Report of Task Force II: Best Practices in the Use of Medical Imaging Techniques in Clinical Trials

Consensus from a Public Meeting, October 16–17, 2007
The Medical Imaging Stakeholders Call for Action: Harmonization Across Key Elements and Integration of Imaging in Therapeutic Development—Pharmaceutical Industry, CRO, FDA, and Allied Working Groups Collaborate for Regulatory Guidance

Robert Ford, MD
Chairman, Task Force II; Cofounder and Chief Medical Officer, RadPharm

P. David Mozley, MD
Cochairman, PhRMA Imaging Group, PhRMA Innovation and Research Committee

There are few explicit guidelines governing how independent imaging core laboratories should operate or manage the procedures they use to support clinical trials of investigational new drugs. This task force was charged with harmonizing, and in some cases standardizing, the operating procedures that are used to analyze images by central laboratories. A group of about twenty-five imaging professionals worked to produce consensus on exactly what constituted good imaging practices by imaging core laboratories. The task force held bimonthly teleconferences, participated in three face-to-face meetings, and often split itself into smaller subgroups to address specific topics. The task force found that a variety of imaging operation and analysis approaches are common across most medical imaging techniques and therapeutic areas. Many seem to meet minimum threshold criteria for classification as good imaging practices, as defined by their ability to deliver reproducible, truly independent, and unbiased assessments that characterize the impact of drugs on the state of disease. This report describes some of the procedures that seem essential for using medical imaging techniques to support new drug applications.

Key Words
Independent review; Central review; Imaging core labs; Medical imaging; Clinical trials

Correspondence Address
Robert Ford, MD, RadPharm, 100 Overlook Center, Princeton, NJ 08502 (email: ford@radpharm.com).

INTRODUCTION TO THE SUPPLEMENT OF REPORTS ON THE USE OF MEDICAL IMAGING TECHNIQUES IN CLINICAL TRIALS

In October 2006, officers in the US Food and Drug Administration (FDA) met face-to-face with a group of imaging specialists representing (1) the Pharmaceutical Research and Manufacturers Association (PhRMA), (2) the imaging core laboratory (ICL) or imaging contract research organization (I-CRO) industry, and (3) a variety of other imaging stakeholders from academic, government, and allied institutions. The FDA observed that practices for using medical imaging techniques in clinical trials sometimes appear to vary widely. While acknowledging the need to make imaging fit for purpose might require unique elements of image acquisition and analysis for each clinical trial, the agency challenged the field to standardize those elements that were common to good imaging practice. In particular, the FDA officers observed that (1) the format of most imaging charters seemed very different, even though most of the key elements they contained were the same; (2) the definitions of some of the terms seemed to vary, and some of the differences appeared to be meaningful; (3) the standard operating procedures (SOPs) by which central reading laboratories conducted the image analyses were often similar but sometimes different in ways that could have a meaningful impact on the outcome; (4) sites around the world that participated in clinical trials often handled the images differently; and (5) the statistical methods for handling the results were likewise often similar but sometimes meaningfully different. On the basis of these observations, a group of professionals who use medical imaging techniques to augment new drug development made a commitment to work together in a public forum with

Submitted for Publication: May 9, 2008
Accepted for Publication: May 20, 2008

a goal to produce recommendations for using imaging in drug development that the FDA could react to as indicated.

Imaging research per se and the use of imaging in exploratory medicine were both classified as outside the scope of the mission. The practice of medicine was not considered. On the contrary, attempts were made to clearly demarcate sharp lines between real-time patient management and research that takes place much later in places that are completely isolated from clinical settings.

