic areas, notably cancer and immunosuppression. Their targets are extracellular and they are excluded from some important compartments, such as the brain. They remain relatively expensive in an era of increasing focus on cost effectiveness and improving sales in emerging markets. They are also not immune from late-stage withdrawal or restriction. The problems encountered with Rituxan®, Tysabri® and Raptiva®, for example, have been commented upon elsewhere [3].

Division of drugs by therapy area is instructive. Closer examination of the drugs entering each therapy area shows several targets being addressed several times. A probable cause is the paucity of clinically testable targets and commercial competition for market share between the major players. The lessons are: do not be fixated on the oral route, small molecules are still very important and, currently, only a few targets are successfully exploited in each therapeutic area.

Trials measure simple outcomes

Key trials for drugs entering the market in 2008 (Table 1) show that the measures are usually simple ones. Bowel movement, urination, fever, emesis and death are objective and easily measurable criteria, relevant both clinically and to the patient. Blood pressure, intraocular pressure, lung function and rating scores are widely agreed by the medical community as being clinically relevant and predictive of future health outcomes. Blood has many uses; platelet count, viral RNA copy number, clotting measures and lipid levels. Few other biological tissues are as easy to obtain routinely.

The trial durations are usually short as this reduces cost and improves the signal:noise ratio by reducing patient symptom variation during the trial period. Patient selection and trial duration are especially important where sufficient adverse occurrences, such as unwanted thrombotic events, need to accumulate in each

TABLE 1

Examples of trials used to test market entrants in 2008

Drug	Measure	Time	Comparator
Alvimopan	Time to first bowel movement	24 h	Placebo
Biolimus drug-eluting stent	Re-stenosis and time to repeat operation	6-month trial	Uncoated stent
Blonanserin	Global improvement score	8 weeks	Haloperidol
Ceftobiprole medocaril	Cure rate	7–14 days	Vancomycin
Certolizumab pegol	Crohn's disease index	4–24 weeks	Placebo
Choline fenofibrate	Blood test; % change in lipids	12 and 52 weeks	Statin ± fibrate
Clevidipine	Systolic blood pressure	Minutes	Placebo
Dabigatran etexilate	Thrombotic events and death	Up to 35 days	Enoxaparin (intravenous)
Desvenlafaxine	Hamilton Rating Score for depression	8 weeks	Placebo
Etravirine	HIV-1 RNA copies/mL blood	8 weeks	Placebo
Fesoterodine	Change in the number of urge urinary incontinence episodes	12 weeks	Placebo
Fosaprepitant dimeglumine	Emesis during cancer treatment	24 h	Ondansetron
Icatibant	Laryngeal angioedema	Hours	Placebo
Lacosamide	Decrease in seizure frequency	8 weeks	Placebo
Methylnaltrexone bromide	Bowel movement	Within 4 h of dose	Placebo
Pirfenidone	Lung function and survival	6 months	
Rilonacept	Joint pain, rash, fever and fatigue	Up to 26 weeks	Placebo
Rivaroxaban	Thrombotic events and death	Up to 9 days	Enoxaparin (intravenous)
Romiplostim	Platelet count	Up to 24 weeks	
Sitafloxacin hydrate	Cure rate	Days	Imipenem and cilastatin
Sugammadex	Reversal of rocuronium blockade	Minutes	
Tafluprost	Decreased intraocular pressure	6 months	Timolol

arm of a trial involving anticoagulants, before statistical significance is obtained. The choice of patient population is also important because efficacy is sometimes only seen in a small subset of the patient population. For instance, mepolizumab only reduces exacerbations in patients with severe eosinophilic asthma, an adult-onset subgroup that represents less than 5% of all patients with asthma. Drugs are often first tested in small groups of very ill or carefully categorized patients. This gives the first label indication, which can then be extended in subsequent trials. For example, a treatment for thrombotic events after knee surgery could be extended into stroke prevention; one for rhinitis treatment could be extended to asthma and chronic obstructive pulmonary disease (COPD). The lesson is that robust measures and short duration trials are useful criteria by which to judge the probable successful outcome of a project. These and other translatability criteria have recently been reviewed elsewhere [4].

The comparator in a trial is often a placebo or some long-established agent. Given that the criteria are clinical outcomes, the comparator need not work through the same mechanism. Instead, it simply needs to produce the same outcome. An example of this is the use of ondansetron [a serotonin 5-hydroxytriptamine ($5\text{-}HT_3$) antagonist] to benchmark the efficacy of fosaprepitant [a neurokinin (NK_1) antagonist]. Finer comparisons between more recent, similar drugs can only be done later, when larger groups of patients have been treated. Differentiation from existing agents is a concern in many areas and post-marketing comparisons, driven by payer organizations, are becoming increasing prevalent. These comparisons are even more difficult in well-established areas where, for ethical reasons, the new drug will usually be used in addition to an existing drug regimen, rather than as monotherapy.

It is important for medicinal chemists to have at least a basic understanding of how a drug will be tested in the clinic because this is fundamental to the design of an acceptable property profile. The heart of the discovery process is the design of tests that discriminate on relevant criteria and of a molecule that fulfils these. Medicinal chemists are responsible for delivering molecules with the required profile and must play their full part in setting and refining project criteria. A company might plan its project portfolio by deciding which measures would provide acceptable trial criteria and how many such trials it can undertake. It could then decide upon the number and types of program that are necessary to deliver this goal. Experience suggests that this is rarely the case. The larger the organization, the more difficult this connectivity can be to achieve, but the recent trend towards the removal of organizational barriers between research and early development might go some way to address the problem. The goal is a bidirectional flow of information between the clinical and research teams. The current model is often a linear monodirectional flow.

Novelty: only a few new targets are represented among the entrants, despite modern target identification technologies

'How many legs does a dog have if you call the tail a leg? Four. Calling a tail a leg doesn't make it a leg'. (Abraham Lincoln)

TABLE 2

Entrants to market during 2008 and the date of registration of structurally or therapeutically similar agents

Drug	Company at launch	Mechanism	Competitor	USAN date	Competitor's company
Alvimopan	GSK, Adolor	μ-opioid antagonist	LY255582	1993	Lilly
Biolimus	Biosensors	*Mammalian target of rapamycin (mTOR)*	Sirolimus	1993	Wyeth
			Everolimus	2003	Novartis
			Temsirolimus	2004	Wyeth
Blonanserin	Dainippon	Dopamine receptor 2 (D2) and 5-HT2	Olanzapine	1992	Lilly
			Quetiapine	1996	AstraZeneca
			Risperidone	1989	Janssen
			Ziprasidone	1994	Pfizer
			Paliperidone	2007	Johnson & Johnson (J&J)
Ceftobiprole medocaril	J&J	Cephalosporin	15 marketed		
			Cefonicid	1979	GSK
			Cefdinir	1991	Abbott
Certolizumab pegol	UCB	TNF-α inhibitor	Infliximab	1996	Centocor
			Etanercept	1998	Amgen/Wyeth
			Adalimumab	2002	Abbott
Choline fenofibrate	Solvay	*Peroxisome proliferator-activated receptor* (PPAR)-α agonist	Clofibrate	1963	Wyeth
			Fenofibrate	1976	Abbott
			Ciprofibrate	1976	Sterling
			Gemfibrozil	1980	Pfizer
Clevidipine butyrate	Medicines Co.	Calcium channel blocker	Six marketed		
			Nimodipine	1979	Nimotop
			Amlodipine	1988	Norvasc
Dabigatran etexilate	Boehringer	Anti-thrombin	Argatroban	1997	
			Ximelagatran	2002	AstraZeneca
Desvenlafaxine	Wyeth	Serotonin–norepinephrine reuptake inhibitor	Venlafaxine	1989	Wyeth
			Duloxetine	1992	Lilly
Etravirine	Tibotec	*Non-nucleoside reverse transcriptase inhibitor*	Nevirapine	1991	Boehringer
			Efavirenz	1994	BMS
			Delavirdine	1994	Agouron
Fesoterodine	Pfizer	Muscarinic antagonist	Five marketed		
			Tolterodine	1997	Pfizer
			Darifenacin	2005	Novartis
Fosaprepitant dimeglumine	Merck	NK_1 antagonist	Aprepitant	2000	Merck
Icatibant	Jerini	Bradykinin 2 antagonist			
Lacosamide	Schwarz	Possibly collapsin response mediator protein (CRMP)-2			
Methylnaltrexone bromide	Progenics	μ-opioid antagonist	Naloxone	1963	BMS
Pirfenidone	Shinogi	Unknown		1975	
Rilonacept	Regeneron	IL-1 antagonist	Anakinra	1994	Amgen
Rivaroxaban	Bayer	Factor Xa	Fondaparinux		GSK
			Enoxaparin		Sanofi
Romiplostim	Amgen	Thrombopoietin receptor precursor (TpoR) agonist	First in class		
Sitafloxacin hydrate	Sankyo	Quinolone antibacterial	Many marketed		
		Quinolone	Ciprofloxacin	1987	Bayer
			Moxifloxacin	1998	Bayer
Sugammadex	Schering	Drug binder			
Tafluprost	Asahi Glass	Prostaglandin F	Latanoprost	1996	Pfizer
			Bimatoprost	2001	Allergan

