
1

INCORPORATING IMAGING INTO DRUG DEVELOPMENT: AN INDUSTRY PERSPECTIVE

PHILIP S. MURPHY

Oncology Clinical Development, GlaxoSmithKline, Stockley Park West, Middlesex, UK

DEBASISH ROYCHOWDHURY

Oncology Clinical Development, GlaxoSmithKline, Collegeville, Pennsylvania

INTRODUCTION

Significant bottlenecks in clinical development currently limit the rate at which novel medicines can progress toward benefiting the patient. Supplementing existing endpoints with qualified biomarkers would provide significant advancement over current drug development practices. Such biomarkers have the potential to expedite development, reduce program cost, and inform both internal and regulatory decision making. Medical imaging promises to be a key source of such biomarkers for drug development.

In this chapter we describe how industry is embracing quantitative imaging methodologies. Applications of imaging biomarkers are considered, with an emphasis on the challenges, including bottlenecks to development, deployment across multiple study centers, and cost. The role of industry in helping overcome these challenges is proposed. The rapid development of high-resolution morphometric methods and functional and metabolic techniques represents both excitement and challenge. The current priority is to transition existing robust radiological methodologies into quantitative decision-making

Quantitative Imaging Tools for Lung Cancer Drug Assessment, Edited by James L. Mulshine and Thomas M. Baer

Copyright © 2008 John Wiley & Sons, Inc.

2 INCORPORATING IMAGING INTO DRUG DEVELOPMENT

tools. The next challenge is to accelerate the most promising emerging techniques toward utility. The role of industry in the implementation of existing and new methodologies is discussed.

CRITICAL PATH INITIATIVE

The U.S. Food and Drug Administration (FDA) launched the Critical Path Initiative in March 2004 with a report entitled “Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products” (<http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>). This report examined why despite the numerous advances in biomedical science, the number of medical products submitted for approval has declined. A key conclusion was that a bottleneck has arisen because the applied sciences that support medical product development have not kept pace with the basic sciences. Specifically, it stated that too little effort has been given to developing new tools to understand the safety and effectiveness of new products “in faster timeframes, with more certainty, and at lower costs.” This results in significant time and money being invested in ultimately failed programs and means that even successful candidates follow a long, costly, and inefficient path toward the market.

From the recommendations provided, biomarkers for safety and efficacy were highlighted as important areas for future focus. Imaging, in particular, was identified as one of the tools where scientific innovation provides substantial opportunity, but this requires translation toward drug development utility through extensive and collaborative efforts.

IMAGING AS A CRITICAL PATH TOOL

The Critical Path Initiative report in 2004 was seen as the first step to guide further consultation with public and private stakeholders. In March 2006, the “Critical Path Opportunities Report” was published to define specific areas of focus warranting further work (http://www.fda.gov/oc/initiatives/criticalpath/reports/opp_report.pdf). Biomarker development was emphasized as one of six key areas of focus with requirements for standardization and qualification highlighted for imaging. Subsequently, a list of tangible opportunities was published (<http://www.fda.gov/oc/initiatives/criticalpath/opportunities06.html>). Under the title “better evaluation tools,” initiatives relevant to imaging include:

1. Development of a concept paper on biomarkers, aiming to provide a conceptual framework around biomarker development and application.

2. Qualification of oncology biomarkers, describing a collaborative effort to qualify cancer biomarkers. Through these collaborative activities, projects aim to assess the performance of fluorine-18-labeled deoxyglucose positron-emission tomography (FDG-PET) for defining patient response in the study of non-Hodgkin's lymphoma and non-small cell lung cancer.
3. The launch of the Biomarkers Consortium to identify, promote, and accelerate the qualification of biomarkers for various diseases.
4. Development of standardized protocols for imaging application in clinical trials. This was a clear recognition that the diversity of imaging acquisition, analysis, and interpretation presents a significant challenge to the use of imaging biomarkers for consistent decision making within and across the industry.

These broad aims are complementary and should, in concert, promote imaging biomarker development and successful deployment. In particular, development of standardized acquisition protocols will facilitate efficient and cost-effective qualification of biomarkers. There is optimism that activity resulting from these initiatives will promote currently accepted radiological techniques, such as high-resolution computed tomography (CT) and FDG-PET, toward quantitative decision-making tools. In addition, it will define a path by which future advancements in image acquisition and analysis can follow to provide maximum impact on novel product development.