Representatives from most of the biopharmaceutical companies who belong to PhRMA, over 20 I-CRO companies, many academicians, and a number of officers employed by the FDA eventually participated. After several months of preliminary work, the greater group divided itself into four task forces as follows:

- Task Force I was charged with standardizing imaging charters. They were asked to define what an imaging charter should be and describe a variety of intimately associated documents that should govern image acquisition, processing, transfer to a central image analysis facility, and archiving.
- Task Force II was asked to characterize the procedures that constitute good imaging practice by independent image analysis laboratories.
- Task Force III was tasked with harmonizing the interface between local imaging facilities that acquire, process, and transfer scans to central laboratories.
- Task Force IV addressed statistical descriptors of imaging outcome measures.

Each task force was required to generate definitions of the terms they used. Many of the definitions they eventually agreed to were compiled in the lexicon that is still under development.

The mission statement adopted by each task force was endorsed by the greater group at a meeting cosponsored by the FDA and Drug Information Agency (DIA) in the Washington, DC, area in June 2007. Drafts of reports by each task force were written, distributed, and then presented at another public meeting held in October 2007. Feedback from peer review was incorporated into each of the reports that follow.

These reports represent the recommendations of an informal coalition of imaging specialists who work in drug development. Individual officers from the FDA actively participated. However, their participation does not reflect endorsement by the FDA, and should not be misconstrued as guidance from the FDA. In fact, the approximately 150 imaging specialists who contributed to these reports do not claim to represent the entire field, nor claim to have fully captured the state of the art. Rather, these reports try to describe current practices by most biopharmaceutical companies and ICLs whose work is primarily, if not exclusively, devoted to new therapeutic drug development. One of the goals of publishing them in this forum is to facilitate wider peer review and invite criticism in the hope of continuously improving the process of transforming drug development with medical imaging techniques.

GENERAL INTRODUCTION

The goal of using imaging outcome measures in clinical trials of investigational new drugs includes enhancing the safety of human research subjects. Enhanced safety follows from the power of medical imaging techniques to quantify the impact of drugs on human health when compared to the use of ordinary or invasive clinical assessments. The basis for this claim is that imaging can reduce the number of subjects who need to be exposed to a relatively unknown new chemical entity, and can decrease the length of time the subjects need to take the drug before its impact on their health can be quantified. As a consequence, imaging can sometimes speed the termination of drugs that will ultimately fail or increase the rate at which successful new drugs are delivered to patients with unmet medical needs. However, the effectiveness of medical imaging in clinical trials seems highly dependent on the design and execution of the study. Decisions about how the image analyses will be performed can be mission critical. Potentially important new drugs have been approved on the basis of imaging alone before clinical outcome measures have become available.[1–4] On the other hand, the design or execution of some trials

that relied on imaging as a primary or secondary outcome measure has been controversial.[5,6]

Sometimes, trials that succeed can be compared to trials that fail, but the distinctions are not always obvious. Some formal guidance by regulatory agencies has been issued,[7] but there is little specific information on how to best operate an independent ICL. The long-term goal of this task force is to promote the continuous evolution of the use of imaging in clinical trials by describing some of the best practices that can be relied on to produce truly independent and unbiased assessments of drug effects in clinical trials. These best practices should be incorporated into the independent review charter (IRC) as procedures to be followed during the course of the independent review. Regulatory agencies (eg, FDA) identify the imaging review charter as a key document in trials that use imaging as an endpoint.

The specific aims were (1) to identify, harmonize, and in some cases standardize, definitions, procedures, and processes for conducting independent image analyses in clinical trial settings where imaging outcome measures serve as a primary or secondary endpoint of safety or efficacy; (2) to promote real-time feedback, discussion, and reaction to the work by the FDA; and (3) to produce reports that foster wider peer review and thereby eventually provide content that supports future regulatory guidance documents issued on these topics.

