THE CANCER LETTER

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Compendia Publishers Must Tell CMS How They Manage Conflicts Of Interest

By Paul Goldberg

The Centers for Medicare and Medicaid Services has instructed the publishers of drug compendia to provide information on their processes for managing conflicts of interest.

The compendia are immensely important in oncology. A listing in one of the compendia—there are four—is usually all a drug maker needs to ensure that off-label uses of a drug or biologic are eligible for coverage.

Nonetheless, processes for determining conflicts of interests that can come into play as listing decisions are made vary from compendium to compendium.

CMS has been gradually focusing its attention on conflicts in the

(Continued to page 2)

NCI News:

New Version Of NCI Proposed IP Agreement Quiets Some Unease At Cooperative Groups

By Kirsten Boyd Goldberg and Paul Goldberg

NCI officials have reworked the intellectual property language of cooperative agreements with the industry, quelling at least some unease at the NCI-supported clinical trials cooperative groups.

Responding to pressure from the pharmaceutical industry earlier this summer, the institute proposed making a sweeping change: if a drug company provided an experimental agent to a cooperative group trial, it would be entitled to a royalty-free commercial license to inventions stemming from studies of biomarkers obtained during such a trial.

The proposal caused great concern among clinical researchers, who argued that automatically granting commercial licenses to drug companies would diminish the incentives for university scientists to take part in biomarker research. The concern was not just that drug companies would get valuable licenses, but also that they would be in a position to squelch biomarker findings that would limit the use of their drugs (The Cancer Letter, Oct. 16).

At the NCI Clinical Trials and Translational Research Advisory Committee meeting Nov. 4, institute officials presented a reworded biomarker studies proposal:

—Essentially reverting to the current state of affairs, IP drug sponsors would get royalty-free worldwide non-exclusive licenses.

(Continued to page 5)

CMS News:
White Paper Presents Snapshot Of Conflicts
. . . Page 2

NCI News:
Advisors Urge NCI To Move Ahead With IP Agreements
. . . Page 5

NCI Advisors Approve Expansion Of CCOPs, Minority-Based CCOPs; Approve Reissuance Of BMT Network RFA, RFPs For Preclinical Drug Studies
. . . Page 6

Listing In Compendium Means Payment For Off-Label Use

(Continued from page 1)

compendia, and now it is under the mandate from Congress to start regulating such conflicts. Last year, the Medicare Improvement of Patients and Providers Act stated that as of Jan. 1, 2010, "no compendia may be included on the list of compendia… unless the compendia has a publicly transparent process for evaluating therapies and for identifying potential conflicts of interests."

Recently, CMS cited this law as it instructed the compendia to provide information on their policies for managing conflicts, if they are "to remain on the list of recognized compendia.

"No compendium can be on the list if it does not fully meet the standard" of public transparency, the agency said.

The agency has amassed a wealth of information on conflicts of interest affecting the compendia. Last year, the Agency for Healthcare Research and Quality and CMS commissioned a white paper on the subject. The 111-page report, prepared by Duke Evidence-based Practice Center at Duke Center for Clinical Health Policy Research, is posted on the CMS website: http://www.cms.hhs.gov/determinationprocess/downloads/id64TA.pdf.

"This would appear to be CMS taking our concerns into account and requesting that the compendia develop procedures that identify and manage their conflicts of interest more effectively," said Ross McKinney, one of the authors of the report and an expert on conflicts of interest and pediatric infectious diseases. "I don't know whether the four compendia will have to manage conflict the same way, because the companies have different strategies. I bet CMS would allow them to take different approaches. They would just have to solve the problem."

The white paper was posted last April. One of its highlights is a table (on pages 71-73) that summarizes conflict of interest policies of the four compendia.

Earlier this year, the agency has provided greater detail on the sort of information it expects disclosed by the publishers of compendia. The 2010 Medicare Physician Fee Schedule, published in draft from in July and reissued as a final rule last month contains the following language on conflicts of interest:

• To revise the definition of "compendium" by adding an additional requirement that a compendium have a publicly transparent process for evaluating therapies and for identifying potential conflicts of interests.