HOW IMAGING ADDS VALUE

There is widespread multitherapeutic area use of imaging within drug development [1–3]. Imaging is likely to continue to increase our understanding of tumor biology from studies of experimental models through to clinical manifestations. Within drug development specifically, imaging is likely to have a significant impact in three broad domains: (1) progressing our understanding of tumor biology, (2) translational imaging to bridge preclinical models to the clinical condition, (3) clinical imaging for internal program decision-making at Phase 1 and 2, and (4) acquiring evidence of disease response to therapy to support regulatory submissions at Phase 3.

Translational Imaging

One of the key advantages of imaging-derived biomarkers relates to the translatability between a preclinical model and the clinical condition. This can potentially (1) allow studies of pharmacology, particularly studies of dose

4 INCORPORATING IMAGING INTO DRUG DEVELOPMENT

and dose scheduling; (2) allow study of the intrinsic relationships between a preclinical model and the clinical condition, potentially highlighting discordance; and (3) be used to plan and qualify clinical imaging biomarkers by providing histological correlation and acquisition of multiple imaging time points that may not be clinically practical. However, to compare the biology rather than methodological differences, careful implementation is required between the clinical and preclinical imaging platforms. This represents a considerable challenge, owing to the disparity between imaging hardware and other aspects of the experimentation (e.g., anesthesia requirements for animal experimentation). Many imaging-derived endpoints are theoretically independent of hardware (e.g., standard uptake values for FDG-PET, K^{trans} from dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) time series data, tumor volume from high-resolution CT), but hardware will influence such measurements if careful calibration and implementation are not carried out. Significant attention to the imaging acquisitions is required to enable a successful comparison. This can be achieved by close collaboration between clinical and preclinical imaging groups within industry. If the technical challenges can be overcome, translational imaging offers a key bridge, potentially reducing the risk of failure of compounds in early clinical development.

Early Development

There are multiple examples of imaging techniques applicable to support programs in Phases 1 and 2. Here imaging can be used to study dose and dose scheduling; provide early indicators of efficacy, describe aspects of mechanism, and can potentially be applied to patient stratification. As examples of commonly applied techniques, FDG-PET can be used to demonstrate early pharmacological activity [4, 5] and DCE-MRI can verify the drug mechanism for antiangiogenic targets [6, 7]. Although functional imaging endpoints remain important, improvements in morphometric description of tumor response could readily be applied at such a stage of drug development. For internal decision making, there should be sufficient confidence in an imaging technique to support go/no-go decisions and sufficiently de-risk subsequent candidate investment. The use of informative imaging components within Phase 1 and 2 studies is likely to increase, ensuring that the best candidates progress to pivotal Phase 3 studies, and consequently, that program costs are reduced. Furthermore, early development can provide an important framework to enable novel imaging biomarkers to be explored.

Late Development

There are limited opportunities currently for the use of imaging in Phase 3 studies other than to define tumor response with simple morphological

description [i.e., the Response Evaluation Criteria in Solid Tumors (RECIST)]. For any new imaging acquisition and analysis combination, a substantive body of evidence is required to demonstrate surrogacy and therefore the potential for such an endpoint to support a regulatory submission. Furthermore, novel imaging techniques may prove too costly for ultimate Phase 3 application. It has been suggested that biomarkers could be used for patient stratification in clinical studies and subsequently to define the treatment of patients with approved medicines [8]. For such approaches to become more widespread there is a need for further industrialization of biomarkers, together with acceptance of an adjusted business model for product development.

Imaging techniques currently used in early development may not progress to wider use in late stage development. Many imaging methods used in early development will always be restricted to that domain; for example, the method is too complex to be robust across multiple sites, or a signal of mechanism doesn't clearly relate to efficacy. Nevertheless, such methods will continue to be valuable. However, some methods such as FDG-PET and high-resolution CT morphometry may ultimately transition toward broad late-stage use for some applications, although the cost implications will need to be considered carefully. By focusing on the current use of imaging in early development, we can infer future issues faced by potential Phase 3 applications, such as measurement robustness, methodological and biological reproducibility, cross-center/cross-scanner manufacturer limitations, site training requirements, imaging and data processing needs, and imaging expertise of third-party imaging core labs. There is significant momentum from both ongoing activities and critical path plans that will reinforce the importance of developing imaging science to meet the needs of clinical drug development. In addition, the growing role of functional and metabolic imaging technologies within routine clinical practice (for example, staging of lymphoma with FDG-PET) will add to this momentum, driving the scientific acceptance and accessibility for clinical trial use.

