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Driving earlier clinical attrition: if you want to find the needle, burn down the haystack. Considerations for biomarker development

Richard W. Peck

Lilly Research Centre, Erl Wood Manor, Sunninghill Road, Windlesham, Surrey, GU20 6PH, UK

Drug development attrition rates are rising and late phase attrition remains high, contributing to an unsustainable increase in R&D spending. Consequently, there is much effort to identify the potentially successful molecules earlier in development with the use of biomarkers to predict potential efficacy and safety. However, focussing only on picking the winners earlier will not solve the problem. It is essential that the evaluation of these biomarkers also enables the earlier termination of the molecules that will not have the required activity.

The drug development challenge

The pharmaceutical industry continues to discover and develop new drugs successfully [1]. However, the costs of this innovation are rising disproportionately to the increase in successful approvals, whether measured as total R&D spend [2] or estimated as development cost per new drug approved [3]. Furthermore, although the long term trend shows an increase in approvals, the short term trend is for a substantial decrease, despite the record levels of R&D investment, with just 20 new drugs approved by the FDA in 2005 [4]. Thus, the pharmaceutical industry is looking closely at how to reduce the cost of discovering and developing new drugs. Increasing attrition rates are a significant contributor to increasing R&D costs, with a recent estimate from the FDA suggesting that only 8% of the molecules that enter clinical development are being successfully registered compared with 14% ten years ago (http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html). The latest surveys confirm that success rates from the first study in humans to launch are now <10% [2]. Thus, a substantial, and increasing, part of the overall cost of drug development is the investment in molecules that fail in development and the later in development this failure occurs the more the associated costs [5]. The attrition rate in phase II is now over 70% and rising, and even in phase III almost one-third of molecules fail [2,6,7]. It is therefore easy to see how large sums of money are being wasted on studying inactive or poorly tolerated molecules. Faced with all these challenges, the pharmaceutical industry is responding by rethinking how to manage the development of new drugs.

Corresponding author: Peck, R.W. (peck_richard_w@lilly.com)

Reducing development attrition

In general, the impact of development failures on development costs could be decreased by (Box 1):

- improved target validation;
- selecting candidate molecules with a greater chance of success;
- identifying earlier in development those molecules that will eventually fail.

It is anticipated that greater understanding of the molecular pathophysiology of disease (i.e. the heterogeneity of many diseases and the linkage between molecular targets and diseases) will eventually lead to improved target validation. This, in turn, should enable selection of molecular targets that are more likely to produce effective treatments for diseases, particularly when there is a better understanding of the subgroups of patients who respond best to drugs against that target. Unfortunately, in most therapeutic areas, this has yet to have any obvious impact on success rates of development. One exception to this is the infectious diseases area, where disease pathogenesis is generally well understood, the variation in drug sensitivity of the causal organisms and the relationship of drug levels to organism growth and survival can be studied extensively in preclinical systems, and models are already well characterized. The net result of this is much lower failure rates for lack of efficacy than in other therapeutic areas [2,6,7], giving confidence that improved disease understanding and better disease models in other therapeutic areas will also lead

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BOX 1

Strategies to improve development success rates

Improved target validation

- Improves overall development success rates
  - Increased understanding of molecular pathophysiology of disease
  - Increased understanding of disease heterogeneity
  - Improved ability to identify potential responder subsets
  - Increased understanding of the required level (maximum effect, extent and time-course) of drug activity and/or drug concentrations required to deliver efficacy

Improved candidates

- Improves overall development success rates
  - Increased testing and screening of potential candidates before GLP studies and a commitment to human studies
    - Focus on preclinical screening for toxicology, ADME and biopharmaceutic properties
    - Builds on the progress already made in decreasing clinical failure for poor pharmacokinetics

Earlier development attrition

- Increase early development attrition in order to increase late stage success rates
- No impact on overall attrition rates but decreases development costs
  - Confirm drug pharmacology in initial human studies and terminate if inadequate pharmacology
  - Explore effect of pharmacologically active doses on biomarkers of efficacy and/or safety prior to clinical endpoint trials

to increased success rates in the long term. Furthermore, in the last decade the failure rate from unacceptable pharmacokinetics in clinical development has been greatly reduced by improved preclinical screening of drug candidates [6]. Thus, the molecules that will fail in development for pharmacokinetic reasons are identified and eliminated much earlier and at lower cost. These successes provide encouragement that similar success might also be possible in reducing late development failures arising from lack of efficacy.