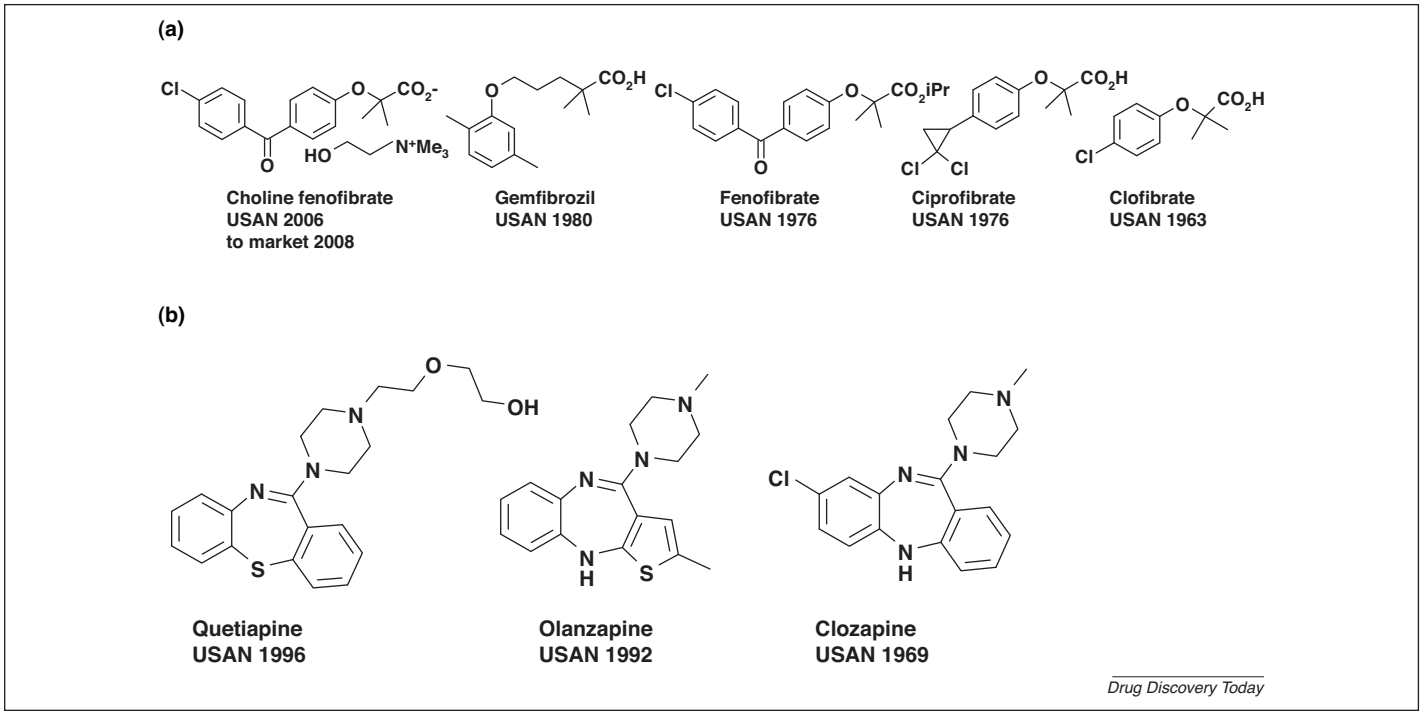

FIGURE 2

Structural similarities between novel drugs entering the market over decades. **(a)** Fibrates entering the market over 41 years and **(b)** structural variety in schizophrenia treatments over a similar length of time.

It is possible to call any gene product a target. RNA expression data and plausible arguments can be used to construct a theoretical linkage between many proteins and a disease. However, as with a dog's legs, there are still a limited number of valid targets. Examination of the entrants to market in 2008 shows that few of these targets are new (Table 2). The age of an existing drug using the same or closely related mechanisms can be gauged using the date of first registration of a US adopted name (USAN), which is obtained from the United States Pharmacopeia (USP) dictionary [5]. Where many similar agents are available (e.g. ceftobiprole, with 15 similar agents), an early and a late entrant to the class are shown in Table 2. Several of those where no similar agent is indicated have unclear mechanisms or serve small patient groups. The period over which drugs have entered a class is often very long. 2008 was not exceptional in any of these respects. Clearly this trend is unsustainable, with improvements being incrementally harder to uncover and generics entering the market [6].

Novelty can also be assessed by comparing the structures of successively introduced drugs where each is active at the same receptor or receptors. Examples are shown in Fig. 2. For example, fibrate registrations over 41 years show variations in the hydrophobic moiety; and, despite many years of research, there is still great structural similarity between the -apine schizophrenia treatments. This lack of structural diversity also results in limited clinical difference in trials and has been the subject of critical comment [7]. There are other examples of high structural similarity within classes of drug that have entered the market over periods of decades. Novelty, defined as clinical efficacy at a hitherto unutilized target, is low. This lack of 'first-in-class agents' is much lamented. It has never been high, as the analysis of entrants over the past decade shows (Table 3).

The importance of this trend needs to be balanced against the considerable patient benefit and commercial success that can still be gained from incremental improvements in existing therapies. It is worth remembering that this process often takes decades as shown by comparative clinical data from the angiotensin antagonist candesartan cilexetil [8]. Also, no two drugs or patients are the same and the availability of more than one drug acting at each target provides valuable choice. In a market that is functioning correctly, choice should also lower the cost to the patient. Some commentaries suggest that the high cost of anidulafungin, caspofungin and micafungin, which show little differentiation in the clinical setting, is one example showing that this is not always the case [9]

Novelty has many shades of meaning and a patent attorney or journal editor will interpret it quite differently. It is a dichotomous variable, but is often treated as a continuous one. Its importance in some organizations has a quality reminiscent of a religious calling, especially to those steeped in academic value systems. This can

TABLE 3

Count of drugs entering the market each year and the number of first-in-class agents

Year	Drug total	First in class
2008	24	1
2007	20	4
2006	27	6
2005	24	5
2004	19	5
2003	27	8
2002	33	4
2001	25	9