DEVELOPING NEW IMAGING BIOMARKERS

It is apparent that new imaging endpoints are required with either greater linkage to disease, increased mechanistic insight, or greater sensitivity to a given class of drug. Within the last 20 years, developments in the primary imaging modalities [MRI, CT, PET, single-photon-emission CT (SPECT), ultrasound] have been immense. A combination of new hardware, new tracers, and image analysis methods are contributing to major improvements in morphological descriptors of disease, together with delivery of novel and improved physiological and metabolic imaging methods [9]. For example,

6 INCORPORATING IMAGING INTO DRUG DEVELOPMENT

tracer developments for use with PET or SPECT will provide increasing specificity to the pathophysiology and its response to treatment [10, 11]. Newer contrast mechanisms available from MRI, such as diffusion-weighted imaging, will define aspects of tumor physiology and microstructure [12]. High-resolution CT, in combination with image analysis tools, will enable ever smaller changes in tumor extent to be described or substructural measurements such as lesion heterogeneity to be investigated. How do we take these techniques and advance them toward a more industrialized use within drug development? First, industry needs to triage the collection of new imaging opportunities and select the most promising techniques for further investment.

To advance an imaging biomarker toward clinical trial utility, a number of basic requirements should be met. For this, a methodology trial may be necessary to establish some basic knowledge around the robustness, biological linkage, and practicality of a given imaging biomarker. A number of issues must be considered for each imaging biomarker, as we discuss next.

Qualification

To use an imaging endpoint for regulatory purposes, extensive data collection is required. A framework guiding the qualification of a biomarker will be a likely output from the critical path initiative. To qualify a biomarker for a given use in early development, sufficient information needs to be amassed to establish confidence that it can be used for a given purpose. Questions may include: Is the imaging endpoint sufficiently understood for its intended purpose, and is there histological correlation? Has treatment response been defined previously using the technique? Is reproducibility known to enable sufficient statistical powering to be determined? Such qualification steps may be undertaken through (1) a company-funded methodology development program, (2) implementation into existing clinical trials where the imaging is performed solely for exploratory purposes, or (3) consortia-funded programs.

Standardization Across Multiple Centers

Clinical programs are constantly challenged to deliver clinical trials in a timely and cost-efficient manner. To achieve this, clinical trial sites are carefully selected to deliver the necessary recruitment, clinical trial proficiency, and medical expertise. If imaging is to be incorporated across industry, the necessary techniques need to be available across multiple trial sites. For Phase 1 or Phase 2 trials, studies are generally conducted at relatively few sites, commonly at large academic centers where imaging infrastructure and

expertise are generally accessible. However, when large Phase 3 studies are required, expediency of patient recruitment is a priority. Here, centers may be selected where imaging resource, infrastructure, and experience of clinical trial imaging are limited to diagnostic radiology. Therefore, depending on the stage of clinical development, the standardization is markedly more or less challenging.

For a given clinical trial endpoint, multiple options must be considered before a technique and a protocol are chosen and deployed. For example, to measure tumor response to an antivascular/antiangiogenic therapy, numerous techniques could be chosen: DCE-CT, DCE-MRI, power Doppler ultrasound, and [^{15}O]H $_2$ O PET. All potential approaches need to be considered carefully for a given study, with all factors taken into account: the biophysical parameter that needs to be characterized; the number of study sites and the probable imaging expertise at those sites; the probable tumor location and size; cost; and translatability to preclinical application, if required. Further studies are required to inform such decision making, particularly comparing techniques such as DCE-MRI and DCE-CT. Even after a modality is chosen, there are multiple technique types and acquisition options to select. For structural definition of response, issues are different but no less challenging. There exists currently little standardization of acquisition parameters for techniques used across different clinical trials. This is partly due to the diversity of hardware across clinical trial sites and to a lack of consensus.

Imaging standardization should be considered an ongoing process by which imaging protocols are optimized to account for differences in hardware and software of the platforms used across multiple centers (within studies and across studies). Since imaging hardware is always evolving, exemplified by the development of multislice CT scanners and the latest MR advancements, especially field strength and parallel imaging, this will always be a continual process. Also, many of the technical changes mark highly significant advancements in imaging that can be exploited in drug development. These can potentially result in more robust, reproducible, and sensitive measurements. Balancing the need for consistency across studies with the need to embrace new and improved methods is challenging.

