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Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival

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In an effort to uncover systematic learnings that can be applied to improve compound survival, an analysis was performed on data from Phase II decisions for 44 programs at Pfizer. It was found that not only were the majority of failures caused by lack of efficacy but also that, in a large number of cases (43%), it was not possible to conclude whether the mechanism had been tested adequately. A key finding was that an integrated understanding of the fundamental pharmacokinetic/pharmacodynamic principles of exposure at the site of action, target binding and expression of functional pharmacological activity (termed together as the 'three Pillars of survival') all determine the likelihood of candidate survival in Phase II trials and improve the chance of progression to Phase III.

Introduction

Enhancing survival of new molecular entities (NMEs) through the discovery and development lifecycle is a key productivity driver for the pharmaceutical industry. NME survival is significantly impacted by the continued issue of insufficient or lack of clinical efficacy as the principal cause of program termination during development [1,2]. Moreover, earlier evidence indicates that NME survival is at its lowest during Phase II development with small- and large-molecule survival of 38% and 53%, respectively, during Phase II for the period of 1993–2004 [3]. Indeed, the Centre for Medicines Research reports that, out of a group of 16 companies representing ~60% of global R&D spend, the Phase II success rates for NMEs has fallen from 28% (2006–2007) to 18% (2008–2009), although success rates do vary between therapeutic areas and between small molecules *versus* biologics [4].

In an effort to uncover any systematic learnings that can be applied to improve Phase II decision-making and survival, a detailed analysis was performed on 44 Phase II programs at Pfizer that reached a decision point during the period 2005–2009. This manuscript discusses the findings of this analysis for the Pfizer dataset and illustrates the importance of acquiring data and knowledge on fundamental pharmacokinetic (PK) and pharmacodynamic (PD) principles to increase the likelihood of testing the mechanism of action and progressing beyond Phase II development.

Analysis of Phase II survival and attrition

Background

From 44 NME programs that reached a decision point during Phase II clinical development between 2005 and 2009, only 32% were deemed to have achieved a positive readout in their clinical proof-of-concept (POC) study by meeting the agreed POC criteria for that program. A structured interview, termed an after action review (AAR), was conducted with the teams supporting these programs with the aim of identifying all trends that could shed light on the reasons for such high attrition during Phase II.

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The AAR contained three categories of questions – regarding the candidate compound, the program strategy and the team dynamics – for which the teams were asked to score their response on a five-point scale (five being strongly agree and one being strongly disagree). Teams could also provide free text responses.

Results

Analysis of the overall team feedback suggested that the principal reason for program termination was insufficient or lack of clinical efficacy. This finding concurs with analyses of industry-wide data where lack of efficacy results in termination of the majority of programs [1,2,5]. Deeper analysis of the Pfizer dataset showed that those programs that had a positive readout at clinical POC (32%) had also tested the mechanism of action in humans with data that showed the pharmacological target was modulated as expected to elicit an effect. A smaller number of programs successfully tested the mechanism but failed to demonstrate sufficient efficacy and/or safety (25%) and, although this is disappointing, efficacy failures where the mechanism is fully tested confirm that the pharmacological target is not relevant to the disease state and teams can 'walk away with confidence' from the project avoiding the cost of conducting further clinical studies. Conversely, a significant percentage of those programs that were terminated owing to a negative outcome at clinical POC did not adequately demonstrate whether the mechanism was tested (43%).

Conclusions

This analysis highlights that success in Phase II clinical development is dependent upon testing the mechanism of action and on the confidence in rationale being validated in the chosen indication [6]. The fact that several programs failed owing to the rationale not being validated in patients is not a surprise because this level of attrition, across a wide portfolio, should be expected where the initial biological and/or medical rationale is not upheld in clinical development. In fact, the number of novel targets approved by the FDA each year is usually between two and four. Something that came as a surprise was the observation that a significant number of programs failed to gather a compelling body of evidence to demonstrate a thorough understanding of the degree of modulation of the pharmacological target by the NME under investigation. As a consequence, a team in this situation was unable to deduce whether lack of efficacy in the clinical POC study was caused by the NME not achieving pharmacologically relevant activity or whether the target was not relevant for the chosen indication.