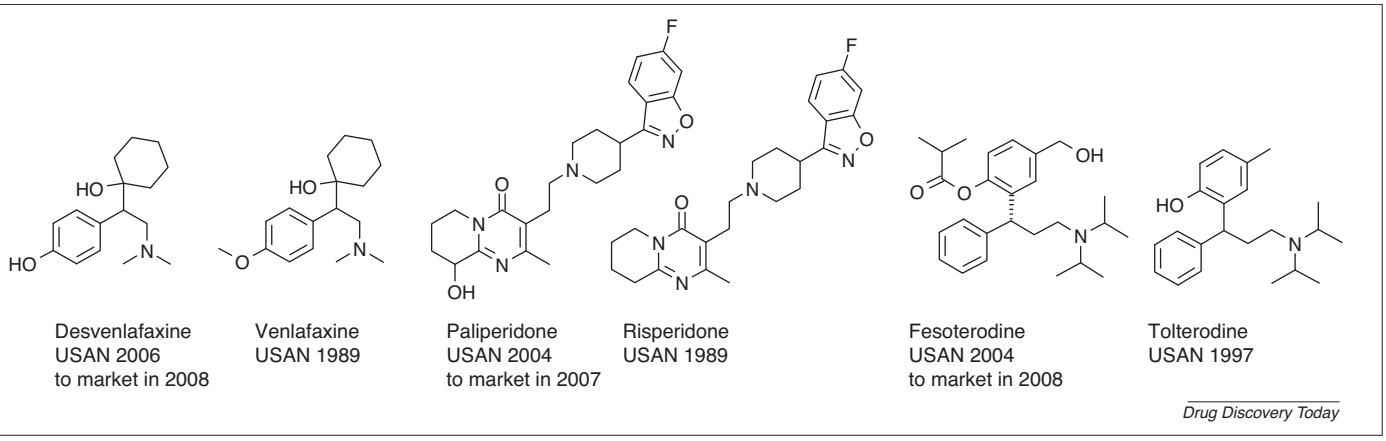

FIGURE 3

Metabolites of existing agents entering the market during 2006–2008.

sometimes be unhelpful when assessing the relative value of different projects. Bringing a single isomer of an existing agent to market might be considered to have little novelty, but arformoterol entered the market in 2007 and joined a growing number of 'racemic switch' compounds including escitalopram–citalopram, omeprazole–esomeprazole, albuterol–levalbuterol, bupivacaine–ropivacaine, levofloxacin–ofloxacin and levetiracetam–piracetam. Some metabolites of established agents have also entered the market during 2006–2008 (Fig. 3), including desvenlafaxine, paliperidone and fesoterodine. The advantage claimed is a reduction in drug–drug interactions. These introductions have often been combined with improvements in coverage using a slow release formulation. In the case of fesoterodine, the removal of a cytochrome P450 enzyme (CYP) 2D6-dependent transformation to an active metabolite was claimed to reduce inter-patient variation. Fashion in the pharmaceutical industry could have been acknowledged by referring to it as a depersonalized medicine. In the past, the metabolite strategy has been successful, for instance by the replacement of terfenadine with fexofenadine, loratadine with desloratadine and carbamazepine with oxcarbazepine. It also extends the period of exclusivity when sufficient marketing, supported by a little science, is used to accentuate the differences between the new and existing agent.

It is sometimes claimed that macromolecular drugs show more novelty and so offer a better investment choice, although this assertion has been challenged [10]. Careful examination of macromolecular drugs shows similar patterns to those observed with small molecules. Small clusters of agents, each from a different company, address those validated targets that are available. Omnitrope®, Valtropin® or Genotropin® are used for growth hormone supplementation. Likewise, Prolastin®, Zemaira® or Aralast® are available as α1-antitrypsin agents. The same division of the market among a few players is seen with antibodies, such as anti-EGFR, anti-interleukin (IL)-1, anti-IL-2, anti-CD20 and anti-TNF (e.g. certolizumab, infliximab, etanercept and adalimumab). With small molecules, the USAN suffix is usually indicative of the targeted receptor and so offers a clue to mechanistic similarity. For antibodies, however, the USAN suffix is based on therapeutic area (see http://en.wikipedia.org/wiki/Antibody_nomenclature). For instance, -tuzumab indicates a cancer treatment, -lizumab one acting on the immune system and -cizumab one involving the cardiovascular system. This system of nomenclature makes the target novelty of an antibody more difficult to assess from the name than is the case with small molecules. The tensions between the need for cost reduction and the claim that a product is both the drug and its process of manufacture, have been reviewed elsewhere [11]. Comparison between macromolecules and small molecules is instructive because it offers the opportunity to distinguish between those factors affecting productivity that are common to all drugs and those that are a result of the current limitations in small molecule design. The lesson is that, despite fewer concerns about bioavailability, duration, toxicity and affinity for the required protein, the number of antibodies entering the market is still low, emphasizing the importance of the scarcity of clinically validated targets in relevant diseases that affect large patient groups. Most therapeutic approaches using macromolecules are crowded and competitive. Productivity problems in the industry are the same for both small and large molecules.

Differentiation and commercial imperatives

Most of the drugs entering the market use known mechanisms and are directed towards existing markets. Therefore, it is instructive to examine the ways in which they are claimed to differ from existing drugs. The market entrants for 2007 are listed in Table 4, together with their mechanism and differentiation.

'First in class' is difficult to define in diseases that are a collection of disorders of varying etiology. Thus, rufinamide is not the first anticonvulsive and trabectedin is not the only agent to alkylate DNA; nonetheless, in some sense they exploit new biology and treat a subgroup of patients. Retapamulin is first in class for human application of this type of previously veterinary drug. Rapamycin and epothilone were never used extensively in the clinic, but helped to validate the biology in the disease state and make the entry of temsirolimus possible. In the cancer area, an agent can be introduced and licensed for one patient population, when the same mechanism is exploited but licensed for a different group, as is the case for lapatinib. Treatment of each patient population with the drugs from a competitor that use the same mechanism would require off-label prescribing. This creates a localized monopoly with agents being first in class for that subgroup of patients using that particular mechanism. The disparity in cost between two *vascular endothelial growth factor* (VEGF)-A antibodies, bevacizu-

TABLE 4

Entrants to market in 2007 and the differentiation claimed from existing agents

Drug	Mechanism	Competitor	Differentiation
Aliskiren	Renin antagonist	Angiotensin-converting enzyme, angiotensin II antagonists; many other antihypertensives	First in class; good adverse effect profile; reduced angioedema and cough
Ambrisentan	Endothelin antagonist	Bosentan and sitaxsentan	More ET_A selective relative to ET_B compared with competitors
Arformoterol	β2-Agonist	Formoterol	Racemic switch; (SS)-enantiomer 'impurity' in formoterol is an inverse agonist; trial against salmeterol
Clevudine	Antiviral	5th to market	Slower rebound of viremia; slightly different mechanism with drug not incorporated into viral DNA
Eculizumab	Anti-C5	Orphan drug	
Fluticasone furoate	Glucocorticoid	Fluticasone propionate and ciclesonide	Compared with placebo
Garenoxacin	Antimicrobial	Gemifloxacin and moxifloxacin	Better PK/PD, which might mean that resistance is slower to develop
Imidafenacin	Muscarinic antagonist	7th to market	Higher M3 selectivity; more bladder selective (in rat)
Ixabepilone	Anticancer	Epothilone	Improved metabolic stability and PK; active in taxane- and anthracycline-resistant tumors
Lapatinib	EGFR human epidermal growth factor receptor 2 inhibitor	Erlotinib and Gefitinib	Trialed in breast cancer; competitors trialed in lung cancer
Lisdexamfetamine	ADHD	D-amphetamine	Reduced abuse potential; prodrug gives slows release and suppresses 'rush'
Maraviroc	CCR5 antagonist		First in class; joins more than 20 other antivirals in HIV
Nilotinib	BCR-ABL kinase inhibitor	Imatinib and dasatinib	Overcomes resistance mutations in patients pretreated with imatinib
Paliperidone	D2-$5HT_{2A}$ antagonist	Risperidone; also ziprasidone, olanzapine and quetiapine	Improved PK; metabolite of risperidone; reduced drug–drug interactions
Raltegravir	Antiviral		First in class; trialed in patients with resistance to other anti-HIV mechanisms
Retapamulin	Anti-infective	Mupirocin, fusidic acid and bacitracin	First in class; tiamulin and valnemulin analogs used in veterinary science; natural product lead discovered in 1951
Rufinamide	Anticonvulsive	Many drugs used clinically	Effective in one type of refractory epilepsy (Lennox–Gastaut)
Temsirolimus	mTOR inhibitor	Rapamycin; also anti-VEGF sunitinib, sorafenib and bevacizumab	Improved aqueous solubility over rapamycin
Trabectedin	Anticancer	Anthracycline and ifosfamide	DNA alkylation for heavily pretreated patients
Vildagliptin	Dipeptidyl peptidase-4 inhibitor	Sitagliptin	Better lipid effects than rosiglitazone and useful add-on to metformin

mab (licensed for cancer treatment) and ranibizumab (licensed for ophthalmology), has also caused controversy. In modern times, drug 'class' is defined by the target protein, not therapeutic application. Therefore, aliskiren has a novel mechanism and so is in a new class, but addresses hypertension, which is an otherwise easy to test and well exploited clinical measure.