There are many benefits of achieving standardized imaging protocols within a given company and across the industry. First, it reduces the risk of methodological failure of the imaging within a trial. Also, it allows comparison of results between studies, ultimately enabling candidates to be compared. By keeping the acquisition and reporting the same, data can be collected across multiple programs in order to begin metaanalyses. If clinical indices can be stored alongside imaging results, such a repository will enable data to be assessed against clinical outcome, supporting qualification and therefore future biomarker application.

8 INCORPORATING IMAGING INTO DRUG DEVELOPMENT

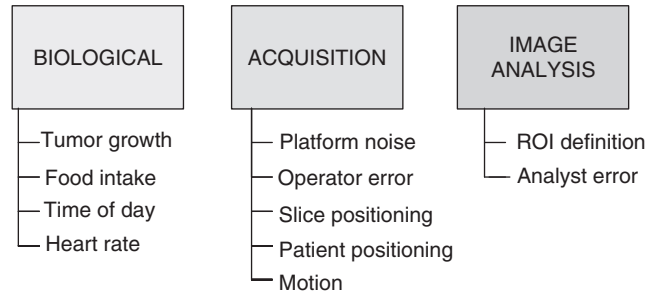


FIGURE 1 Factors that may contribute to measurement variability. This assumes that measurements were undertaken on the same acquisition platform and that image analysis was performed using the same software.

Reproducibility

The purpose of the imaging experiment is to define the impact of drug intervention. Many drug-independent parameters have the potential to add variation to an imaging measurement (see Figure 1). The aim of producing a carefully developed standardized protocol is to minimize these factors to an acceptable level. For each technique, reproducibility should be quantified to ensure that sufficient statistical power is achieved for a planned trial. Without this it may not be possible to interpret a clinical trial endpoint: Is a lack of response due to an ineffective drug or to poor methodological performance?

Previously published studies of reproducibility are important to guide study planning and can also indicate general robustness of a biomarker. Examples have been published for DCE-MRI, FDG-PET, and CT lesion size [13–17]. However, it is important to measure reproducibility within a given clinical trial setting. For that reason, where practically possible it is always advantageous that a repeat baseline scan be acquired to get a study-specific measure of reproducibility.

More data are required on quantitative imaging reproducibility. It is important to study what factors contribute to variation in a given method. In doing so it may be possible to improve measurement reproducibility and thereby reduce sample size.

In addition to reproducibility, general robustness is important. How frequently will the equipment or technique fail? During an imaging procedure involving administration of a tracer or contrast agent, it may not be possible to rescan for at least 24 hours, or longer. Therefore, if a scan failure occurs, costly data can easily be lost. This issue may be particularly pertinent for new imaging hardware for which extensive field testing has not been performed.

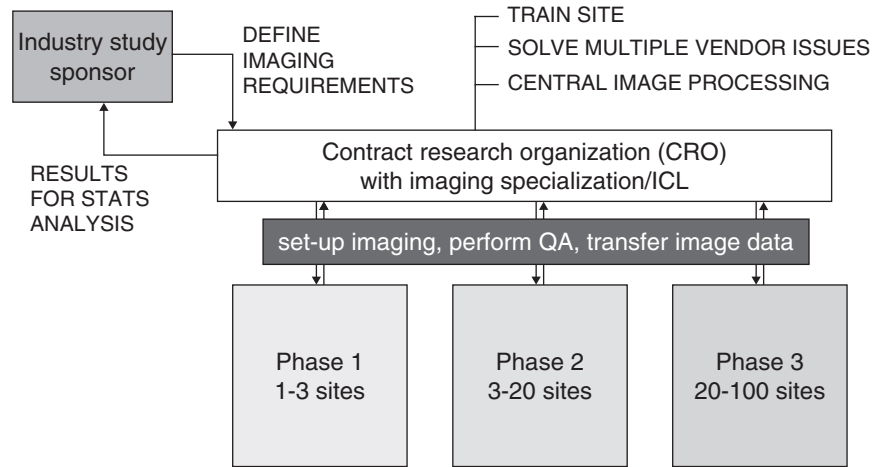


FIGURE 2 An overview of image acquisition and analysis management within a clinical trial.

