BJP British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2012.02215.x
www.brjpharmacol.org

EDITORIAL

Why is publication of negative clinical trial data important?

Ann Hayes[1] and Jackie Hunter[2]

[1]*The Ann Hayes Consultancy Ltd, Buntingford, UK, and* [2]*OI Pharma Partners Ltd, Weston, UK*

Correspondence
Ann Hayes, The Ann Hayes Consultancy Ltd, Buntingford, Hertfordshire, UK. E-mail: annghayes@yahoo.co.uk; Jackie Hunter, OI Pharma Partners Ltd, Weston, Hertfordshire, UK. E-mail: jackie@oipharmapartners.com

Keywords
Clinical trial; negative data

The pharmaceutical industry is facing troubled times, both in the UK and globally. Revenues are being hit by patent expiries on blockbuster drugs like atorvastatin, salmeterol xinafoate/fluticasone propionate and olanzapine; and development pipelines are insufficiently robust to replace these lost revenues. Drug discovery productivity has failed to improve over the last 15 years, despite the large sums of money that have been spent on research and development (R&D) to attempt to capitalize on the huge technological advances provided by molecular biology and genetics (Paul *et al.*, 2010). The key issue behind low productivity has been the low success rates (high attrition) seen in all areas of drug discovery, but particularly in therapeutic areas like psychiatry and neurology (CNS; Pangalos *et al.*, 2007) although phase III failure rates in CNS are lower than those in oncology (Arrowsmith, 2011a). This has resulted in several large companies scaling down their research operations (GlaxoSmithKline in the UK and Verona, Merck in the UK, Pfizer in the UK at Sandwich, Novartis in Switzerland and AstraZeneca at Loughborough in the UK) in an effort to reduce costs and refocus research on areas seen to be less risky. Such closures can have a direct effect on the regional economy in these areas and also an impact on national academic research as there are fewer opportunities for collaboration and for leveraging industry funding. Various solutions have been implemented with a view to improving productivity: research operations are being split into smaller units in an effort to recapitulate the innovative culture of the small biotechnology companies, such as the GSK CEDDs (Centres of Excellence for Drug Discovery) and DPUs (Discovery Performance Units) and Pfizer's NewMeds business units; pipelines are being replenished from small and larger biotechnology companies through a range of different deal types; and contract research is being sourced in Asia where costs are currently lower. However, there is no clear indication that such changes will increase the probability of success, although they may reduce the cost of failure. Clearly, methods of reducing attrition should be pursued at all points along the drug discovery and development process. However, the impact of reducing failure in clinical trials should be greater than reducing failure in the discovery phase, as this is where the most spend occurs.

This is supported by an analysis by Paul *et al.* (2010), which clearly showed that improving R&D efficiency and productivity depends strongly on reducing phase II and III attrition. In addition, various studies have shown that the key point where attrition is highest is in the first clinical proof-of-concept (PoC) study (Arrowsmith, 2011b), where compounds often fail for lack of therapeutic efficacy or side effects. This reflects the fact that preclinical 'target validation' studies do not always translate into man, where ultimate target validation must be established. Given these facts, it is easy to see the importance of the results from those first clinical validation studies. Positive data are greeted with great enthusiasm and are often made public relatively rapidly. Negative data, on the other hand, are often not published for several years. They may be published on company websites but are often difficult to locate. Sometimes they are not published at all, yet they are equally important for target validation or invalidation purposes. This is especially important because, for key targets, many companies will be working on the same target in parallel, but without sharing all their knowledge in the hope of retaining important commercial advantage. This gives rise to the potential waste of vast sums of money on compounds for which the molecular target has essentially been invalidated, but the data are not publicly available. This becomes even more important if data that has been published to validate these targets pre-clinically is not always reproducible (Prinz *et al.*, 2011). Because most compounds do fail at phase IIa (Arrowsmith, 2011b), spending large sums of money on compounds doomed to fail is to the commercial disadvantage of everyone; therefore, we strongly believe that all clinical trial data should be made publicly available in a timely manner. This allows assessment as to whether a particular molecular target has been invalidated or not, which, in the long run, is to the benefit of everyone working in the industry. Indeed, Arrowsmith's (2011b) analy-

sis of phase II failures concluded that an increase in collaborative efforts between companies up to the point of PoC for novel targets or mechanisms might be more cost-effective and time-efficient.

A retrospective examination of the published pipelines of a number of companies or an examination of the clinical trials that have terminated in clinical trials databases, such as http://www.clinicaltrials.gov, reveals that a number of projects have not progressed further than the PoC phase. For example, examination of GSK's published pipeline in 2007 versus that in 2011 and Pfizer's pipeline of 2008 versus 2011 reveals that over 90% of compounds that were in phase II in 2007 and 2008, respectively, were no longer in the pipeline in 2011. Of course, some of the attrition will be due to unexpected toxicity or for strategic reasons, but a significant proportion of attrition (51%) in this phase is due to lack of efficacy (Arrowsmith, 2011b). This 'failure of efficacy' information is of course valuable given the cost of phase II trials, but it is either unavailable or extremely hard to find.