METHODS

Task Force II, on best practices, attempted to describe operating procedures by independent central ICLs that produce truly independent and unbiased assessments of drug effects on human diseases. The precise mission statement and charge were developed and subsequently endorsed by the greater group during a meeting held in Washington, DC, on June 7, 2007. Task Force II was composed of about 25 imaging experts from the pharmaceutical industry, ICL industry, academia, governmental research organizations, and patient advocacy groups. It was guided by informal advice on processes and procedures from scientists within the FDA. Most of the work was conducted virtually through mass emailings that were open to any interested stakeholders. The DIA sponsored bimonthly teleconferences to discuss the work products that would be delivered. Drafts of the report were widely distributed and then reviewed at a public meeting held with the FDA and other stakeholders on October 16–17, 2007. A transcript of the proceedings may be found on the DIA website.[8]

Efforts were made to invite participation by all interested academic groups, ICLs, and pharmaceutical companies belonging to PhRMA, as well as a variety of other stakeholders.

A list of priorities was developed. Weighting factors that contributed to the list included the amenability of an item for progress during a 6–12-month time frame. Some topics were assigned a lower priority than might be expected when only their scientific importance was considered, simply because some of the issues surrounding them did not seem immediately translatable into action items for the field or the regulatory agencies. These needs will be addressed during future iterations of the task force.

Task Force II developed a grid of nine parameters describing image analysis practices across five therapeutic areas: oncology, rheumatology, osteoporosis, the central nervous system, and cardiopulmonary medicine. An attempt was made to identify features that were common to all of these therapeutic areas.

Subgroups of the task force were formed during the course of this project. These subgroups were made up of volunteers who agreed to address specific issues and write up subsections of the text that follows in the results section. These snippets were distributed to the entire task force multiple times for peer review. The work of the task force was presented to a relatively wide audience of stakeholders at the DIA meeting Medical Imaging Stakeholders Call for Action: Harmonization Across Key Elements and Integration of Imaging in Therapeutic Drug Development—Pharmaceutical Industry, CRO, FDA, and Allied Working Groups Collaborate for Regulatory Guidance, held October 16–17, 2007, at

TABLE 1

Blinding: Features of a Case That Image Analysts Should Not Know
Treatment arm (or any data that might unblind the treatment arm)
Subject demographics
Clinical data other than as described in the IRC
Site assessments (including site choice of lesions)
Results or assessments of other reviewers participating in the reading process (except during adjudication)
Situation-specific descriptions of the images (such as confirmation or end of treatment scans)
Total number of time points for a subject
Exam date if randomized temporal presentation is used (see text)

the University of Maryland Marriott Conference Center in Adelphi, Maryland. The task force asked officers from the FDA many specific as well as general questions. Responses by individual officers in the agency, as well as participants from a wide variety of allied organizations, were noted and accounted for. A transcript may be found at the website cited in Reference 8.

RESULTS

Task Force II found that the following procedures and practices are sufficiently well established to justify endorsement at this time.

REVIEWER BLINDING

In order to fulfill requirements for truly independent image analysis or assessment and ensure that the results are unbiased, the circumstances to which reviewers must be blinded should be identified in the IRC. It is understood that the circumstances may be specific to the therapeutic area. Examples of circumstances to which reviewers may be blinded are listed in Table 1.

In order to promote the independence of the central image analyses, Task Force II also recommended that reviewers should be restricted from communicating with sites during the course of a trial. When using novel or complex imaging procedures, if sponsors need to set up central imaging experts as resources for local sites to use in patient management, then these experts should be distinct from, and have no communication with, the independent reviewers who will eventually produce the outcome measures in support of registration.

REVIEW PARADIGM

Reviews can be performed for eligibility, safety, or efficacy. The review paradigm may be different given the type of review and the type of analyses that are required to achieve the specific aims of the clinical trial.

- Computer-Generated Quantitative Analysis: Analysis is performed by a computer algorithm with little or no human interaction or influence over the operation. This type of analysis should be deterministic (always produce identical output from the same input) or have low variability and therefore usually does not need to be executed repeatedly. There may still be the requirement for expert reviewer oversight and quality assurance to detect exceptional cases in which the algorithm fails. Computer-generated analysis tools should strive to meet the validation guidelines required by regulatory agencies.[9]
- Human-Interfaced Analysis: Analysis is driven primarily by a human reviewer who may also use computer-generated analysis tools that meet required validation guidelines. This analysis may be quantitative, categorical, or subjective.