PRACTICAL IMAGING IMPLEMENTATION

Within industry a simple, transparent, and process-driven approach to imaging is required. After selection of an imaging endpoint, an implementation plan is needed to ensure successful deployment and analysis of the imaging without delaying the start of a clinical study. Many components of the imaging can be developed generically in advance: for example, systems for storing data, processes for data transfer, standard case report forms, and site education modules. Then study-specific activities are required to prepare sites for standardized imaging, such as protocol-specific training. Many of these activities are commonly undertaken in collaboration with a third-party CRO with imaging expertise, as outlined in Figure 2.

Figure 2 provides an overview of how imaging may be performed within industry where central analysis is performed. Typically, the study-sponsoring company selects an imaging technique through previous experience or consultation with external experts. The imaging requirements are communicated to a third-party contractor/imaging core lab (ICL). Such companies have extensive and up-to-date experience of imaging across multiple sites with different imaging platforms so they can readily assess feasibility. Their role is to ensure successful translation of the concept to trial use. They have multiple tasks in managing the imaging component of the trial, including assessment of site imaging facilities, provision of site education, quality assurance at selected intervals during the study, and coordination of image transfer from the study sites for central reading. Centralized image analysis is then performed

10 INCORPORATING IMAGING INTO DRUG DEVELOPMENT

before results are tabulated and sent to the sponsoring company for statistical analysis.

With increasingly complex imaging techniques comes an increase in the complexity of the process to train sites, acquire, and analyze data. A clear work flow is required to ensure quality of acquisition, processing, and reporting. Imaging core labs will need to adapt their processes and expertise from the relatively simple endpoints they currently provide as imaging endpoints evolve. Where centralized reading is not performed, standardized site training is paramount to ensure consistency of imaging interpretation.

ROLE OF INDUSTRY IN IMAGING BIOMARKER DEVELOPMENT

Oncology imaging biomarkers will be advanced only through extensive collaborative work. This will ensure that consensus is reached around technical protocols and that sufficient funding is available to support large qualification studies. Industry can be a key contributor to biomarker development through the following areas:

1. *Investing in and facilitating biomarker development.* Industry can directly fund, manage, and publish methodological investigations that support the use of biomarkers. The drug development process provides a framework to develop imaging biomarkers since patients are typically well phenotyped and histological correlates may be available. If no ongoing programs are able to support biomarker development, dedicated methodological studies may be required.
2. *Sharing requirements and educating.* Since industry is a major user of new endpoints, it is important that industry requirements are communicated unambiguously to academic partners, ICLs, and imaging equipment vendors. For specific studies, industry can provide education programs to promote consistency of measurement across multiple centers. This is exemplified by tumor size measurements undertaken at various centers which frequently lead to high variability. Education programs around such measurements can remedy these problems.
3. *Developing and maintaining imaging experience.* A core expertise within industry is needed to manage imaging biomarker development. This will promote the utility of quantitative imaging for drug development and act as a bridge between external imaging expertise at academic sites and ICLs. Internal expertise will promote imaging as a core component of the drug development business model.

4. *Contributing to protocol consensus.* Together with ICL partners, the pharmaceutical industry has developed extensive experience in cross-center imaging implementation and more recently, with functional imaging biomarkers. Therefore, industry often offers an important pragmatic view when developing consensus on imaging protocols.
5. *Establishing databases to facilitate metaanalyses.* Industry is in an opportunistic position to develop large multistudy standardized imaging databases given the number of imaging studies that are performed. Relationships between imaging and either long-term outcome or acute treatment response can be studied. Furthermore, such databases can be used to identify and refine new image analysis methods. Initially, such databases are likely to be accessible within a company, and associations between imaging and other parameters can be published. However, through consortia there is a potential to expand such databases and study relationships across multiple tumor types within a shorter period of time. Many of the biomarker qualification challenges will be overcome only through such data collection opportunities via expanded consortia. An example of such a concept is the NCI: RIDER project (see Appendix A). This initiative was instigated to build an imaging database (CT and PET-CT) to facilitate the development of new tools for use in lung cancer clinical trials.
6. *Broadening biomarker application throughout the company.* Although cancer imaging is the focus of this review, other disease areas within industry benefit from imaging (central nervous system and cardiovascular, in particular). It is important that cross-therapeutic area benefits be gained from imaging investments. In addition to the cost benefit, breadth of application may enhance biomarker qualification. For example, DCE-MRI has been used to describe abnormal vasculature in multiple indications, including rheumatoid arthritis and Crohn's disease. Some of the standardized methodologies developed for oncology could be used across these areas. Other examples should be sought to emphasize the value that imaging brings.