These findings led us to articulate, for future projects, the fundamental data and knowledge that are needed, from early stages of development, to assess whether an NME has the potential to elicit a pharmacological effect and thereby test the mechanism of action in humans. These fundamental elements of data and knowledge were described as the 'three Pillars of survival'.

Definition of the three Pillars of survival

For a development candidate to have potential to elicit the desired effect over the necessary period of time, three fundamental elements need to be demonstrated:

i. Exposure at the target site of action over a desired period of time
ii. Binding to the pharmacological target as expected for its mode of action
iii. Expression of pharmacological activity commensurate with the demonstrated target exposure and target binding

Pillar 1: exposure at the target site of action

Fundamental principle: drug exposure at the target site of action is necessary to elicit a pharmacological effect over a desired time period

Demonstration of free drug exposure at the target site of action at a level that exceeds pharmacological potency over the desired period of time gives maximum confidence that adequate exposure has been achieved. Every deviation away from this statement will introduce the risk that target exposure might not be adequate. Direct measurement of drug exposure at the target site of action is often not attainable experimentally and in these cases drug exposure is measured using blood samples. Therefore, consideration should be given whether blood concentrations are freely in equilibrium with the target and, if there is a strong scientific rationale for this, then blood exposure might be considered to be an adequate surrogate of target site exposure. In cases where blood and the target are separated by a barrier (*e.g.* blood–brain barrier or intracellular target), or where drug is administered directly to the target tissue, then consideration should be given to demonstrating the ability of the drug to traverse the barrier rapidly and/or to measuring drug in a surrogate compartment. Consideration should also be given to the potential role of pharmacologically active metabolites. A suitable PKPD model should be developed to relate drug exposure (and possibly derived PK measures such as C_{max}, C_{min} and AUC), in the compartment measured, to the pharmacological effect at the site of action. We also believe that physiologically based PK (PBPK) modeling will become an integral part of building understanding and confidence in Pillar 1 [7].

Pillar 2: binding to the pharmacological target

Fundamental principle: target occupancy is a prerequisite for expression of pharmacology and target modulation

The highest level of confidence and direct evidence at the site of action that required levels of target binding were being achieved is most probably obtained from PKPD studies of *in vivo* occupancy measurements with positron emission tomography (PET) or radiolabeled ligands.

Some confidence can be derived in an indirect manner if the binding properties and potency against the target are well understood (including potential impact of species differences, polymorphisms or other target phenotypes) combined with a high degree of confidence that adequate target exposure is being achieved (Pillar 1).

In addition to occupancy, consideration also needs to be given to target-binding kinetics and how this translates across *in vitro* and *in vivo* assays and species. Ramsey *et al.* [8] provide a recent example of a translational PKPD approach that integrates *in vitro* and *in vivo* target binding kinetics in a drug discovery setting and they also demonstrate how the absence of such a framework might have resulted in a 'Pillar 2 failure' in the case of corticotrophin-releasing factor-1 (CRF-1) receptor antagonists.

Pillar 3: expression of pharmacology

Fundamental principle: functional modulation of the target is a prerequisite for expression of pharmacological activity to test the mechanism

The highest level of confidence and direct evidence at the site of action that sufficient levels of target modulation are being achieved is most probably obtained from PKPD studies of biomarkers that reflect expression of primary pharmacology at the site of action. Some confidence can be derived in an indirect manner if the functional pharmacological properties and mode of action of the compound are well understood, combined with a high degree of confidence in Pillars 1 and 2.