Burning down the haystack: biomarkers and proof of concept

The main reason for drugs failing in development is either inadequate efficacy or poor safety [2,6]. The development strategy proposed in response is to identify biomarkers of efficacy and safety that can be used in early clinical development to identify which molecules to progress. A biomarker is a 'characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention' [8]. The proposal is to find biomarkers predictive of safety or efficacy that can be used in small, intensive phase I and phase IIa trials to build confidence in which molecules to progress to phase IIb and phase III development.

Studying the effect of a drug on a marker of activity, efficacy or safety is not new. Over 20 years ago, early trials of the anti-convulsant lamotrigine showed that it decreased epileptiform activity on the EEG [9] and reduced sensitivity to photoconvulsive stimuli [10]. These results gave encouragement that the molecule would indeed be a clinically effective anti-convulsant [11]. But what is new is the extent of the focus on biomarkers as tools to drive decisions about which molecules to develop and thereby improving the efficiency of R&D investments. The use of biomarkers to support development decisions has been strongly encouraged by the FDA and the development and use of biomarkers is a major component of the Strategic Research Agenda for the European Union's Innovative Medicines Initiative (http://www.imi-europe.org/Publications.aspx?viewCategory= Researchx20Agenda).

This approach to early phase drug development is often called 'proof of concept' which is usually interpreted as the demonstration of probable or possible clinical efficacy based upon effects on a biomarker. In fact for an individual project, proof of concept is not necessarily evidence to suggest efficacy. It is better thought of as evidence to suggest that the molecule will have the desired clinical profile based upon the key needs of and greatest risks for achieving that profile. In many cases the key risk is whether the drug target can produce clinical efficacy but in others it might be the absence of a safety risk (either clinical or preclinical), a duration of effect long enough to support the desired frequency of dosing or the absence of a drug–drug interaction potential.

However, this misses the need to drive down development costs by earlier elimination of the molecules that will fail in development. Consider the analogy of looking for a needle in a haystack. The picture this usually evokes is one of a lengthy search through the haystack to find the needle. But actually the first step should be to burn down the haystack because the needle will be much easier to find in the pile of ash that remains. Instead of concentrating on finding the successes, the challenge of reducing late phase development attrition must be focussed on terminating development of the molecules that are unlikely to succeed, thereby decreasing development costs by reducing the expenditure on failures. Proof of concept is as much about eliminating the molecules that will fail as it is about finding the ones that might work.

'Validating' biomarkers to prove a negative

The potential value of biomarkers of clinical efficacy that can be used as surrogate markers to support drug approval is obvious. Much effort is being expended by the pharmaceutical and diagnostic industries, clinical researchers, regulators and healthcare providers, either individually or in a growing number of consortia, to identify novel surrogates for diseases such as cancer, atherosclerosis and neurodegeneration. The required level of evidence for a biomarker to be accepted as a true surrogate of the clinical endpoint is very high (Figure 1). Consider how many decades of research have been required to establish plasma cholesterol lowering as an efficacy biomarker. Developing novel biomarkers of efficacy to support regulatory approval will be a lengthy and expensive process and the impact on the costs of developing new drugs will take many years to realize.