CHALLENGES TO IMAGING APPLICATION WITHIN CLINICAL TRIALS

Drug development will benefit from the data that can be collected from the latest generation of morphological, functional, and metabolic imaging techniques. The extent to which new drugs will be accelerated through development at a lower cost will depend on acceptance of techniques throughout

12 INCORPORATING IMAGING INTO DRUG DEVELOPMENT

the scientific community. It will also depend on the rigor and expediency of biomarker development. More tangible examples are required where a favorable cost–benefit relationship has been demonstrated. In addition, return on investment (ROI) needs to be quantified, taking into account failed biomarker development. There is enthusiasm, but industry is aware of the challenges faced:

1. *Time required to develop new imaging biomarkers.* Imaging biomarker development is currently slow and costly. FDG-PET has been in clinical practice for many years and is only beginning to demonstrate a consistent role in clinical drug development. A clear framework for biomarker development will partly address this issue. Furthermore, collaboration between industry partners, academia, and other bodies has the potential to speed up biomarker development by rapid collection of large volumes of standardized data, as described previously.
2. *Stage at which to invest.* At a given point in time there are hundreds of potential imaging biomarkers, ranging from nascent through promising to developed. Industry cannot invest in research programs to assess all potential avenues and will tend to avoid immature technologies. Industry is likely to invest in biomarker development only when a technique has been developed to the point where some biological linkage has been established and a clear route to clinical trial implementation can be envisaged.
3. *Ever-increasing diversity of hardware and software systems.* The issue of different platforms is likely to continue to challenge our ability to use imaging. It is likely to get more complex, not less. To overcome these problems, extensive collaboration with ICLs, imaging equipment vendors, and academic experts is required. This should aim to minimize the impact of technical evolution while benefiting from real improvements. This issue gives credence to the idea that successful imaging endpoints should be simple.
4. *Transparency of software systems.* To achieve consistency of analysis across the industry for a given application, it is imperative that data analyzed with one software system be comparable with another (given the inconsistency of any manual intervention). However, it may not necessarily be in the interests of software development companies or ICLs to harmonize measurements among one another. It may be part of their business model to differentiate their capabilities from other vendors, offering more elaborate analyses and improving performance. As endpoints become increasing complex (e.g., the quantified heterogeneity of a lesion measured by CT or perfusion endpoints extracted

from a DCE-CT time series), software systems are likely to diverge. A greater transparency of software platforms will be required to ensure consistency of parameters extracted. Such transparency will still need to ensure a favorable business environment for software vendors and ICLs to ensure market competitiveness of products and services. If transparency of software systems is not possible, demonstration of equivalence between two software systems is required using test data sets.

5. *New contrast agents.* Many opportunities exist in the development of targeted tracers using PET, SPECT, or MRI methodology. Although there are multiple preclinical examples, it remains to be seen how many of these agents will become approved and widely applicable to clinical trials [18]. Even with a clear business rationale and a successful development program, getting such tracers to market is slow. However, the development of the exploratory IND offers a new paradigm by which new agents, including molecular imaging agents, could be assessed at a very early stage and development expedited [20].

CONCLUSIONS

The use of imaging in industry is necessarily conservative. The use of very novel approaches with little qualification may add further uncertainty if results cannot be explained. This will add further risk to the already challenging environment of drug development. However, the promise of a new generation of more specific and sensitive endpoints could overcome some of the bottlenecks currently facing oncology drug development. Initiatives involving qualification activities around FDG-PET are likely to create a structural framework within which future imaging endpoints can be developed. For incorporation into drug development, new imaging endpoints need to be significantly qualified and offer robust performance across multiple centers. These issues should be assessed via dedicated methodology studies or as additional exploratory endpoints in ongoing programs.

Cost is an important consideration for both deployment of existing techniques and development of new methods. For incorporation of existing techniques (such as FDG-PET), will the expenditure reduce program cost by reducing study size, duration or reducing the risk of failed compounds progressing or will the data collected benefit future programs? As current exploratory methods become accepted into routine practice, cost is likely to reduce. However, for many techniques cost will continue to be prohibitive for extensive use within large clinical trials. Although imaging can be performed

14 INCORPORATING IMAGING INTO DRUG DEVELOPMENT

on a subset of patients to reduce costs, will sufficient data be generated to benefit the study? Such questions need to be carefully considered for a given study and the value needs to be quantified if the acceptance of imaging within oncology drug development is to be increased.