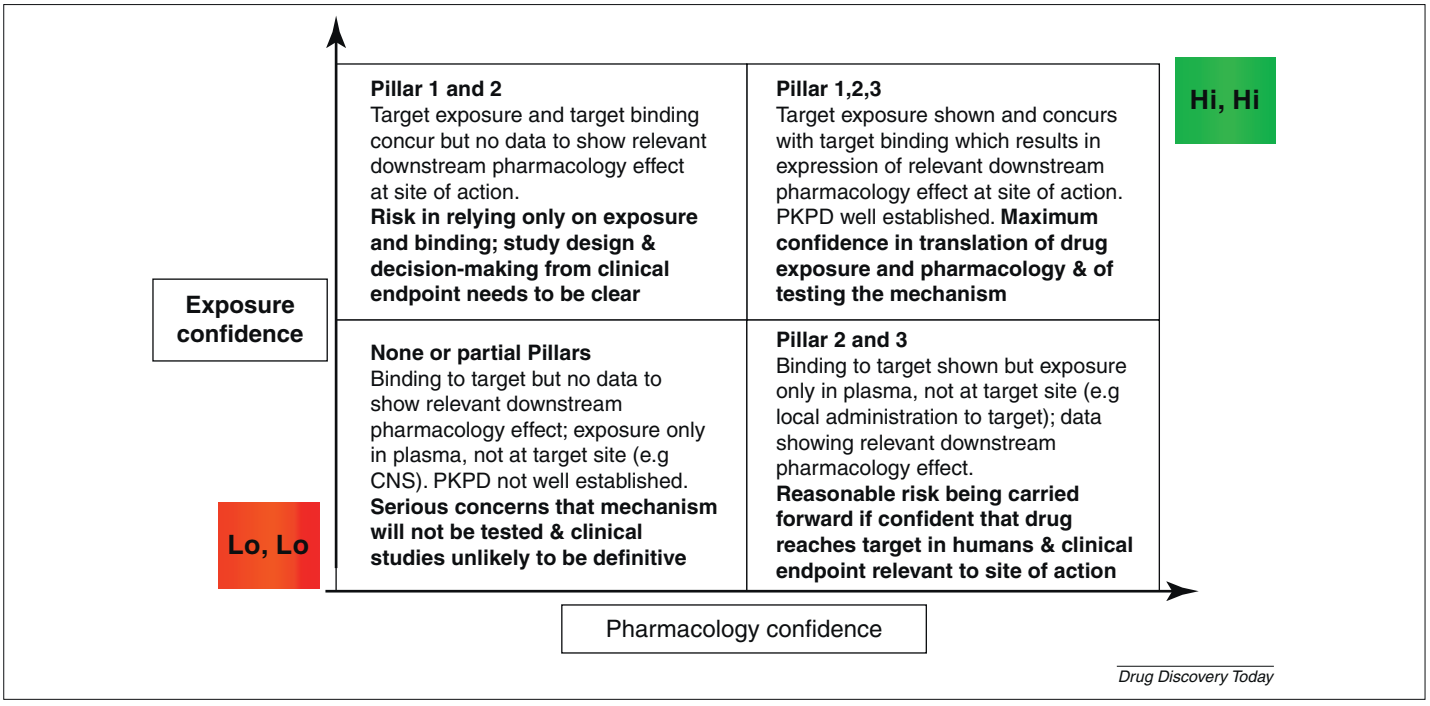

FIGURE 1

Risk management matrix, based on three Pillars of survival, for use in clinical development to assess likelihood of testing the mechanism and program progression.

Use of three Pillars of survival to manage risk in Phase II clinical development

A simple matrix (Fig. 1) was developed by which the alignment with the three Pillars of survival could be used to assess the likelihood that the mechanism of action will be tested in the clinical POC study and thus give further confidence regarding the likelihood of attaining a positive POC with subsequent progress into Phase IIb.

This matrix can be applied to individual programs and across a portfolio of programs, and the placement of a program in the matrix depends upon the data and knowledge acquired in advance of decision-making studies in patients (*i.e.* the clinical POC study).

Alignment with the three Pillars of survival was retrospectively assessed for the 44 programs in Phase II development in the Pfizer dataset and the results were applied to the risk management matrix to determine whether alignment with the three Pillars of survival provides a positive correlation with program progression or termination. The results of this retrospective analysis are shown in Fig. 2. Encouragingly, this assessment supports the point that the three Pillars of survival are the fundamental building blocks of the profile of a compound, and collectively they are