The review paradigm should be driven by the phase of the study and the intended use of the results by the sponsors. Safety reviews, eligibility reviews, and early phase efficacy studies that are not intended for registration in support of accelerated approval can be performed with a sin-

gle reviewer if this is the choice of the sponsors. Phase 2 efficacy studies targeted for accelerated approval and Phase 3 efficacy studies may require two or more completely independent reviewers, to account for variation in human performance and demonstrate the reproducibility of the results. The results of the two reviewers may need adjudication in some cases (eg, categorical assessments of response in oncology) whereas in other cases the assessments may be averaged (eg, semiquantitative scores in arthritis).

IMAGE PRESENTATION ORDER

There are several scenarios identified for the order of presentation of images to the reviewers. The type of presentation often depends on the therapeutic area, the imaging technology being deployed, and the reasons for the review. The procedures for the temporal presentation of the images should be explicitly described in the IRC. In each scenario, the name of the time point as identified by the site should not unblind the reviewer. For example, if a site has labeled a time point as an end of treatment study, this should be presented to the reviewer (aliased) as a sequential number without indicating the notion of "end."

- Sequential Chronologic Presentation: Images are shown to the reviewer in the order in which they were actually acquired. In this format, the reviewer should not know the total number of time points to be assessed unless that information has been prespecified in the IRC. (For example, prespecification of the number of time points is usual and customary in imaging studies of some neurodegenerative disorders, arthritis, osteoporosis, and congestive heart failure.)
- Simultaneous Chronological Presentation: All images associated with a subject are presented to the reviewer simultaneously without blinding the date, sequence, or total number.
- Simultaneous Randomized Temporal Presentation with Unknown Sequence: All images associated with a subject are shown to the reviewer at the same time in a random order with blinding for date and sequence but without blinding to total number.
- Baseline Followed by Randomized Temporal Presentation: The baseline (earliest) time point is presented to the reviewer for the purpose of lesion selection. Subsequent time points are presented in a random order with respect to the date of the follow-up examinations.
- Randomized Independent Temporal Presentation: Each time point is presented alone, in a random order with respect to the date of acquisition, and reviewed independently without access to other time points.
- Hybrid Randomization Designs: In this paradigm, the first stage of the assessment is fully randomized or the postbaseline scans are randomized. Once the results have been locked for each time point, the images are re-presented in known chronological order for reconsideration. Changes in any of the randomized assessments are tracked and highlighted in the final assessment.

DATA LOCK

At a predetermined point during the review process, the results of the image analyses produced by the reviewers must be locked or frozen. Locking must not be construed to mean an assessment cannot be overturned by emerging data as long as (1) the process is predefined in the IRC; (2) the process is driven by data that, by design, emerge after the initial assessment; and (3) there are adequate audit trails that can substantiate the changes.

DEFINITIONS

- Examination or exam: A single set of intimately related images acquired contemporaneously with a single technology, such as a CT scan of the chest, a whole body bone scintigram, or an echocardiogram.
- Time point: A discrete period during the course of a clinical trial when a group of imaging exams is scheduled as defined in the study protocol.
- Results data (ie, metadata): Information that results from or is produced by the image analysis or review processes (such as lesion selection and their associated spatial measurements), which may be distinct from algorithmically derived assessments specified in the protocol. In this context, the term also refers to marks placed on images, such as regions of interest boundaries, annotations such as "Target Lesion 4," and so on.

Task Force II found that there are four common scenarios as to when the data should be locked.