There is much less recognition and understanding of the potential value of biomarkers to drive earlier development attrition and much less consideration of the requirements for such biomarkers. However, improved use of biomarkers to drive earlier attrition of the molecules that fail will decrease development costs and improve development productivity much more quickly than can be achieved by developing novel surrogate markers to support

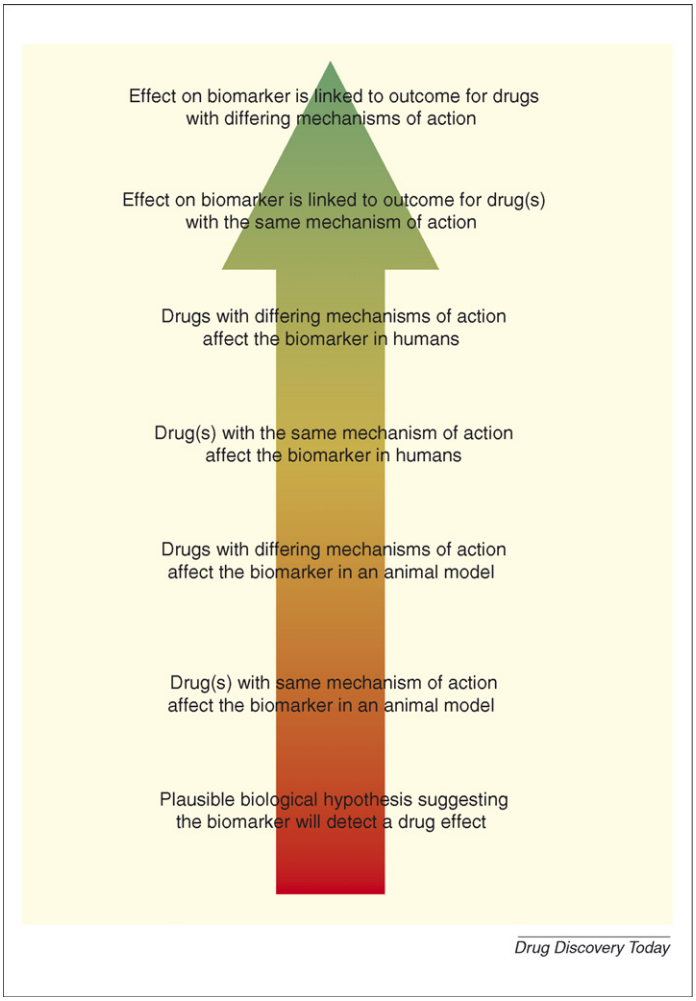

FIGURE 1

Biomarker evaluation hierarchy illustrating the type of data required to establish increasing levels of confidence in a biomarker. The minimum requirement and lowest level of validation is a plausible hypothesis linking the biomarker to the true endpoint of interest and the level of confidence in the biomarker increases as the type of data available moves up the arrow. At the top of the arrow is the type of data required to establish a biomarker as a surrogate marker of efficacy to support registration. The higher a biomarker is positioned in the hierarchy, the greater the level of confidence that it represents the true measure of interest and that it can be used to support decision making.

approval of some of the few successful drugs. Decisions to stop development of a drug candidate based on the absence of an effect on the biomarker can be very hard. Given the high attrition rates in development there is often a concern that one of the few successful molecules in the pipeline is being terminated and this concern is increased if there is doubt about the ability of the biomarker to detect the effect of the drug being tested. This is a key challenge in developing and evaluating potential biomarkers for use in early development.

To terminate a drug development project it is necessary to be confident in the predictive value of the data driving the decision. This is a challenge for decisions based on biomarkers because their predictive value is often unknown and there are several reasons why biomarkers might fail to detect the real effects of the drug under investigation [12]. Validity is not an 'all or none' phenomenon but a continuum [13], thus biomarker validation is better considered as an evaluation of the level of validity of the marker. That, in turn, depends upon the purpose for which it will be used. Biomarkers need to be 'fit for purpose' for whatever purpose they are to be used but there should not need to be rigid criteria for levels of 'fitness' or validity except when the biomarker is being used as a true surrogate of disease effect in support of drug approval. Most important is an assessment of how valid the biomarker is for the purpose or decision for which it is being used. A biomarker that will be used as the pivotal evidence for registration of a new drug requires a higher level of validity than one that will be used for a decision to continue development in phase I/II. The level of validity necessary to support a decision to stop development in the absence of effects on the biomarker will also differ. The acceptable level of validity or confidence in the marker will be different for a company that has few development projects compared with one that has far more than it can handle. The acceptable level of validity or confidence will be different for molecules with broad disease modifying impact compared with those that represent only small incremental improvement over current therapy.