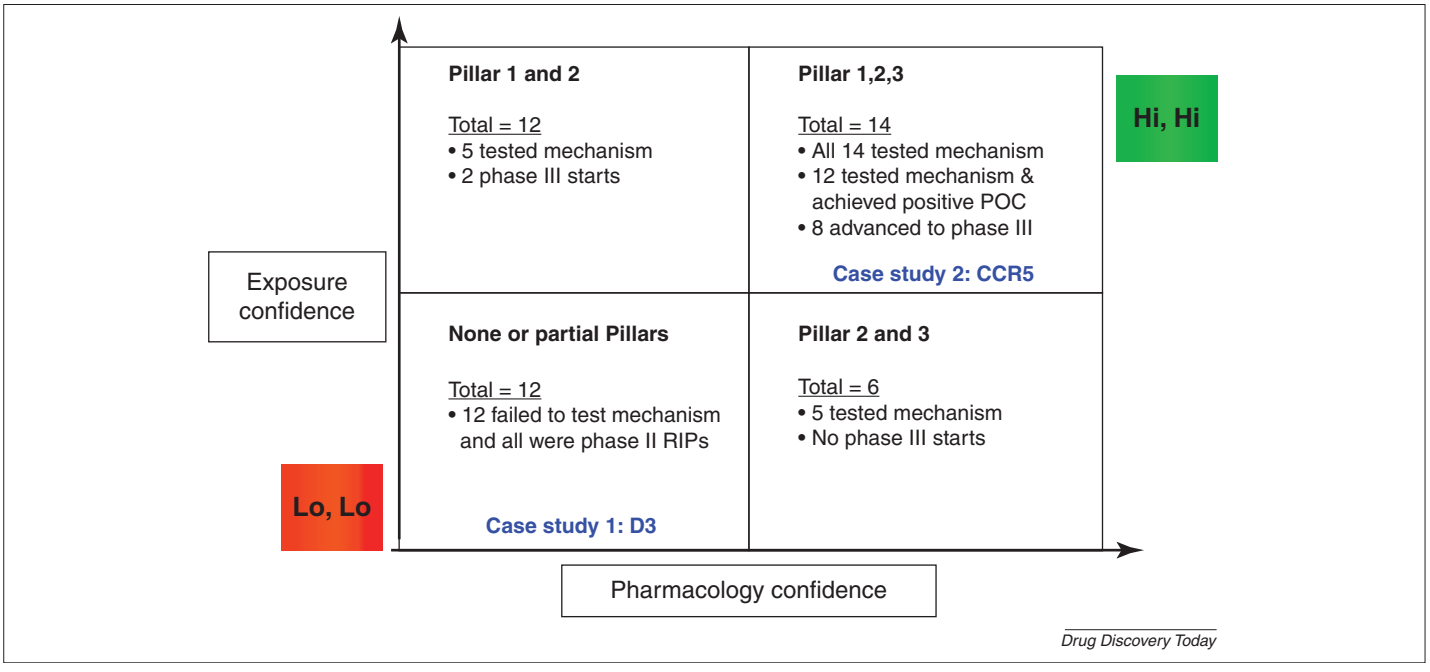

FIGURE 2

Alignment with three Pillars of survival for 44 Phase II programs between 2005 and 2009 in the Pfizer dataset.

highly correlated with the probable success of a candidate drug in development and the ability to test the mechanism. The retrospective analysis of this Pfizer dataset demonstrates that a development candidate that satisfies all three Pillars will:

i. Have increased likelihood of surviving through Phase II into Phase III
ii. Enable efficient and effective development through POC and Phase II

The importance of acquiring data and knowledge on the three Pillars of survival through preclinical and clinical development, to aid decision-making on the mechanism of action and clinical POC, is best illustrated through two case studies from the Pfizer dataset contrasting situations where knowledge on these fundamental principles was either poor (case study 1) or high (case study 2).

Case study 1: dopamine D3 receptor agonist for treating sexual dysfunction and neuropathic pain

Pursuing an unprecedented target with low confidence in three Pillars

Dopamine is one of the key neurotransmitters in the central nervous system (CNS) and a range of neurological and psychiatric disorders have been associated with dysfunction of the dopaminergic system, for example Parkinson's disease, restless leg syndrome, schizophrenia, anxiety and bipolar disorders. Dopamine receptors are commonly divided into two clusters, the D1-like (D1 and D5 receptors) and D2-like (D2, D3 and D4 receptors) families. There has been considerable interest in the development of agonists for the D2-like receptor family, for example 'non-ergots' such as pramipexole, ropinirole and rotigitine for the treatment of Parkinson's disease and 'D2 partial agonists' such as aripiprazole for schizophrenia.