- Scenario 1: Exam Lock. In this scenario, the data are locked in final form after each exam is assessed. The purpose of the exam lock is to assess the differential contribution of each exam to the overall assessment. Various time point locking procedures (vide infra) can also be applied to each exam type in the exam lock paradigm.
- Scenario 2: Time Point Lock. In this scenario, the data are locked after all of the prespecified information associated with each time point is assessed. In some paradigms, the time points are known to be presented in chronological order; in others, the time points may be randomized during the early stages of the image analysis process (vida infra).
- Scenario 3: N-Time Point Lock. In this scenario, a variable, number of time points N, can be combined and shown together at a particular stage of the review process. For example, the baseline/screening and the first subsequent time point after baseline/screening may be reviewed together to establish the baseline extent of disease.
- Scenario 4: End of Review Lock or End of Subject Lock. In this scenario, the data are locked when the reviews of all the time points for the subject have been completed.

The commonality is that one or more data locks should be applied at predetermined stages of the review. The point at which a lock is applied may be dependent on the setting and vary according to the imaging modality, therapeutic area, or specific aims of a particular study. Regardless, data locks should be described a priori in the IRC. In addition, if any information is changed after the lock, then there must be a means of capturing the description and reason for the change at the review milestone at which it is made (ie, an audit trail that captures the changed information and the reason).

Task Force II recognized that assessments are most likely to change in reading paradigms that present examinations in random temporal order during the first stage of review, and then present all of the images again for final review in proper chronological sequence.

ELIGIBILITY REVIEW

Eligibility review based on imaging can be used for several different purposes. Examples include confirmation of measurable disease, verifying progressive disease prior to enrollment, and certifying that certain anatomic or pathologic characteristics of the disease are present or absent.

In all instances, the eligibility review is for the purpose of confirming if eligibility criteria specified by the sponsor in the protocol are met. The eligibility review must not impact the site decision making with respect to being construed as the practice of medicine, nor impact treatment, which should be based on the site's normal standard of care.

All other standards and best practices in this document apply also to eligibility review, with the exception that the subject may not have been imaged according to a specified protocol during the prior treatment. Images should be reviewed from a quality perspective on the basis of the study-specific needs that are identified in the study-specific documentation and the IRC.

ON-PROTOCOL AND OFF-PROTOCOL IMAGES VERSUS UNSCHEDULED EXAMINATIONS

Task Force II recommends that ICLs make a distinction between the review of on-protocol images and off-protocol images. On-protocol images are those that are acquired as part of regularly scheduled assessments or are performed ad hoc for evaluation of symptoms. Off-protocol images are those that may have been acquired by the site for clinical or experimental purposes, but are not a standardized feature of the protocol that can be said to apply to all subjects in all arms of a clinical trial. An example of an off-protocol image would be magnetic resonance spectroscopy of the brain in a few patients who participated in a neurooncology study where post-gadolinium T1W images of the brain were predefined as the method for assessing response. Each study protocol and its associated imaging charter should explicitly define on-protocol images. The IRC should classify any other imaging data as off-protocol.

Unscheduled examinations are images that are acquired at unscheduled times (eg, triggered by clinical symptoms). Unscheduled examinations that are identical to scheduled ex-

aminations should be allowed to contribute to the quantitative imaging outcome measures. For example, a study of lung cancer that relies on CT scans of the chest at the end of each cycle should treat an unscheduled CT scan of the chest that was acquired during the middle of a cycle just like any other regularly scheduled examination.

In some cases, unscheduled radiological examinations that are not comparable should be read by the independent ICL central reading laboratory. For example, an MRI scan of the head in a patient with cancer who develops headaches might show metastatic disease as the etiology of the new symptom and trigger a change in the response assessment. As an additional example, an imaging technique that shows a new myocardial infarction might be relevant to the assessment of a new drug for atherosclerosis regardless of the primary imaging technique used to quantify effectiveness. The use of unscheduled, noncomparable imaging data by an IRC should be prespecified in the imaging charter in order to avoid introducing bias.

SITE VERSUS INDEPENDENT REVIEW RESULTS: EXPECTATIONS OF CONCORDANCE

Independent reviews of images or data should be classified as distinct sets of research procedures that are unrelated to the clinical care of the subjects enrolled in a particular clinical trial. Independent reviewers should be blinded to all of the clinical circumstances surrounding a case other than as described in the IRC. In contrast, on-site reviewers (radiologists and attending physicians serving as site investigators) are contributing to patient care and as a consequence are expected to assess images in light of all the information about a case that can be ascertained at the time of review, such as the symptoms that led to an unscheduled examination.