In all cases, biomarker evaluation starts with identifying the decision(s) for which the biomarker is intended to be used and the level of tolerance that exists for false decisions. This step is of crucial importance in dealing with the reluctance to make decisions based on biomarkers, especially novel biomarkers, for which there is residual uncertainty about the linkage to the true endpoint. Agreement on the level of confidence required from a proposed biomarker for a specific situation provides a framework to assess whether the biomarker is fit for the intended purpose and eliminates post hoc debate about subsequent decisions based on that biomarker.

The greater the level of certainty required in the decision, the greater the level of investment required, either because there must be more extensive evaluation of the biomarker or because the development program will rely on clinical endpoint studies with no opportunity for early, cheaper terminations. The decision on the required level of confidence required of the biomarker is a balance between the size of the investment required to develop the biomarker (including an assessment of the likelihood of success) and the tolerance for an incorrect decision. The latter must take account of the impact of false progression decisions as well as false terminations. All too often the only consideration is that of not progressing a molecule that might have worked, leading inevitably to a great reluctance to make early termination decisions. However, the costs (including opportunity costs) and the typically high probabilities of false progression decisions in the face of absence of effects on biomarkers must also be taken into account in setting realistic requirements for the biomarker.

Detailed evaluation of a potential biomarker then consists of (Box 2):

- technical (analytical) validation;
- assessing operational feasibility, including cost;
- evaluating the extent of linkage to the desired endpoint.

Technical validation

Technical validation adopts the same principles as would be demanded of a bioanalytical assay including accuracy, precision, sensitivity and specificity. To illustrate with some examples, block-

BOX 2

Components of biomarker evaluation

Tolerance level for false decisions and hence the required level of confidence needed for the decision(s) based on that biomarker

- Critically dependent on the specific situation in which the marker will be used
- Generally driven by the characteristics of the situation and decision rather than of the marker
- Likely to be different for the same marker in different situations
- Consider tolerance for false negative (termination) and false positive (progression) decisions

Technical validation

- Accuracy
- Precision
- Sensitivity
- Specificity
- Normal range and variability in the population to be studied
- Expected size of change due to intervention to be studied

Operational feasibility

- Cost
- Availability (e.g. compare PET imaging with plasma cholesterol measurements
- Suitability for use in the population to be studied (e.g. compare tissue biopsies in healthy subjects compared to cancer patients)
- Inter and intra operator or site variability

Extent of linkage between marker and true endpoint (evaluation and qualification)

- Strength of biological hypothesis
- Proximity of marker to true endpoint
- Strength of preclinical data across species and across drugs
- Human data on effects of related or similar drugs on biomarker

ade of the increase in growth hormone after administration of the $5HT_{1D}$ agonist zolmitriptan [14] could be a potential biomarker of $5HT_{1D}$ antagonist activity. However, in a pilot study using ketanserin, which has $5HT_{1D}$ antagonist activity, we were unable to show a clear effect unless we considered only the subset of patients who showed an apparently reproducible growth hormone rise after zolmitriptan*. In a subsequent study to examine the reproducibility of zolmitriptan's effect on growth hormone, it seemed that there was a period effect, with decreased response on the third administration and considerable variability in response within and between subjects*. Thus, the zolmitriptan effect was considered unacceptable as a biomarker to drive decisions about the presence or absence of $5HT_{1D}$ antagonist activity. It is important to explore the sensitivity of a marker to understand whether the marker will be able to detect a pharmacologically or clinical meaningful effect and perhaps to compare between biomarkers as to which is the most sensitive or has the best balance of sensitivity and feasibility. For example, resting, supine systolic and diastolic blood pressure could be the most sensitive and most feasible indicators of the peripheral vascular effects of $5HT_{1D}$ agonists [15]. Specificity must also be explored, because other interventions or study factors may confound interpretation of changes in the marker. Serum levels of aspartate and alanine transaminase are widely used in drug studies to monitor potential liver damage yet they are also increased when subjects are fed high calorie, high carbohydrate diets, which used to be common during residential periods in clinical study units [16].