Sexual dysfunction

It has also been reported that agonists for the D2-like receptor family, such as pramipexole and ropinirole, could be used in the treatment of male and female sexual dysfunction. In fact, the non-selective dopamine agonist apomorphine was marketed in the form of a sublingual tablet as Uprima™ for the treatment of male erectile dysfunction (MED); however, lack of efficacy and competition from Pfizer's Viagra® were cited among the reasons for its recent withdrawal. The efficacy of apomorphine in the treatment of MED is compromised by dose-limiting side effects such as nausea, emesis, dizziness, sweating, somnolence as well as cardiovascular effects such as hypotension, bradycardia and syncope [9]. As a result, a discovery program was initiated at Pfizer to examine the hypothesis that a selective D3 agonist would prove effective in the treatment of MED while reducing the levels of nausea, emesis and cardiovascular effects observed with non-selective apomorphine. Apomorphine displayed no selectivity between D2 and D3 receptors in our functional *in vitro* assays, whereas tool compounds reported in the literature only demonstrated marginal D3 selectivity. Encouragement was provided by preliminary observations that pramipexole, which was ~30-fold selective for the D3 receptor in Pfizer labs, displayed equivalent efficacy in animal models of *in vivo* pro-erectile activity compared to apomorphine but appeared to display a greater therapeutic window over cardiovascular effects and nausea in preclinical safety studies. A medicinal chemistry program subsequently identified potent D3 agonists that were highly selective over D2, and PF592379 was selected as a clinical candidate based on a combination of favorable pharmacological properties and predicted human PK [10,11]. PF592379 inhibited forskolin-stimulated cAMP accumulation in CHO cells stably expressing the recombinant human D3 and D2 receptors with EC_{50} values of 21 nM and >10 μM, respectively (corresponding to a D3 functional selectivity of >476-fold). It also displayed excellent functional selectivity (186-fold) against the 3rd member of the D2-like family, the D4 receptor, and minimal binding activity (IC_{50} > 10 μM) against a wide panel of other targets, including the D1 receptor.

PF592379 showed good efficacy in several *in vivo* models of male sexual function. Specifically, PF592379 was efficacious in a conscious rat telemetry model of erectile function and the pelvic nerve stimulated intracavernosal pressure in an anaesthetized dog model of penile erection. Exposure-response modeling of the data indicated that free plasma exposure levels required to achieve maximum effect in these models ranged from 50 to 200 pM (*i.e.* the compound appeared to be at least 10-fold more potent *in vivo* compared with its *in vitro* potency in the human D3 functional assay). PF592379 was also efficacious in a female rat model of proceptive sexual behavior in a similar concentration range. By contrast, PF592379 produced no biologically relevant effect on the cardiovascular system or emesis up to 1 μM unbound plasma concentrations in an anaesthetized dog *in vivo* safety pharmacology model, indicative of a therapeutic window in excess of 1000.

Because the *in vivo* preclinical data suggested that PF592379 was efficacious at concentrations when only a small (<10%) fraction of D3 receptors would be occupied (indicative of 'receptor reserve'), no attempts were made to develop a biomarker to assess 'Pillar 2'. Attempts to develop a 'Pillar 3' biomarker to confirm pharmacological activity (for example oxytocin plasma levels) were not successful.

Clinical data verified that PF592379 was a low-clearance compound in human (oral clearance of 6.5 ml/min/kg following a 200 mg dose) and, as such, seemed to have ideal PK properties for an oral D3 agonist, intended for on-demand dosing [11] albeit that exposure at the target site of action in the brain was assumed to be sufficient given the anticipation that brain penetration is good. The efficacy of PF592379 was subsequently assessed in a randomized, double-blind, placebo-controlled, balanced, four-way cross-over study using penile plethysmography (RigiScan) and sildenafil (100 mg) as positive control in 32 male subjects with mild-to-moderate erectile dysfunction. In summary, PF592379 was well tolerated at all doses tested (0.1–100 mg) but, in contrast to sildenafil, did not show a statistically or clinically significant improvement in erectile activity, despite the fact that peak unbound plasma concentrations at the highest (100 mg) dose tested were ~30-fold in excess of the EC_{50} against the human D3 receptor. It should be noted, of course, that agonist potency is known to be assay- and system-dependent [12] and therefore exposure alone cannot be used as evidence that pharmacology was expressed.