• To add a definition of a "publicly transparent process" for evaluating therapies whereby a compendium publisher would publish on its Web site the complete application for inclusion of a therapy including criteria used to evaluate the request; disclosure of the evidence considered; the names of the individuals who have substantively participated in the development of the compendia recommendations; and transcripts of meetings and records of votes for disposition of the request. We requested comments on the requirement for publication of the transcript and the suitability of other alternatives such as minutes or other documents.

• To add a definition of a "publicly transparent process for identifying potential conflicts of interests" whereby a compendium publisher would disclose by publication on its website information regarding potential conflicts of interests associated with individuals who are responsible for the compendium's recommendations, as well as their immediate family members.

The physician fee schedule, which includes a more detailed discussion of conflicts in the compendia, is posted at http://www.federalregister.gov/inspection.aspx#special.

CMS recognizes four compendia: American Hospital Formulary Service Drug Information (AHFS-DI), the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium6, DRUGDEX, and Clinical Pharmacology.

William McGivney, CEO of the National

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Comprehensive Cancer Network, said he doesn't expect to run into problems with the agency. Since the end of 2008, NCCN has been changing disclosure requirements for its panel members.

"We went down and talked with Medicare," McGivney said in an interview. "We've discussed specifically what we need to do to continue our leadership role and fulfill what CMS wants us to do."

The changes are extensive in part because of the scale at which NCCN operates.

"The other compendia may have a cancer panel of 12 to 15 docs," McGivney said. "We have 44 panels with 20 to 30 docs on each one. We are a little different. When you tell us we have to basically provide minutes of meetings, you have to remember, our breast cancer panel meets for two days. They don't meet for 45 minutes on the phone and discuss one or two drugs."

In the past, NCCN panel members—mostly academics—had to compete disclosure forms listing their "relationships with external entities." However, these forms were held by NCCN as confidential.

This changed in late 2008, when NCCN started to post each member's disclosures. Starting next year, NCCN will also publish the range of money involved. Moreover, the network will publish detailed minutes of guideline meetings and list the votes of each panel member. This would make it possible to look up the disclosures and correlate them with the votes.

The Duke group's white paper includes discussion of the review processes used by the four compendia as they existed last year, before the federal government and the media started to scrutinize the relationships between the compendia and drug companies.

An excerpt from the white paper follows:

Among the four, Clinical Pharmacology has implemented the most conservative approach to conflict of interest in evidence review.

By strictly limiting outside affiliations of its reviewers, who are internal staff rather than external experts, the company effectively minimizes the possibility of personal conflict of interest among its reviewers. This compendium, thus, appears fairly well insulated from personal conflicts of interest, though corporate conflicts of interest remain a possibility.

Clinical Pharmacology has recently changed ownership.

In May 2006, Gold Standard was purchased by Reed Elsevier, a large Dutch publishing and information services conglomerate. This large company contains a business services component that creates risk for corporate conflict of interest.

There is potential concern that internal corporate policy could favor the products of Reed Elsevier's business services clients, in order to make working with Reed Elsevier more attractive.

This study's teleconference interview with the staff at Gold Standard gave no indication that this concern is based on anything more than a structural possibility, but it should be noted.

The use of external reviewers by the other three compendia decreases their ability to control conflicts of interest.

AHFS-DI maintains a unique arrangement for obtaining evidence, namely, a requirement that applicants seeking expedited review of a new indication submit an application, with an application fee, to the FEBM. *[TCL Editor's Note: The collaboration described in the white paper was ended earlier this year, but remains illustrative of potential conflicts of interests that can arise in the compendia. A announcement of termination of the program is posted at* http://www.ashp.org/import/news/pressreleases/pressrelease.aspx?id=519].

This arrangement may place the compendium at risk for influence by conflict of interest. Drug companies are not likely to look favorably upon the requirement to pay $50,000 to get their off-label indication listed in a compendium—especially if that compendium elects not to approve their indication.

If AHFS-DI frequently fails to approve applications, the flow of applications will almost certainly cease. Drug companies will opt to seek listings of their indications in other compendia, which do not charge a fee. Thus, there is a significant economic pressure on the FEBM for AHFS-DI to approve applications.

Although not specifically a conflict-of-interest question, presence of the $50,000 fee may also discourage requests for off-label uses of lower priced therapies and for those directed at low frequency conditions. The FEBM notes they may waive the application fee in the case of limited population therapies.