Improvement of existing agents is easiest to justify in the anti-infective, antiviral and anticancer areas, where the target is the product of an evolving genome. This enables pathogens to acquire resistance and makes improvement in existing agents and the introduction of novel ones a necessity. Some agents, such as temsirolimus, intervene in known therapeutic pathways, but at an alternative point. Maraviroc requires pre-assessment of patient genotype to assess whether their infection is C–C chemokine *receptor* type 5 (CCR5) or C–X chemokine receptor (CXCR4) inhibitor sensitive. This personalization adds complexity and cost to treatment where alternatives are available and has limited the use of the drug [12], showing that personalization is not always as much of an advantage as many would suggest. An attempt to a rehabilitate lumiracoxib is currently underway using a companion diagnostic test for a genetic marker, which is claimed to identify patients who are at risk from its hepatotoxicity. It is notable that successful personalization in the case of a drug such as rufinamide is less trumpeted, because there is little sequencing and rationalization to be expounded upon.

Maintaining a continuous presence in a therapeutic area with a portfolio of products addressing related or co-morbid disease, sometimes called a franchise, is expensive. Even the largest companies specialize in just a few therapeutic areas and maintain their presence through a combination of in-house

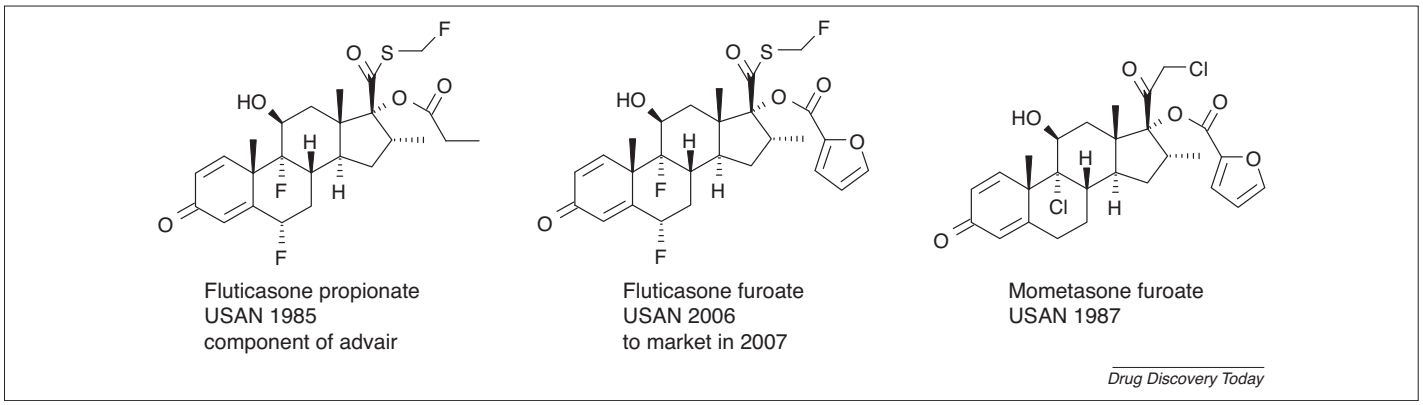

FIGURE 4

The novel agent fluticasone furoate and existing glucocorticoids.

and in-licensed products. One of the most important priorities is to renew and refresh key products in the portfolio and some launches are clearly designed to address this issue. With Advair®, a blockbuster, soon to lose exclusivity, a strategy to maintain the respiratory franchise of GlaxoSmithKline (GSK) is needed. Fluticasone furoate, a novel glucocorticoid, entered the market in 2007 [13]. Knowledge of mometasone furoate, a product from a competitor, might have assisted in the design and de-risking of this introduction (Fig. 4). Portfolio considerations might even result in companies undertaking research in areas where generic competition would otherwise be discouraging, such as antihistamines in rhinitis, where GSK and Schering dominate the market [14]

A related phenomenon is that first-in-class agents rarely remain the only drug to exploit that clinically validated target for long. Vildagliptin and sitagliptin entered the market almost contemporaneously, as did infliximab and etanercept. Post-merger analysis shows a great deal of commonality between project portfolios, even when companies have been selected for diversity in therapeutic interests. Examination of the patent literature has always shown this trend strongly. There are important commercial forces that reduce any industry drive to focus solely on novelty and first-in-class agents.

Animal models: still important because disease is expressed at the whole-organism level

To design the drug ticagrelor (Brilinta®) [15], the requirement was to make compounds that inhibit platelet aggregation while not significantly increasing bleeding time. Blood flow in the exposed femoral artery of an anaesthetized dog decreases when it is flicked, owing to platelet aggregation on the vessel wall. This response was dose-dependently reduced using test compounds, which were P2Y12 receptor antagonists. The unwanted effect on bleeding time was simultaneously assessed by observing the clotting of a small cut in the tongue of the dog. These tests were reminiscent of the multifactorial biological responses that are measured in a clinical trial. Their purpose was to assess progress, rather than to increase understanding.

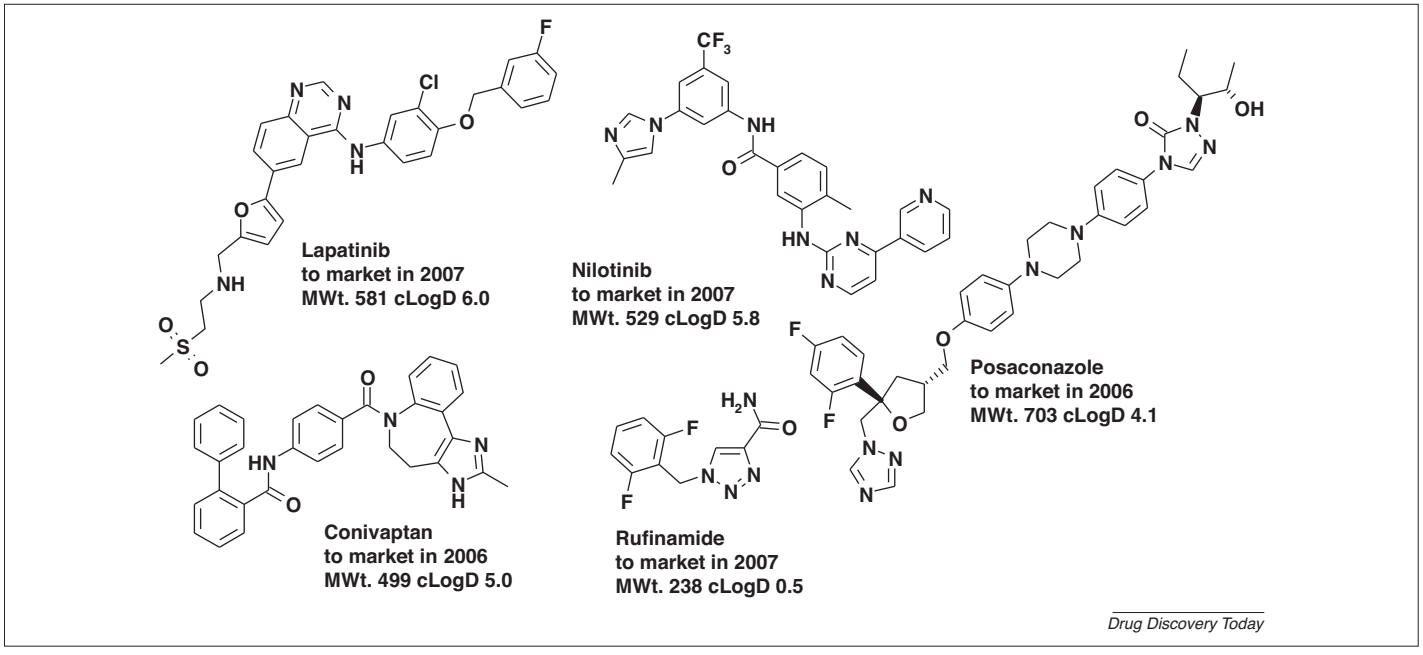

FIGURE 5

Orally administered drugs introduced during 2006–2008 with extreme properties.