Given the workflow differences between sites and ICLs and differences in the data sets being analyzed, the task force found no scientifically sound reason to expect a high rate of concordance between assessments by the ICL central reviewers and the sites when imaging is used to assess a therapeutic drug. This is distinct from the situation that occurs when developing a novel diagnostic imaging agent. The performance of a novel diagnostic imaging agent in the hands of clinical practitioners might be relevant to its overall evaluation, but in clinical trials of therapeutic drugs, only the unbiased, controlled independent image analyses can be relied on to test the imaging hypotheses surrounding drug development when imaging contributes to the study endpoint.

REVIEWER QUALIFICATIONS

Reviewers should be qualified by experience as documented on the curriculum vitae with respect to criteria specified in the protocol or IRC. Reviewers must comply with 21 CFR 54 (financial disclosure)[10] or applicable local legislation.

Board certification or its equivalent in a relevant medical specialty is a minimum requirement. In addition, reviewers must successfully complete protocol-specific training procedures as described in a training manual or SOP. Procedures described in the manual or SOP should include mock reviews on test cases not drawn from subjects enrolled in the trial. Reviewers may not review cases from their own institutions or exams to which they have been previously exposed.

REVIEWER PERFORMANCE AND QUALITY METRICS

The task force agreed that reviewer performance should be evaluated by rigorously defined metrics. The task force noted that there are several other working groups dedicated to creating metrics that attempt to quantify the quality of imaging operations and image analyses.[11] As a consequence, the task force agreed to limit the scope of its current recommendations on the topic to the following observations.

The task force agreed that adjudication rates are highly dependent on the selection of lesions to be assessed, the number of lesions assessed, the complexity of the imaging outcome measure, the number of imaging variables that are generated, the efficacy of the drug, the tu-

mor type, the duration of treatment, the subjectivity of assessment, the measurement precision, the response criteria used, the quality of the images, the proportion of missing data, and whether the output variables are continuous or categorical. As a consequence, simple scalar values that describe adjudication rates are not very amenable to characterizing quality or comparing the outcomes of different trials. The task force observed that few, if any, standards for computing adjudication rates have been established. A variety of methods are currently applied that can produce apparently different values when applied to the same data. For these reasons, the task force recommends using caution when trying to understand the meaning of adjudication rates.

DISCUSSION

The task force found that operational and image analysis strategies varied according to therapeutic area and the imaging technology in play, but the scientific principles upon which most of the processes and procedures seemed based were similar.

The strongest consensus surrounded the need for independence to prevent bias and process consistency to promote reproducibility. It was agreed that in most scenarios, sound scientific principles required the ICL image analysts to focus exclusively on the presented data only. Few, if any, of the clinical details surrounding a case should be disclosed; the opinions of the treating physicians should not be revealed; and no collaboration between central readers should be allowed. Procedures that promote these principles promote unbiased interpretations by the ICL.

The distinctions between this research enterprise and the practice of medicine is, and should be, stark. Standards for clinical care endorse physicians consulting with other physicians, encourage health care professionals to account for all the information that is available, and advocate thinking outside the box. In contrast, good science relies on rigorously defined and applied methods that lead to reproducible results. In general, ICLs produce their results long after treatment decisions have been made, and have no influence on patient care.

As a consequence, some of the procedures that promote good imaging practices by ICLs are not only unique to clinical trials, they make no sense in clinical settings. Data locking would be contraindicated in most medical practices, but in strictly scientific settings, locking the results on a step-by-step basis helps reduce bias. Keeping these ideas in mind when designing and executing clinical trials that will use imaging to generate outcome measures should tend to ensure that the specific aims of the study will be achieved. Because imaging produces only one type of data that is used to evaluate the performance of investigational new drugs, these principles might not be easily extrapolated to some clinical domains where concepts like judgment and the art of medicine could still apply. But the task force does strongly recommend isolating central image analysis laboratories from any factors that could influence the assessment of the information contained solely within the images themselves.