Neuropathic pain

PF592379 was also tested in a variety of preclinical rat *in vivo* models of nociceptive and neuropathic pain. In summary, positive effects were observed at several different endpoints believed to reflect nociceptive pain states [monosodium iodoacetate (MIA)-induced static allodynia and weight deficit, plantar surgery-induced static and dynamic allodynia, and capsaicin-induced hyperalgesia], but no significant effects were seen in the hotplate paw withdrawal latency test (also believed to represent a nociceptive pain model) and chronic constriction injury (CCI)-induced static and dynamic allodynia, which is considered to be a model of neuropathic pain. Overall, these combined results were interpreted to underwrite the therapeutic potential of the D3 agonist PF592379 in the clinical treatment of nociceptive pain states such as osteoarthritis (OA). Subsequently, a randomized, double-blind, placebo- and active-controlled, crossover study was conducted to investigate the effects of PF592379 on pain thresholds of patients with severe pain caused by OA of the thumb. In summary, in

contrast to the positive control, oxycodone (20 mg controlled release), PF592379 (75 mg) did not show a significant effect on pressure pain threshold (as determined using a pressure algometer) or pain intensity (assessed using an 11-point numerical rating scale). It was shown that PF592379 produced a decrease in serum prolactin levels, indicative of an agonistic action at the dopamine D2 receptor. However, as before, no evidence could be obtained of modulation of the target of interest (*i.e.* the D3 receptor) at the site of action in the brain.

In conclusion, PF592379 was assessed in clinical POC studies for two indications on the basis of supportive data in preclinical *in vivo* models, encouraging human PK and an apparently good therapeutic window. However, the lack of data and knowledge fully consistent with the three Pillars of survival means that it cannot be conclusively determined whether the negative results in patient studies are caused by insufficient pharmacological modulation of the D3 receptor by PF592379 or as a result of selective D3 receptor agonism having no clinical rationale in male erectile dysfunction and nociceptive pain.

Case study 2: CCR5 antagonist for treatment of HIV infection

Developing high confidence in three Pillars of survival through preclinical and early clinical investigation

C–C chemokine receptor type 5 (CCR5), which belongs to the G-protein-coupled receptor superfamily, is an attractive target for HIV-1 therapy given that the genetic absence of surface-expressed CCR5Δ32 in the homozygous population leads to this population being highly protected against HIV-1 infection [13,14]; and the reduced cell-surface-expression in the CCR5Δ32 heterozygote population is associated with a slower disease progression [15]. From an antiviral perspective, CCR5 is the co-receptor for the most commonly transmitted HIV-1 strains that predominate during early stages of infection and remain the dominant form in >50% of late-stage HIV-1-infected patients [16]. Early evidence that a small-molecule CCR5 antagonist could be efficacious for the treatment of HIV-1 infection was provided by the exploratory clinical development data for SCH351125, which was shown to be efficacious *in vitro* and *in vivo* [17].

PKPD understanding of maraviroc provides confidence in effective treatment of HIV infection

Maraviroc (UK427857) is a small-molecule CCR5 antagonist which is a product of a medicinal chemistry program following identification of an imidazopyridine CCR5 ligand from a high-throughput screen of the Pfizer compound file. Maraviroc demonstrates potent antiviral activity against all CCR5-tropic HIV-1 viruses tested with a geometric mean IC_{90} of 2 nM. In addition, maraviroc is active against 200 clinically derived HIV-1 envelope-recombinant pseudoviruses, including those derived from viruses resistant to existing HIV-1 inhibitor drug classes [18]. PK profiling in preclinical species and subsequently in human volunteers gave confidence that continuous systemic exposure (unbound C_{min} >5 nM) could be achieved above the geometric mean antiviral IC_{90} (2 nM) following oral dosing of >100 mg twice daily [18,19]. These data gave confidence that exposure at the target site of action (Pillar 1) could be achieved in humans. In addition, evidence that maraviroc could functionally bind to the target receptor at pharmacologically relevant concentrations (Pillar 2) was established using cell-based assays. In particular, maraviroc was shown to inhibit virus attachment to CCR5 in a CD4 cell preparation with an IC_{50} of 11 nM. In addition, maraviroc blocked binding of viral envelope, gp120, to CCR5 with an IC_{50} of 0.22 nM to prevent the membrane fusion events necessary for viral entry to CD4 cells [18].