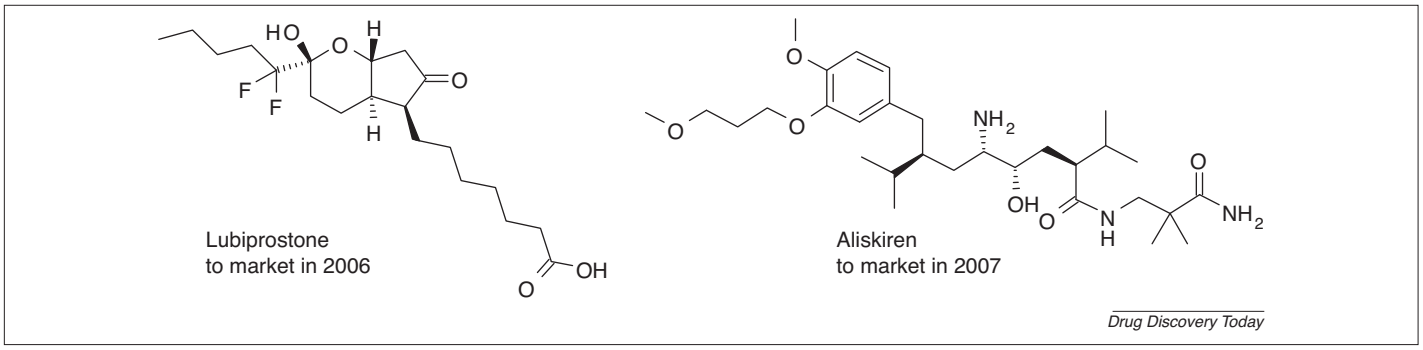

FIGURE 6

Effective drugs with unusual PK–PD relationships.

Protest and direct action against animal experimentation has had a profound effect upon the pharmaceutical industry. Many small biotech companies are prevented from doing such work by the leases on their university-owned facilities. Prolonged introspection by some pharmacologists has resulted in them spending an inordinate amount of time on reducing and even avoiding experimentation. However, the lesson is that the availability of well-characterized, reproducible and moderate throughput animal models remains an enormous advantage during drug design. The societal and regulatory effects on animal experimentation have resulted in much of the work being relocated to other countries, impacting the competitiveness of some jurisdictions.

Many disorders, such as angina and epilepsy, can only be addressed using intact animals and two drugs, ranolazine and rufinamide, entered the market for these indications in this period. The failure of rational strategies in the discovery of anti-epileptic drugs as well as the role of random screening in animal models has been noted [16]. Examples include valproic acid, which was discovered when it was used as solvent for another agent under investigation, and lamotrigine, which resulted from an incorrect theory concerning linkage between anticonvulsants and antifolates [17]. Approval for use in humans does not require knowledge of the mechanism of a compound, as demonstrated by entry to the market of lenalidomide, lacosamide and pirfenidone during 2006–2008. Indeed, it can be argued that the mechanism of a drug is never known with complete certainty. The observed biological activity is just more or less explained by referring to those proteins with which it is currently known to interact while ignoring the possibility that there might be many others involved but that are currently unknown. Clearly, animal models do have limitations. They are generally better at modeling processes, such as clotting, bronchioconstriction or blood pressure, than they are at reproducing the myriad of symptoms that constitute a disease. In COPD, for instance, chronic exposure to cigarette smoke showed a range of responses dependent on the strain of mouse [18]. The usefulness of a variety of disease state models has recently been reviewed elsewhere [19].

Clinically the most relevant animal species is human. Sodium cromoglycate was discovered at Fisons, later to become AstraZeneca, by Roger Altounyan [20] an asthmatic physician and pharmacologist. He and a likeminded panel of individuals would inhale allergens, followed by compounds prepared by the medicinal chemistry group, to determine efficacy. His plea in 1976, concerning fears associated with testing compounds in humans and the general trend to reductionism in drug discovery, was for 'more common sense lest we stop research altogether'. This comment now seems particularly prescient. In Sweden, Bengt Lundqvist optimized local anesthetics, such as xylocaine, by injecting samples of test compounds into his knuckles. The contraceptive progestin, drospirenone, was discovered by testing in a single male human [21]. A generation later, such experiments would be frowned upon. The recent guidelines by the US Food and Drug Administration (FDA) for eIND (Phase 0) studies [22], although a welcome innovation aimed at addressing stagnation in the industry, certainly looks timid by comparison (eIND is an electronic application through the FDA for an investigational new drug). In developed countries, the desire to avoid exposure to chemicals of all types has reached near phobic levels, even among individuals who are well placed to assess factors such as dose, coverage and the relative risks of single and repeated exposure. This aspect of the culture of risk aversion is difficult to address empirically. The concerns often continue despite risk–benefit analyses and evidence derived from experience.

Prodrugs and formulation

During 2006–2008, many prodrugs entered the market. Most are esters or amides that are hydrolyzed *in vivo*, including ceftobiprole medocaril, dabigatran etexilate, fosaprepitant, tafluprost, lisdexamfetamine and fesoterodine. Nelarabine is demethylated to Ara-G, whose activity and selectivity has been known for many years [23]. One unintended consequence of reduced animal experimentation might be that most prodrugs are now simple derivatives of the active molecule where the process to liberate the active drug is a simple and predictable biotransformation. Historically, this was less apparent, as shown by the subtle bioactivation of drugs such as omeprazole [24], proguanil [25], allopurinol [26] and nabumetone [27], whose discovery involved serendipitous events that were only made possible through the use of whole-animal experimentation. Prodrugs that entered the market during 2006–2008 are sometimes used to address problems associated with solubility or absorption, such as fosaprepitant and tafluprost. Formulation is used to improve duration or compliance. Examples are osmotic release in paliperidone and patches with rotigotine. Clevidipine butyrate is an example of a soft drug, where duration is controlled by provision of a metabolically labile site. One lesson is that it is often not possible to achieve the therapeutic goal without using

one or more of these techniques. However, in many organizations, there are too many late-phase compounds competing for formulation and allied pharmaceutical science support. These groups are often fully occupied with product support and line extensions, which have a higher priority. Too often, the discovery team is sent away to discover a 'better' molecule.

Acceptable toxicity profiles

Assessment of therapeutic margin is better than considering toxicity as an isolated parameter. This survey of recent market entrants shows that either profound efficacy with some toxicity or very low toxicity with measurable efficacy can be acceptable. Tolerance of toxicity also depends upon the therapeutic area, the degree of impact that the disease or treatment has upon the patient's life and the alternatives available. Therapeutic setting is also important. Phototoxic antibacterials, for instance, might be appropriate in hospital; likewise, the effects of drug–drug interactions might be tolerable with careful prescribing and routine measurement of plasma drug levels.