A biomarker needs to be operationally feasible to be useful. If a biomarker study is as complex and expensive as a clinical endpoint trial then it is not likely to be worth performing. Acute migraine is a good example of a disease where there is little to be gained by developing potential biomarkers of drug efficacy, because clinical endpoint trials are straightforward and relatively cheap. However, in general, phase I type studies using biomarkers are cheaper and faster than phase II clinical endpoint trials, especially if the clinical trials require longer term toxicology studies to support them.

Biomarker identification and evaluation

An understanding of the extent of linkage of the biomarker to the endpoint of interest is obviously crucial in developing and interpreting the effects of drugs on biomarkers. This step is often now called 'evaluation' or 'qualification' of the biomarker to distinguish it from technical validation. There is a hierarchy of evidence supporting biomarker evaluation (Figure 1). The more evidence that accrues and the higher up the pathway the biomarker is positioned the greater the level of confidence that the biomarker represents the measure of interest and, usually, the greater the confidence that a lack of effects on the biomarker is also a true result. The hierarchy is the same regardless of the actual endpoint of interest, whether it is pharmacological activity, safety or clinical efficacy, although obtaining evidence for novel biomarkers of pharmacological effects is generally much easier than for biomarkers of safety or clinical benefit.

Potential biomarkers are usually identified from an understanding of the pharmacology of the target or the pathophysiology of the disease or safety concern that the biomarker is intended to predict. In some cases it is possible to establish the criterion-related or predictive validity [17] of the biomarker by studying one or more existing drugs with the same or a similar pharmacology or mechanism of action or that have the desired clinical effect. Such evidence is at the top of the evaluation hierarchy and provides high confidence in that biomarker. For example, right shifting the dose–response curve for the increase in heart rate after bolus injection of isoprenaline is accepted as a biomarker of adrenergic β_1 blockade [18] because it has been shown for several β_1 blockers and viral load is generally accepted as a biomarker of the activity of treatments for hepatitis C virus [19]. Absence of effects on isoprenaline induced heart rate or on viral load in well designed trials would generally be quite sufficient to terminate development of a novel β_1 blocker or antiviral, respectively.

* Kelly, R.P. *et al.* (2004) The impact of inter- and intra-subject variability on assessing zolmitriptan induced growth hormone release. *11th International Society for Psychoneuroendocrinology,* 18–21 July 2004, Glasgow,UK. (Abstract 017).

However, many molecules in development have activities for which there are no similar agents already approved for human use. In these cases it is not possible to reach the top of the evaluation hierarchy. Yet to build confidence that the biomarker can be used to support termination decisions, it is most important to have confidence that a lack of effect is a true result and not a false negative. This comes from evidence suggesting that the biomarker is truly connected to the activity of the drug such that a lack of effect of the drug on the biomarker can be taken as evidence that the drug is ineffective and its development should be terminated. When the drug in question is novel, it is necessary to rely on face, construct, and sometimes content, validity [17] based on a sound theoretical basis for believing the drug effect to be linked to the biomarker, supported where possible by evidence from animal models that the drug does indeed affect the proposed biomarker. For example, the decrease in rapid eye movement (REM) sleep in cannabinoid CB1 receptor knockout mice and the decrease in REM sleep in rats after dosing with a CB1 antagonist [20] suggest the possibility that reduction in REM sleep could be used to define a dose response for effects of CB1 antagonists in humans. Given that there are several CB1 antagonists in clinical trials it may soon be clear whether this biomarker with construct validity actually has criterion-related validity.

To extend the example to a potential efficacy biomarker, reduction in calorie intake has obvious face validity as a biomarker for drugs that lead to weight loss by suppressing appetite and food intake. The dose responses for the effects of sibutramine on calorie intake and weight loss in humans are similar [21–23]; thus, calorie intake could be considered to have predictive validity for other sibutramine-like drugs but it also provides support to the possibility that decreasing calorie intake might be a useful biomarker of weight loss for novel, centrally acting, appetite suppressing agents with alternative molecular targets. The ability to translate calorie intake into rats and the demonstration that sibutramine has similar effects to humans in rats [24] further strengthens the construct validity of calorie intake as a biomarker for weight loss and also provides an animal model to screen potential weight loss drugs and to predict the effective doses and/or exposures that might be required. It would be reasonable to believe that a novel drug acting at a molecular target involved in appetite control and showing effects on calorie intake in rats should also show an effect in humans. The presence of a reduction in calorie intake in humans might provide confidence to proceed; its absence leads to termination of development of the molecule and perhaps also of other molecules with the same molecular target.