Designation of the FEBM as a gateway to the AHFS-DI can be viewed as a strategy for skirting the issue of conflict of interest arising from the compendium's financial relationships with industry.

Although the business reasons for the separation of AHFS-DI and FEBM may be legitimate, this configuration has the appearance of "plausible deniability." This arrangement allows AHFS-DI to truthfully state that it does not receive payments from the pharmaceutical industry as part of their review process, and thus that their review remains "independent."

Yet their mandatory partner receives $50,000 from industry for every off-label indication request.

As a counter-balance to these structural concerns created by the fee system, a spokesman for AHFS-DI noted that the actual determinations of accepted indications are made by a volunteer committee.

The members of that committee do not, therefore, have a direct financial COI as a result of the fee-based process.

However it continues to be true that these reviewers would surely know that regularly rejecting new indications would have an impact on the revenue stream of the FEBM. What effect that knowledge will have on the reviewers cannot be determined.

The NCCN Drugs & Biologics Compendium process draws directly from clinical practice guidelines developed by expert committees convened by the NCCN.

The NCCN maintains a clearly articulated commitment to transparency with regard to conflict of interest. It also maintains a commitment to engaging leading experts in its reviews of the evidence and development of clinical practice guidelines. In addition, it uses fairly large panels, which has the effect of diluting the effect of any one individual's conflict of interest.

Because of the frequency with which widely known physicians and scientists at esteemed institutions in academia and research have some form of potential conflict of interest—whether it be research funding, speaker fees, consultant roles, or stock ownership—NCCN is open in acknowledging the difficulty of recruiting sufficiently experienced panels without conflicts of interest.

Many external members have conflicts of interest; up to 78% of faculty have disclosed conflicts on some panels. These disclosures call into question the objectivity and neutrality of the review process.

Additionally, unlike with drug review articles, where the reader can consider the possible effects of known conflicts and decide whether or not to believe the writer's opinion, with guidelines that are used as a binary determinant by some payers (pay/no pay), knowledge of conflicts is of little use.

If the compendium approves a drug for a given indication, payment will be expected, regardless of knowledge regarding whether a majority of the panel members had potential conflicts of interest.

Another area of COI risk for the NCCN is the level of support it receives from external sponsors that include pharmaceutical companies, insurance companies, medical centers, and information providers [List available at http://www.nccn.org/about/financial_support.asp].

Since NCCN compendia entries are derived from NCCN guidelines, and the guidelines are produced primarily by external reviewers, the main risks by this pattern of sponsorship would seem to be either in information provided by staff to the committees (if staff members were aware of the sponsors), or in the process of converting the guidelines to compendia entries.

A third concern regarding NCCN is the fact that as a network it performs clinical trials sponsored by corporate entities. It is conceivable that both the volunteer faculty and the NCCN staff could be inclined to write more favorable guideline and compendia reviews in order to curry favor with potential research sponsors.

The biases introduced by such a desire are probably small, given the size and diversity of the guideline writing committees, but should be noted.

Conflict of interest for the fourth compendium, Thomson Micromedex' DRUGDEX, was the subject of a pointed critique by the Wall Street Journal in 2003.

The first issue raised by the Journal was the fact that DRUGDEX has a much longer list of recommendations than the other compendia, a fact confirmed last year by a Duke evaluation of the compendia.

Specific concerns were raised regarding the fact that other divisions of Thomson perform marketing services for the pharmaceutical industry.

The impact of these institutional conflicts of interest can be nearly impossible to describe or quantify.

For example, Thomson may have had an internal, unpublished, corporate policy of favoring its marketing clients, but this policy might not be discoverable. From the point of view of conflict of interest, Thomson ameliorated this concern by divesting itself of its medical education division in 2007.

Although Thomson clearly and openly presents on the Internet its conflict of interest policies for DRUGDEX, this compendium may be at risk for intrusion of conflict of interest due to its cut-off points for disclosure.

These thresholds are set substantially higher than are those of the other three compendia. Thomson's threshold of $100,000, beyond which reviewers may not participate in evaluation of evidence, may explain the relatively small number of conflicted individuals.

The public could reasonably wonder if someone receiving slightly less than $100,000 per year might be biased. In addition, while the presence of a financial conflict of interest is disclosed on the website.