From entrants during 2006–2008, examples include ivabradine, which is toxic to embryos and teratogenic in animal tests. Ambrisentan is an endothelin antagonist, a class of drugs known to show dose-dependent hepatic injury. Phototoxicity is a common source of toxicity; pirfenidone saw 24% of patients withdraw because of skin rashes. Sitafloxacin is largely confined to hospital use for this reason. The quinolone antibacterials (-oxacins) provide an interesting study of the many factors that remove some members of a class from the market, while others remain (see http://en.wikipedia.org/wiki/Quinolone). Drug–drug interactions are also common; for example, etravirine is an inducer and inhibitor of several CYPs. In one case, a drug–drug interaction is even a requirement for the licensed clinical use of the drug in that darunavir must be taken with ritonavir. The oral bioavailability of a single dose of darunavir is approximately doubled by co-administration with ritonavir. Darunavir is contraindicated with a range of other drugs, including anticonvulsives and sedatives, where it is known that life-threatening adverse effects can occur. HIV protease inhibitors often cause a profound disturbance of metabolism, with body fat becoming redistributed. The long-term consequences are unknown, but with good efficacy this toxicity is simply monitored and tolerated. Among drugs already on the market, several anti-epileptic drugs produce developmental defects in up to 10% of the offspring of female patients [28]. For cancer treatments, the focus on margin and tolerance for some toxicity is even more pronounced: lapatinib decreases left ventricular ejection fraction and prolongs QT interval (time between Q and T wave during cardiac function), while only adding around five weeks to the life of approximately one third of the patients; nilotinib affects a range of clinically significant enzymes; nelarabine is neurotoxic, and careful monitoring is required; aprepitant shows a range of drug–drug interactions, and its co-administration with warfarin requires monitoring of prothrombin time for two weeks after treatment. Medicinal chemists use several empirical rules in an attempt to avoid toxicity. One of these is to reduce the number of anilines present in a molecule. In one of many apparent exceptions, lenalidomide was derived from thalidomide by adding an aniline. It shows none of the mutagenicity or fertility effects demonstrated by the earlier drug. This might be an exception to an otherwise useful rule of thumb and be influenced by the use of the compound in oncology, where moderate therapeutic margins are sometimes tolerated. However, it does show how rough-and-ready rules concerning the undesirability of certain functional groups irrespective of the situation need be applied cautiously.

Unfortunately, efficacy in humans is usually measured late during the development of a drug. Toxicity in animals is measured earlier. The result is that every potential product passes through an extended period where the therapeutic margin is unknowable. Often, the level of anxiety within the organization rises and the project champion is kept busy preventing the premature demise of the project. One wonders why toxicity (undesired efficacy) is believed to be accurately modeled in animals, whereas it is simultaneously believed that the determination of efficacy using animal disease models is an imprecise art. One reason might be that the veracity of human toxicity predictions is rarely tested, with most compounds never getting to the clinic. Intriguingly, artemisinin, a drug with a rather atypical route to market, shows lack of toxicity in humans despite the severe toxicity observed in laboratory animals [29,30]. Many analgesic, acid-containing drugs are extremely toxic in dogs and cats, where the enterohepatic recirculation is more pronounced than in humans. This often results in tragedy for these companion animals [31]. Likewise, the alarming animal toxicity of diclofenac resulted in a 10-year delay in its entry to the US market, despite its widespread use in Europe [32].

Medicinal chemists can find themselves attempting to design analogs that avoid activity in toxicity screens whose relevance to clinical toxicity is poorly exemplified and that have very limited throughput. In a risk-averse environment, compounds are easily damned. The responsibility of the toxicology professional is to make clear the limitations in predictivity implicit in animal models. Companies can moderate the risk:benefit ratio by focusing on smaller populations of patients, where clinical benefit is unequivocal, and by resisting the temptation to maximize market size early during the lifecycle of a drug. Drugs that prolong the QT interval, for instance, despite what is often claimed, are not banned. The FDA can demonstrate that it continues to apply a risk–benefit approach and assessment committees within companies need to apply the same standards. Non-mechanism-based toxicity at a high dose might simply confirm the view that few mechanisms deliver useful efficacy in complex diseases, where redundancy is commonplace. However, even in pharmaceutical companies, it is common to see them interpreted as confirmation of some mystical belief in the toxicity of all unnatural chemicals. In these cases, having both a small molecule and antibody approach can be informative. When neither approach produces the required therapeutic result, a target can truly be devalidated. For mechanism-based toxicity, the judgments are: which efficacy is most sensitively linked to receptor occupancy, the desired biological effect or the undesired one? Which tissues will receive the greatest dose? Early projects rarely give these considerations equal weight before starting on a long journey aimed at discovering a testable molecule. Toxicity rarely has an associated structure–activity relationship (SAR). It is often best to try and measure the efficacy with an imperfect agent. This tests both margin and perhaps more importantly, the real desire of the organization to find a therapy.

Orally administered drugs

With so many factors influencing the success of a discovery project, it is unsurprising that some have structures that violate reasonable, but generalized rules, for oral drugs. Among the 41 orally administered agents entering the market in this period, some have high molecular weights and high pH-dependent partition coefficient (log *Ds*) (Fig. 5). For example, lapatinib shows incomplete and variable oral absorption, requiring a 1.25 g dose; nilotinib shows an 82% increase in AUC (area under the concentration-time curve following a given dose) when given within 30 min of a high-fat meal and requires 400 mg, twice-daily dosing; the pharmacokinetic (PK) parameters of posaconazole are also affected by food, but are otherwise acceptable; and conivaptan shows some intersubject variability but the pharmacokinetic parameters of a clinically effective, 60-mg dose, are otherwise unremarkable.

There are clear trends showing that, on average, large and lipophilic molecules have poorer PK properties and increased toxicity liabilities. The journey to market might well select the exceptions to these trends [33]. However, it is striking that rufinamide, a molecule at the other extreme of the molecular weight and log *D* range, also shows PK parameters that are improved by food. It also has undetectable solubility in water and gastrointestinal fluid, which would damn it in many screening cascades where efficacy is measured rather late. Trends are important to bear in mind during design, but the success of a drug discovery program has many other, sometimes over-riding, determinants, some of which cannot be expressed as a single number. Where there is a choice in a therapeutic area between a lipophilic agent that violates the rules and one with a better balance of properties, senior management would still be best advised to back the latter. Imperfect agents might simply validate a target and encourage competitors to enter with a drug having the improved properties.

In an idealized drug discovery program, the pharmacodynamics (PD) will precisely mirror the PK throughout the time course of the experiment. The dose will be chosen to exceed some multiple of the effective concentration for a desired period. An explicable PK–PD relationship is intellectually satisfying, but unfortunately for the purists, not all useful drugs have one. Some reports suggest that many drugs show a separation between PK and PD owing to a variety of factors, one of which might be a long off-rate from the receptor [34]. Following oral administration, lubiprostone is quickly metabolized, making an accurate assessment of its PK parameters impossible, although several active metabolites can be detected. Aliskiren is detectable in the kidney three weeks after discontinuation, by which time it is undetectable in plasma. It is a successful drug despite a fraction absorbed (Fabs) of only 2.5% and its concentration in plasma being reduced by approximately three quarters if dosed with a high-fat meal (Fig. 6).

The lesson is one kind of pragmatism: that which works is good. The members of any drug discovery team might be recruited from a narrow group, made more homogenous by the temptation to recruit in one's own likeness. This can lead to shared assumptions and a value system that is rarely challenged. Inertia in organizations is also great, which is why having champions for a project can be important. Relative risk is difficult to quantify and even more difficult to make clear to senior management. A compound that shows efficacy in a more predictive screen but fails to fit many other project criteria might be better than one that ticks all the boxes but needs further and more expensive profiling. Believing that such decisions can be made solely on a scientific basis is a profound mistake. Beliefs, presentations and expectations might need to be carefully managed and much time and energy is consumed bringing decisions to a satisfactory conclusion.

Summary and perspectives

'Learn from yesterday, live for today, hope for tomorrow.' (Albert Einstein)

During the 1980s, it was common to work on one project for several years. Today, it is usual to be working hard on several at a time. Yet productivity has not increased. Why? Fewer targets and more whole-animal experimentation were replaced during the 1990s by more targets and *in vitro* screens. Our pharmacology colleagues, champions of a unifying, hierarchically integrated and technologically agnostic discipline, were supplemented or replaced by molecular biologists. The whole process reached a crescendo around 2000. 'Fail often fail early' was the instruction from on high. Reductionism in drug discovery continued apace, with each part of what was now considered a process measured in isolation. In the new millennium, the influence of drug metabolism in early projects grew. Models can now be constructed in which these individual measurements are re-integrated, facilitating prediction of compound behaviour in whole animals. Sometimes it is difficult to avoid the conclusion that, over 30 years, the industry has nearly come full circle.