The final consideration in biomarker evaluation, and one of particular relevance in the evaluation of biomarkers to support decisions to terminate development, is an assessment of the proximity of the marker to the endpoint of interest [13]. The presence of drug activity on the biomarker will usually be interpreted as a reason to continue development (except of course if the biomarker is for a safety concern). The absence of an effect on a novel biomarker for a drug against a novel target will carry more weight if the biomarker is very close to the target or to the real measure of interest, because there is less potential for a false negative. Failure to detect significant receptor occupancy using a novel positron emission tomography (PET) ligand for that molecular target gives great confidence in the expected lack of drug effect, provided of course the analytical validation has been completed appropriately with robust evidence the ligand binds the animal and human receptors *in vivo* in the absence of drug and the drug has been shown to displace the ligand in preclinical studies. The same is true for biomarkers of clinical endpoints when the biomarker is close to the actual endpoint. But the more distal the marker from the true endpoint or molecular target, the greater the possibility of a lack of linkage between the marker and the endpoint and the greater the risk that negative results are a false negative.

The importance of investigating human pharmacology

To make a termination decision for development of a drug candidate based on lack of effect on a biomarker of efficacy requires confidence that the drug had the intended effect at its molecular target. In the absence of such confidence there is always concern that the lack of effect was because of inadequate dosing or that the molecule was flawed in some way that prevented it exerting the required pharmacology. If there is evidence of the required pharmacological effect it is much easier to make a termination decision for subsequent lack of clinical activity on a biomarker or a clinical endpoint. In addition, development of backup molecules with the same pharmacology can also be terminated, thereby redirecting discovery efforts to other, potentially more fruitful, targets.

Investigating human pharmacology is also important for driving early termination decisions for molecules that don't have the required pharmacological effects. Absence of the required pharmacology will lead to absence of clinical effects. If human pharmacology is investigated in the early phase I trials and found to be absent then development can be terminated and discovery efforts directed towards finding alternative molecules with improved chances of having the required pharmacology in humans. To return to the acute migraine example used earlier, although there may be little value in an efficacy biomarker, it is very valuable to have biomarkers of drug target pharmacology. Absence of effect terminates development and saves the costs of the efficacy trials but also enables these saved resources to be reused on other projects that might be effective. This opportunity cost gain can be the biggest benefit from use of biomarkers in early development.

Concluding remarks

'Proof of concept' is as much, if not more, about identifying and terminating development of molecules that will not be successful as it is about identifying the molecules that might become approved medicines. Only by giving as much focus to eliminating failures as to looking for the 'winners' can the opportunity be realized to decrease drug development costs by decreasing expenditure on the majority of molecules that fail in development. The development and use of biomarkers is crucial to success and it is important that they be chosen, developed and evaluated in a way that enables them to provide confidence to terminate a molecule when it has no effect on the biomarker. This is clearly a challenge for novel molecules that are the first in their class, but it can be achieved through building a sound theoretical rationale for the biomarker supported by evidence of linkage to the effect of the drug in appropriate animal models.

It should also be recognized that there is much value in developing biomarkers to explore the pharmacology of new molecules

as well as developing potential biomarkers of efficacy. A molecule that does not have the intended pharmacology is most unlikely to have the desired efficacy and its development can confidently be terminated. Discovery efforts would then be directed at understanding the reasons for the lack of pharmacology and finding improved molecules. For those molecules that have the intended pharmacological effect but then fail to show efficacy, it is possible to say with confidence that the molecular target is ineffective and that discovery effort should be directed to other targets. Thus, determining effects on biomarkers of pharmacology as well as efficacy will ultimately increase the overall success rates of the candidate molecules delivered into clinical development.

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