Building on the knowledge acquired through understanding of the pharmacology and PK in preclinical species and human volunteers, a PKPD model was developed, in advance of clinical trials in HIV patients, to understand better the link between CCR5 pharmacological activity, PK exposure and clinical efficacy. This model was developed consisting of three components: a disease model, a PD model and a PK model, and was based on a published viral dynamic model [20] that was adapted for short-term treatment and for the new mechanism of action owing to CCR5 antagonism. This modular structure allowed for the integration of information from different sources such as the literature and *in vitro* and *in vivo* data [21]. In essence, this PKPD model can be considered to provide knowledge akin to that described in Pillar 3 and, in the early stages of the maraviroc development program, the PKPD model was used to optimize the design of a proof-of-principle study. As further clinical data became available the model was updated and used to optimize the development plan toward the choice of Phase III doses. The model accurately estimated that the maximum $\log_{10}$ viral load drop would be observed with 300 mg bid administration with a $\log_{10}$ viral load decline of −1.6 and fraction inhibition of viral load of 0.93 [22]. A 300 mg bid is the maximum effective dose, described in the US product label, in the absence of cytochrome P450 (CYP) inhibitors or inducers.

Concluding remarks

This analysis demonstrates that there are three fundamental PK and PD principles that collectively determine the likelihood of testing the mechanism of action and influencing the likelihood of candidate survival in Phase II. These fundamental principles, which we have termed the three Pillars of survival, are geared toward understanding the drug exposure, target binding and pharmacological activity at the target site of action in an integrated manner through application of PKPD and PBPK modeling. The importance to R&D productivity of a thorough understanding of whether or not the NME engages its target [23] and has the desired pharmacological activity in humans is being acknowledged in an increasing number of publications on drug survival [5,24]. Furthermore, the data and knowledge enshrined in the three Pillars of survival are acknowledged, in the PhRMA position paper on best practice for clinical POC studies [25], as being crucial to 'achieve a good POC and reach a definitive answer regarding the utility of potential new therapeutic agents'.

This analysis of the Pfizer dataset adds further weight to the importance of these fundamental principles given the high degree of correlation, for programs with good understanding of the three Pillars of survival, with testing the mechanism of action, achieving a positive clinical POC and advancing into Phase III development. The detailed description of the two case studies nicely illustrates the use of data, knowledge and quantitative approaches related to the three Pillars of survival in guiding preclinical and clinical study design and aiding effective decision-making in Phase II development. Others have highlighted the fact that certain therapeutic areas (*i.e.* CNS and oncology) appear to suffer from particularly high Phase II attrition rates [1,5]. However, we believe our present dataset is too small to add further insights into this matter.

Although significant challenges remain regarding the improvement of R&D productivity, this analysis should provide an encouraging 'back to basics' call to all scientists in the industry that paying close attention to basic principles of pharmacology and PK throughout drug discovery and clinical development [26] can pay rich dividends in the improvement of candidate survival.

Conflict of interest

The authors were all employees of Pfizer Limited at the time of conducting the research described in the manuscript.