FUTURE DIRECTIONS

Task Force II agreed to remain active. It will work with allied organizations and stakeholders to expand the scope of its mission into topics including metrics that describe the quality of imaging enterprises in clinical trials such as reader performance, the appropriate use of phantoms for calibrating imaging instruments, and the incorporation of clinical information into independent image analyses.

Comments, criticisms, and suggestions for future efforts should be directed to the chairman, who can be reached at the address above.

Task Force II participants are listed below:

Robert Ford, MD, Chairman, Task Force II, Cofounder and Chief Medical Officer, RadPharm

P. David Mozley, MD, Cochairperson, PhRMA Imaging Group, PhRMA Innovation and Research Committee

In alphabetical order:

Barbara Chandler, Perceptive Informatics

Sandra Chica, MD, Perceptive Informatics

Don Cooper, Biomedical Systems
Thomas Fuerst, PhD, Synarc
Vahe Ghahraman, PhD, Dyax Corp.
Dana Ghiorghiu, MD, AstraZeneca
Alex Gorovitz, MD, FDA
Luna Hilaire, PhD, GE Healthcare
Richard Jacobs, MD, Perceptive Informatics
Christina Mastandrea, Worldcare
Lenore Noonan, Bioimaging
James Paskavitz, MD, Perceptive Informatics
Andrea Perrone, MD, Bio-Imaging Technologies
Charles Peterfy, MD, PhD, Synarc
Stephen J. Pomeranz, MD, Worldcare
Larry Schwartz, MD, Memorial Sloan Kettering Cancer Center
Barbara Stinson, MD, FDA
Joyce Suhy, PhD, Synarc
Saara Totterman, MD, Virtualscopics
Liliana Ulianov, MD, Biomedical Systems
Sarah Warner, PhD, Perceptive Informatics
Helen Young, PhD, Astrazeneca
Souhil Zaim, MD, Synarc

REFERENCES

1. Pfizer. Highlights of prescribing information. Available at: http://www.pfizer.com/files/products/uspi_sutent.pdf.
2. Single-agent SUTENT prolonged progression-free survival across all advanced kidney cancer patient risk groups, including those with poorest prognoses, data show. June 3, 2007. Available at: http://findarticles.com/p/articles/mi_m0EIN/is_2007_June_3/ai_n19188572.
3. Welt Online. Newsticker. http://newsticker.welt.de/index.php?channel=fin&module=smarthouse&id=593480. (In German.)
4. Panitumumab significantly improved progression-free survival and disease control in metastatic colorectal cancer patients, phase III trial. April 9, 2006. Available at: http://www.medicalnewstoday.com/articles/41267.php.
5. Prud'homme A. *Cell Game*. New York: Harper Collins; 2004.
6. Timmerman L. Genentech's Avastin not recommended for breast cancer (Update4). Blooomberg.com. December 5, 2007. Available at: http://wwwbloomberg.com/apps/news?pid=newsarchive&sid=aoRSxqNgis58.
7. US Food and Drug Administration. Subchapter D—Drugs for Human Use, Part 312, Investigational New Drug Application. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312.
8. Drug Information Association. Transcript of October 2007 meeting. Available at: http://www.diahome.org/DIAHome/.
9. FDA Guidance for Industry, Developing Medical Imaging Drugs and Biologic Products, Parts I-IV, June 2004. Available at: http://www.fda.gov/CBER/gdlns/medimagesaf.pdf.
10. National Archives and Records Administration. 2000 CFR Title 21, Vol. 7. Available at: http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr54_00.html.
11. Metrics Champion Consortium. Available at: www.metricschampion.org.

The authors report no relationships to disclose.