The example of TRPV1 antagonists illustrates this point. There was considerable rationale from preclinical models that antagonists of the TRPV1 vanilloid receptor would make good analgesic drugs (Szallasi *et al.*, 2007). In addition, early clinical experimental medicine models had shown that compounds such as SB705498 could antagonize capsaicin induced hyperalgesia in phase I volunteer studies (Chizh *et al.*, 2007). A search of the Thomson Pharma database reveals that currently there are 35 compound entries for TRPV1 antagonists, of which 4 are in phase II, 6 in phase I, 13 in the discovery phase, 7 where no development has been reported and 5 where the compound has been discontinued. We note that even on company clinical trial register websites, there are gaps in dissemination. For example, SB705498 is listed on GSK's website (http://www.gsk-clinicalstudyregister.com) as having completed five phase II trials – two in allergic rhinitis, one in cough, an acute migraine study and a dental pain study. The dental pain study was originally due to complete in 2007 according to clinicaltrials.gov. Of these phase II trials, results are only available on the website for the allergic rhinitis trials. Likewise on the AstraZenca website (http://www.astrazenecaclinicaltrials.com), data for their TRPV1 antagonist (AZD-1386) is listed as having completed phase II trials in gastroesophageal reflux disease (GERD) (2 trials), neuropathic pain, osteoarthritis (OA) pain and dental pain, with all of these trials having started in 2008 or 2009 and having been completed by the end of 2009. Data are available on the AstraZeneca website for the GERD, dental pain and OA studies and show that the compound was largely non-efficacious, although results are not available for the neuropathic pain study. Given that pain is the area where most other companies are pursuing TRPV1 antagonists, this is very relevant information. In addition, clinical information needs to be accompanied by details on the selectivity, potency and pharmacokinetics of the compounds so that the clinical failure can be confirmed as a failure of the target for that indication and not a failure of the molecule or the clinical trial design (e.g. inappropriate exclusion or inclusion criteria). However, such information is again not readily available.

Data sharing between companies has been occurring in a number of different precompetitive initiatives linked to safety such as the Social and Economic Archive Committee (SEAC) and the Observational Medical Outcomes Partnership (OMOP) and is beginning in areas such as biomarker validation and new preclinical model development (Hunter, 2011). Progress is still slow however in the area of clinical PoC studies. Since early 2005, there have been calls for more transparency in clinical trials research postings both of protocols and results (e.g. in the *New England Journal of Medicine*) (Zarin *et al.*, 2005) and by industry associations such as PhRMA (Pharmaceutical Research and Manufacturers of America). The World Health Organization (WHO) also created a program to generate a virtual registry whereby a single portal could link to the various clinical registries that exist around the world, and the WHO successfully launched the database in May of 2007 (http://www.who.int/trialsearch). The publication of clinical trial results on these websites is important, and companies such as Merck have begun to do this, but not yet in a consistent manner. However, the clinical data alone are not sufficient unless it is put into context, as discussed earlier.

Many large companies have stated publicly that they are in agreement with the philosophy we have outlined above; that is, all clinical trial data should be published. Indeed, a group of large pharma companies have founded the 'Medical Publishing Insights and Practices (MPIP) Initiative', a unique collaboration of pharmaceutical co-sponsors (Amgen, AstraZeneca, GlaxoSmithKline, Johnson & Johnson, Merck, Pfizer, Takeda) and the International Society for Medical Publication Professionals to elevate trust, transparency and integrity in publishing industry-sponsored research. They have published on their website (http://www.mpip-initiative.org/) 10 recommendations to close the credibility gap in industry-sponsored research, of which the second is 'Make public all results, including negative or unfavorable ones, in a timely fashion, while avoiding redundancy' (http://www.mpip-initiative.org/publications/10-recommended-best-practices/report-all-results). However, one issue that has been raised by our industry colleagues is that there can be difficulties in finding suitable journals that are willing to publish negative clinical data. The above initiative is hopefully an early sign that this is changing. For example, the editors of the *British Journal of Clinical Pharmacology* (BJCP) and *British Journal of Pharmacology* wonder whether the society should provide some sort of forum for publishing these data, particularly as pharmacology, both clinical and preclinical, is at the heart of target validation.

We hope that this editorial will stimulate further discussion concerning the best way to achieve the publication of negative clinical data. We feel that this issue should be given high priority, not just because of the potential to reduce costs for pharma, to improve future clinical trial design, or even because of the possibility that attrition rates might be reduced, though these are all important. However, an even more important argument is the ethical one of not exposing more subjects than necessary to ineffective treatments, thereby increasing the pool of subjects available for testing other, potentially effective treatments. Hopefully, the increased availability of all trial data will become another weapon in the urgent battle to improve drug discovery productivity and hence facilitate the timely introduction of even better medicines.

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