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References

1 Kola, I. and Landis, J. (2004) Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discov.* 3, 711–715
2 Arrowsmith, J. (2011) Phase III and submission failures: 2007–2010. *Nat. Rev. Drug Discov.* 10, 87
3 DiMasi, J.A. *et al.* (2010) Trends in risks associated with new drug development: success rates for investigational drugs. *Clin. Pharmacol. Ther.* 87, 272–277
4 Arrowsmith, J. (2011) Phase II failures: 2008–2010. *Nat. Rev. Drug Discov.* 10, 328
5 Paul, S.M. *et al.* (2010) How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat. Rev. Drug Discov.* 9, 203–214
6 Wehling, M. (2009) Assessing the translatability of drug projects: what needs to be scored to predict success? *Nat. Rev. Drug Discov.* 8, 541–546
7 Rowland, M. *et al.* (2011) Physiologically-based pharmacokinetics in drug development and regulatory science. *Annu. Rev. Pharmacol. Toxicol.* 51, 45–73
8 Ramsey, S.J. *et al.* (2011) Quantitative pharmacological analysis of antagonist binding kinetics at CRF_1 receptors *in vitro* and *in vivo*. *Br. J. Pharmacol.* 164, 992–1007
9 Dula, E. *et al.* (2001) Double-blind, crossover comparison of 3 mg apomorphine SL with placebo and with 4 mg apomorphine SL in male erectile dysfunction. *Eur. Urol.* 39, 558–563
10 Hepworth, D. *et al.* (2009) Optimization of oral pharmacokinetics in the discovery of clinical candidates for the treatment of sexual dysfunction. *Abstracts of Papers, 237th ACS National Meeting*, March 22–26, 2009, Salt Lake City, UT, USA http://www.acsmedchem.org/mediabstracts2009.pdf
11 Attkins, N. *et al.* (2010) Pharmacokinetics and elucidation of the rates and routes of N-glucuronidation of PF-592379, an oral dopamine 3 agonist in rat, dog and human. *Xenobiotica* 40, 730–742
12 Van der Graaf, P.H. and Benson, N. (2011) Systems pharmacology: bridging systems biology and pharmacokinetics–pharmacodynamics (PKPD) in drug discovery and development. *Pharm. Res.* 28, 1460–1464
13 Dragic, T. *et al.* (1996) HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. *Nature* 381, 667–673
14 Liu, R. *et al.* (1996) Homozygous defect in HIV-1 coreceptor accounts for resistance of some multi-exposed individuals to HIV-1 infection. *Cell* 86, 367–377
15 Pasi, K.J. *et al.* (2000) The effects of the 32-bp CCR-5 deletion on HIV transmission and HIV disease progression in individuals with haemophilia. *Br. J. Haematol.* 111, 136–142
16 Berger, E.A. *et al.* (1999) Chemokine receptors as HIV-1 coreceptors: roles in viral entry, tropism and disease. *Annu. Rev. Immunol.* 17, 657–700
17 Strizki, J.M. *et al.* (2001) SCH-C (SCH 351125) an orally bioavailable, small molecule antagonist of the chemokine receptor CCR5, is a potent inhibitor of HIV-1 infection in *vitro* and in *vivo*. *Proc. Natl. Acad. Sci. U. S. A.* 98, 12718–12723
18 Dorr, P. *et al.* (2005) Maraviroc (UK-427,857), a potent, orally bioavailable and selective small molecule inhibitor of chemokine receptor CCR5 with broad-spectrum anti-human immunodeficiency virus type 1 activity. *Antimicrob. Agents Chemother.* 49, 4721–4732
19 Walker, D.K. *et al.* (2005) Species differences in the disposition of the CCR5 antagonist, UK-427,857, a new potential treatment for HIV. *Drug Metab. Dispos.* 33, 587–595
20 Bonhoeffer, S. *et al.* (1997) Virus dynamics and drug therapy. *Proc. Natl. Acad. Sci. U. S. A.* 271, 1582–1585
21 Rosario, M.C. *et al.* (2005) Pharmacokinetic–pharmacodynamic disease model to predict *in vivo* antiviral activity of maraviroc. *Clin. Pharmacol. Ther.* 78, 508–519
22 Rosario, M.C. *et al.* (2006) Pharmacokinetic–pharmacodynamic model to optimise the Phase IIa development program of maraviroc. *J. Acquir. Immune Defic. Syndr.* 42, 183–191
23 Gabrielsson, J. *et al.* (2011) Pharmacodynamic–pharmacokinetic integration as a guide to medicinal chemistry. *Curr. Top. Med. Chem.* 11, 404–418
24 Empfield, J.R. and Leeson, P.D. (2010) Lessons learned from candidate drug attrition. *IDrugs* 13, 869–873
25 Cartwright, M.E. *et al.* (2010) Proof of concept: a PhRMA position paper with recommendations for best practice. *Clin. Pharmacol. Ther.* 87, 278–285
26 Cohen, A. (2008) Pharmacokinetic and pharmacodynamic data to be derived from early-phase drug development-designing informative human pharmacological studies. *Clin. Pharmacokinet.* 47, 373–381

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