The industry continues to be a slave to fashion. Analysts, venture capitalists, equipment suppliers, conference organizers and even some journals, have a vested interest in accentuating the role of new technologies. Experienced, professional scientists, however, have no such excuse. When selling a technology, the danger is not that the gullible will be unconvinced. It is that, with repetition, one might start to believe it as well. Uncritical optimism might be necessary, briefly, to gain access to resources, which can then be used for good or ill. However regular checks against evidence are needed to avoid constructing shared expectations that have little empirical foundation. It is hoped that this article serves towards this end.

Some of the commonly suggested ways to fill the productivity gap can easily be dismissed. Experience suggests that genomic sequencing will not deliver large numbers of new, valid targets. The anti-infective, antiviral and antiparasitic areas have had the complete genomic sequence of their target organisms available for many years. Target validation, by genetic manipulation, is easier than it will ever be in higher organisms, but the number of first-in-class agents originating from these areas is still low. In anti-infectives, only three new mechanisms have proven successful during the past 40 years. My impression is that this is fewer than the numbers of claims to 'a new paradigm in drug discovery' over the same period. The experiences of one company in antibacterial discovery using comparative genomics and high-throughput screening (HTS) have been reviewed elsewhere [35]. Sequencing methods have been well honed through the human genome project. Perhaps possession of a fine hammer is resulting in too optimistic a search for suitable nails? Also the distribution and

prevalence of many diseases have radically changed over a few decades, suggesting that they are not predominantly genetic in origin. Likewise, understanding the etiology of a disease is not necessary well linked to finding treatments. Cystic fibrosis is well studied and understood, but remains poorly treated [36]. Neither is target newness in an established disease a surefire route to success. Glucocorticoids and β-agonists are still the mainstays in asthma treatment, whereas zileuton and omalizumab languish.

Drug hunters could be demoralized, but there are many reasons for optimism. Improvements in the design process have thrown the spotlight onto the true rate-limiting components of drug discovery: targets, trials and organizations.

Targets

The 'block-buster' model, where companies are only willing to develop products where there is the potential to earn more than a billion dollars, is dying and many will rejoice. Such products served to produce bloated organizations and unsustainable investor return, while ignoring many smaller but achievable improvements for patients. A few diseases have been repeatedly addressed, with increasingly implausible mechanisms being suggested within the early discovery organizations. These therapies would also have to compete with well-established agents, in the event that they did succeed and so become unsupportable as commercially viable potential products. In truth, even some of the 'blockbuster' potential diseases, such as COPD, are really a collection of disorders with some etiology in common [37]. Clearly, the paucity of targets and the blockbuster model are inextricably linked. Addressing more diseases should increase productivity across the industry. It will certainly provide greater opportunity, for both professional satisfaction and for making useful but unexpected observations in the clinic. More targets will become available, with some being identified by insightful investigation of compounds that already show effects in humans. Organizations will benefit by having a more broadly based product portfolio. This challenge is being actively addressed across the industry, with most companies setting up groups to repurpose compounds in new, niche areas and to broaden the number of diseases that are considered worth addressing.

Trials

The change that would benefit the industry most would be to find better, earlier, quicker and more varied ways of measuring efficacy in disease. There are currently too many candidate drugs awaiting clinical testing. Fortunately, there is a greatly increased focus on translational medicine in many countries [38], with the US National Institutes of Health (NIH) setting up 60 academic medical centers in one attempt to address the problem [39]. Large pharmaceutical companies are also making progress using new models of early development, some of which claim twice the speed and a third of the cost of conventional processes [40]. The key to success appears to be a small independent group willing to try decision-making clinical experiments using highly focused trials. If this model continues to be successful, it will be widely imitated. Trials are highly regulated, well-defined, discrete bodies of work that are easier to cost than earlier stage research and, therefore, more suited for out-sourcing. Many trial-service providers are increasing their ability to provide standard measurements, such as forced expiratory volume in 1 s (FEV1), in a highly cost-effective manner. The risk of costly failure in trials will be further eased by the move away from blockbuster areas and investigation of more acute conditions in which robust clinical endpoints can be generated. Increased investment in all types of clinical measurement is desirable. The whole industry is also helped by sharing more precompetitive information and by the reporting of negative as well as positive clinical trial results.

Organizations

All drug discovery is carried out in teams and it is surprising how little emphasis there is within large organizations on how to build, maintain and reward this basic unit. Indeed, global personnel policies are often instituted that disrupt the natural evolution of cohesive teams that would otherwise evolve around shared project goals. Would rewarding only goal scorers be expected to generate a highly successful soccer team? Why is it expected that similar thinking will lead to a highly effective drug discovery team? It might be very difficult indeed for corporate leaders, who have never been involved in research, to understand the cultural chasm that exists between the different functions within a large organization, with research at one extreme. Some of these issues have been examined by highly successful scientists [41–43]. It would be helpful if more overcame their reticence and allowed the industry to learn from their long experience. Incredibly, large pharmaceutical companies have now acknowledged that their current organization is antipathetic to innovation. Having made this remarkable admission, they have attempted to convert their organizations to smaller biotechnology-like units. Many are also removing organizational barriers between research and early development. Both trends are to be applauded where they are carried out intelligently. Further improvement could perhaps be made through an honest and thorough examination of the real value of global technologies, functions, software and committees, when compared with the increased responsiveness and flexibility of their local equivalents. One issue deserves special mention. The role of champions in companies is routinely undervalued [44]. They are often inconvenient for large, process-focused organizations. However, in an industry where ideas and commitment are the limiting resource, they remain one of the biggest single factors in the success of an organization. They can either be a great asset or leaders of a head-long rush that threatens to bankrupt the company, but the degree to which an organization can accommodate them is still crucial. The alternative is a large company ruled by the dead-hand of bureaucrats, who absorb rather than add energy. There are many accounts of the role of these individuals in recent and established drugs. For examples, see the development of aliskiren [45], the 30-year odyssey of the bisphosphonates from water treatment agent, via small Italian company, to blockbuster drug [46] and the tortuous path to market of cyclosporine [47]. To many of us, these stories are all too familiar. The need for a champion is the rule rather than exception in the journey of any drug to market. Crucially, the solutions to organizational issues are largely in the hands of the companies themselves. With the current threat to their very existence, it seems probable that some companies will find innovative solutions; the rest might simply cease to exist.

Conclusions

Studying those drugs that entered the market between 2006 and 2008 provides many lessons about how drugs are discovered. Most

are aimed at therapeutic objectives that have short trial durations and with clinical effects that are simple to measure. Animal models still have an important role because disease and toxicity are expressed at the level of the whole organism rather than the cell. Most small molecule agents are dosed orally, although a significant number are administered topically or by injection. Only a few new disease targets are demonstrated to be clinically exploitable in any one year. Both macromolecular and small molecule drugs cluster into treatments aimed at these same few targets. Differences in nomenclature tend to obscure this effect with macromolecules to a greater extent than with small molecules. Uncertainties about the rules for introducing generic macromolecules currently afford them a considerable commercial advantage over small molecules, but this will not remain the case for many more years. Many strategies have been developed for continued exploitation of the few clinically validated disease targets that are available. These include racemic switches, combinations, reformulation and new methods for administration. Unhelpful levels of risk aversion are apparent in the assessment of human toxicity. However, where significant efficacy is evident, the licensing authorities have shown a more balanced appreciation of drug profiles than is evident within some company drug candidate assessment committees. This situation could be improved by providing companies greater protection against damages provided that they act in good faith and comply with every regulation required at the time of the introduction of the drug. More direct communication between patient groups and companies would also engender greater collaboration and focus on patient needs. This would also assist in biomarker and trial recruitment efforts. Many companies might be guilty of attempting to treat too large and diverse a group of patients too early during the lifecycle of a drug in an attempt to perpetuate the blockbuster model. A move away from concentration on such a limited number of targets would help stabilize the industry. A focus upon achievable improvements in therapy for many different but smaller groups of patients would also benefit the entire industry. An exciting consensus now exists that trials and translational medicine must be made more effective. Whether large pharmaceutical companies can adapt, fragment or diversify in the necessary timescale is an open question. The need for new drugs is still great and commercial disciplines have so far proven the most effective driver for investment, innovation and development of new products. The study of past successes remains a useful tool for choosing the right path forward for the industry.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drudis.2011.03.003.