Although novel endpoints will likely improve the efficiency of cancer drug development, with associated high development costs, there must be caution around how quickly novel endpoints can demonstrate financial return. Significant time and finance are required to conceptualize, develop, and qualify new quantitative imaging techniques as biomarkers. However, through collaborative efforts, development can be expedited. Key examples are required to demonstrate return on financial investment to ensure that funding is available to demonstrate the next generation of imaging-derived biomarkers.

REFERENCES

1. Beckmann N, et al. Magnetic resonance imaging in drug discovery: lessons from disease areas. *Drug Discov Today*. 2004; **9**(1): 35–42.
2. Frank R, Hargreaves R. Clinical biomarkers in drug discovery and development. *Nat Rev Drug Discov*. 2003; **2**(7): 566–580.
3. Rudin M, Weissleder R. Molecular imaging in drug discovery and development. *Nat Rev Drug Discov*. 2003; **2**(2): 123–131.
4. Kelloff GJ, et al. Progress and promise of FDG-PET imaging for cancer patient management and oncologic drug development. *Clin Cancer Res*. 2005; **11**(8): 2785–2808
5. Stroobants S, et al. 18FDG-positron emission tomography for the early prediction of response in advanced soft tissue sarcoma treated with imatinib mesylate (Glivec). *Eur J Cancer*. 2003; **39**(14): 2012–2020.
6. Hylton N. Dynamic contrast-enhanced magnetic resonance imaging as an imaging biomarker. *J Clin Oncol*. 2006; **24**(20): 3293–3298.
7. O'Connor JPB, et al. DCE-MRI biomarkers in the clinical evaluation of antiangiogenic and vascular disrupting agents. *Br J Cancer*. 2007; **96**(2): 189–195
8. Trusheim MR, Berndt ER, Douglas FL. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. *Nat Rev Drug Discov*. 2007; **6**(4): 287–293.
9. Workman P, et al. Minimally invasive pharmacokinetic and pharmacodynamic technologies in hypothesis-testing clinical trials of innovative therapies. *J Natl Cancer Inst*. 2006; **98**(9): 580–598.
10. Gambhir SS. Molecular imaging of cancer with positron emission tomography. *Nat Rev Cancer*. 2002; **2**(9): 683–693.
11. Weber WA. Chaperoning drug development with PET. *J Nucl Med*. 2006; **47**(5): 735–737.

12. Matoba M. Lung carcinoma: diffusion-weighted MR imaging – preliminary evaluation with apparent diffusion coefficient. *Radiology*. 2007; **243**(2): 570–577.
13. Erasmus JJ, et al. Interobserver and intraobserver variability in measurement of non-small-cell carcinoma lung lesions: implications for assessment of tumor response. *J Clin Oncol*. 2003; **21**(13): 2574–2582.
14. Parker GJ, Roberts C, MacDonald A, et al. Experimentally-derived functional form for a population-averaged high-temporal-resolution arterial input function for dynamic contrast-enhanced MRI. *Magn Reson Med*. 2006; **56**(5): 993–1000.
15. Jackson A, et al. Breath-hold perfusion and permeability mapping of hepatic malignancies using magnetic resonance imaging and a first-pass leakage profile model. *NMR Biomed*. 2002; **15**(2): 164–173.
16. Jackson A, et al. Reproducibility of quantitative dynamic contrast-enhanced MRI in newly presenting glioma. *Br J Radiol*. 2003; **76**(903): 153–162.
17. Weber WA, Schwaiger M, Avril N. Quantitative assessment of tumor metabolism using FDG-PET imaging. *Nucl Med Biol*. 2000; **27**(7): 683–687.
18. Nunn AD. The cost of developing imaging agents for routine clinical use. *Invest. Radiol*. 2006; **41**(3): 206–212.
19. Maclean D, Northrop JP, Padgett HC, Walsh JC. Drugs and probes: the symbiotic relationship between pharmaceutical discovery and imaging science. *Mol Imag Biol*. 2003; **5**(5): 304–311.
20. Kummar S. Compressing drug development timelines in oncology using phase ‘0’ trials. *Nat Rev Cancer*. 2007; **7**:131–139.