References

1 Hedge, S. and Schmidt, M. (2009) To market, to market – 2008. *Annu. Rep. Med. Chem.* 44, 577–632
2 Mitri, J. and Pittas, A.G. (2009) Inhaled insulin – what went wrong? *Nat. Rev. Endocrinol.* 5, 24–25
3 Allison, M. (2010) PML problems loom for rituxan. *Nat. Biotechnol.* 28, 105–106
4 Wehling, M. (2009) Assessing the translatability of drug projects: what needs to be scored to predict success? *Nat. Rev. Drug Discov.* 8, 541–546
5 UPS, (2010) *The USP Dictionary of USAN and International Drug Names*. US Pharmacopeial Convention
6 Booth, B. and Zemmel, R. (2004) Prospects for productivity. *Nat. Rev. Drug Discov.* 5, 451–456
7 Lewis, S. and Liberman, J. (2008) CATIE and CUtLASS: can we handle the truth? *Br. J. Psychiatry* 192, 161–163
8 Mallion, J.M. and Baguet, J.P.J. (2000) Putting the efficacy of candestan cilexetil into perspective: a review of new comparative data. *Human Hypertens.* (Suppl. 2), S33–S41
9 Bal, A.M. (2010) The echinocandins: three useful choices or three too many? *Int. J. Antimicrob. Agents* 35, 13–18
10 Nightingale, P. and Martin, P. (2004) The myth of the biotech revolution. *Trends Biotechnol.* 22, 564–569
11 Roger, S.D. (2010) Biosimilars: current status and future directions. *Expert Opin. Biol. Ther.* 10, 1011–1018
12 Yang, H. and Rotstein, D.M. (2009) Novel CCR5 antagonists for the treatment of HIV infection: a review of compounds patented in 2006–2008. *Expert Opin. Ther. Patents* 20, 325–354
13 Biggadike, K. *et al.* (2002) A novel androstane as an anti-inflammatory agent. GlaxoSmithKleine, WO2002012265A1
14 Gore, P.M. *et al.* (2009) Preparation of quinolinyloxypiperidine and pyrrolidine derivatives for the treatment of inflammatory and allergic diseases of the respiratory tract. GlaxoSmithKleine, WO2009021965A2
15 Guile, S. *et al.* (2000) Novel triazolo[4,5-d]pyrimidine compounds. AstraZeneca, WO2000034283A1
16 Klitgaard, H. (2005) Antiepileptic drug discovery: lessons from the past and future challenges. *Acta Neurol. Scand.* 112 (Suppl. 181), 68–72
17 Kwan, P. *et al.* (2001) The mechanism of action of commonly used antiepileptic drugs. *Pharmacol. Therap.* 90, 21–34
18 Lindsay, M.A. (2005) Finding new drug targets in the 21st century. *Drug Discov. Today* 10, 1683–1687
19 Enna, S.J. and Williams, M. (2009) Defining the role of pharmacology in the emerging world of translational research. *Adv. Pharmacol.* 57, 1–30
20 Meyer, U. (2002) From khellin to sodium cromoglycate – a tribute to the work of Dr. R.E.C. Altounyan (1922–1987). *Pharmazie* 57, 62–69
21 Wiechert, R. and Schering, A.G. (2006). The history of drospirenone. Berlin, Germany. Fischer, Janos; Ganellin, C. Robin (Editors). Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, *Analogue-Based Drug Discovery* 395-400.
22 LoRusso, P.M. (2009) Phase 0 clinical trials: an answer to drug development stagnation? *J. Clin. Oncol.* 27, 2586–2588
23 Shewach, D.S. *et al.* (1985) Metabolism and selective cytotoxicity of 9-beta-D-arabinofuranosylguanine in human lymphoblasts. *Cancer Res.* 45, 1008–1014
24 Lindberg, P. *et al.* (1990) Omeprazole: the first proton pump inhibitor. *Med. Res Rev.* 10, 1–54
25 Ryley, J.F. (1953) The node of action of proguanil and related antimalarial drugs. *Br. J. Pharmacol.* 8, 424–430
26 Elion, G.B. *et al.* (1966) Metabolic studies of allopurinol, an inhibitor of xanthine oxidase. *Biochem. Pharmacol.* 15, 863–889
27 Haddock, R.E. *et al.* (1984) Metabolism of nabumetone (BRL 14777) by various species including man. *Xenobiotica* 14, 327–337
28 Brodie, M.J. and Dichter, M.A. (1996) Antiepileptic drugs. *N. Engl. J. Med.* 334, 168–173
29 Gordi, T. and Lepist, E.-I. (2004) Artemisinin derivatives: toxic for laboratory animals, safe for humans? Response to comments. *Toxicol. Lett.* 151, 491–492
30 Efferth, T. and Kaina, B. (2010) Toxicity of the antimalarial artemisinin and its derivatives. *Crit. Rev. Toxicol.* 40, 405–421
31 Fitzgerald, K.T. *et al.* (2006) 'Over the counter' drug toxicity in companion animals. *Clin. Technol. Small Anim. Pract.* 21, 215–226
32 De Stevens, G. (1991) My odyssey in drug discovery. *J. Med. Chem.* 34, 2665–2670

33 Wenlock, M.C. (2003) A comparison of physiochemical property profiles of development marketed oral drugs. *J. Med. Chem.* 46, 1250–1256
34 Copeland, R.A. (2010) The dynamics of drug–target interactions: drug–target residence time and its impact on efficacy and safety. *Expert Opin. Drug Discov.* 5, 305–310
35 Payne, D.J. *et al.* (2007) Drugs for bad bugs: confronting the challenges of antibacterial drug discovery. *Nat. Rev. Drug Discov.* 6, 29–40
36 Pearson, H. (2009) One gene, twenty years. *Nature* 460, 165–169
37 Rennard, S.I. and Vestbo, J.V. (2008) The many 'small COPDs': COPD should be an orphan disease. *Chest* 134, 623–627
38 Adams, J.U. (2008) Building the bridge from bench to bedside. *Nat. Rev. Drug Discov.* 7, 463–465
39 FitzGerald, G.A. (2009) Moving clinical research in academic medical centers up the value chain. *Nat. Rev. Drug Discov.* 8, 597
40 Bonabeau, E.N. *et al.* (2008) A more rational approach to new-product development. *Harvard Bus. Rev.* 86, 96–102
41 Lindberg, P. (2007) Omeprazole. In *Comprehensive Medicinal Chemistry II*, (vol. 8) (Taylor, J.B. and Triggle, D.J., eds) pp. 213–225, Elsevier
42 De Stevens, G. (1986) Serendipity and structured research in drug discovery. *Progr. Drug Res.* 30, 189–203
43 Cuatrecasas, P. (2006) Drug discovery in jeopardy. *J. Clin. Invest.* 116, 2837–2842
44 Erickson, D. (2003) Wanted: drug hunters. *In Vivo* 45–52
45 Huxley, A. and Miles, N. (2005) Speedel on the company's pipeline and future plans. *Drug Discov. Today* 10, 881–883
46 Fleisch, H. (1969) Prevention by a diphosphonate of immobilization 'osteoporosis' in rats. *Nature* 223, 211–212
47 Stahelin, H. (1986) Historical background (Ciclosporin). *Progr. Allergy* 38, 19–27