NCI News:

Advisors Urge "No Paralysis" During IP Agreement Rewrite

(Continued from page 1)

—Also, sponsors would receive a time-limited first option to negotiate an exclusive or co-exclusive royalty-bearing commercial agreement.

—NCI advisors were surprised to find another proposed change: If in the course of a clinical study, scientists make an observation that a drug can be used for another indication, that indication would be subject to a royalty-free, worldwide non-exclusive commercial license.

At the committee meeting, no one seemed to be able to recall the last time observations made while studying a drug for an oncology use led to an unexpected discovery outside that area.

"Let's say you are doing a study of some drug that's intended to have a use in treating cancer, and to follow your analogy, we find that it treats baldness just as well," said CTAC member Richard Schilsky, chief of hematology and oncology at the University of Chicago.

"Usually our drugs cause baldness," another committee member said.

Jason Cristofaro, an attorney in the NCI Division of Cancer Treatment and Diagnosis, acknowledged that such discoveries don't happen often.

"Can you even name one in the last 30 years?" challenged committee member David Parkinson, president and CEO of Nodality Inc., a diagnostics firm based in South San Francisco.

"No," said Cristofaro.

"I'm sure you can't name a single one," Parkinson said.

"David, you make a very good point," chimed in Jeffrey Abrams, associate director of the NCI Cancer Therapy Evaluation Program. "We felt this would take away some of the bickering that we go through with companies, which can sometimes be endless, because they worry about something that really hasn't happened. A lot of the lawyers at these companies want this language, and we didn't feel this was something that the scientific community was really making a lot of inventions in. As you say, it really doesn't occur in oncology."

Parkinson, a former CTEP director, urged NCI officials not to undervalue the institute's role in drug development.

"These companies ought to be thankful that they are able to participate in NCI clinical trials, and the goal of protecting the public good should transcend anything else, and not allow the samples or patient information to be held hostage any company—on the therapeutics side or on the diagnostics side," Parkinson said. "NCI has the high ground on this. You really want to protect the rights of all parties involved, starting with the patient. First, make sure that the fox is not taking control of the samples, that they remain with the investigators, and second, that results be not blocked from the best clinical care of the patient. It becomes easier if those principles are in place. Use of the drug can't be blocked by some little company with magic tests, which is what the great fear of the pharmaceutical companies is, and that pharmaceutical companies can't block the more intelligent use of the drug from the other side."

"Maybe we need to make that more clear and make this more patient-centric," NCI Director John Niederhuber said.

"This is obviously a complex balancing act," said James Doroshow, director of the NCI Division of Cancer Treatment and Diagnosis. "This is a great discussion and it's important that we publicize that this will be out for public comment."

"I would just plead for no paralysis during this period of discussion, which is what I've observed to date," Parkinson said.

"I would just add to that," Schilsky said. "Because this language is out there being discussed, there are many companies trying to negotiate agreements with investigators, cancer centers, and cooperative groups, who are already invoking this language in their negotiations, which are grinding those negotiations to a halt."

"Moving In The Right Direction"

Schilsky, who is stepping down as chairman of Cancer and Leukemia Group B, said the institute appears to have addressed much of the criticism from cooperative groups and produced a proposal clinical trialists can live with.

"They are moving in the right direction," Schilsky said in an interview. "With biospecimens, the issue that touched off this discussion, they have pulled back considerably" to a position not too different from the status quo. "We can be comfortable with that."

The awarding of licensing claims stemming from clinical observations made in cancer clinical trials is largely hypothetical and therefore relatively benign, Schilsky said.

"Let's a say company is developing a drug for a

cancer indication, somebody makes an observation that suggests that suggests the drug may have a completely different use, and the company wants to have a right to commercialize that," Schilsky said. "Certainly, that's completely understandable, since it's their drug. And, frankly, the chances of that happening are extremely small. No one is actually aware of any examples where a cooperative group was studying a drug for one purpose and somebody discovered it was good for something completely different. If this change is necessary to make the companies feel comfortable, we are comfortable with that."

The proposal will go through additional review and will be published in Federal Register for public comment, NCI officials said.

Advisors Approve Increase To Add New CCOP Sites

By Kirsten Boyd Goldberg

Advisors to NCI approved the institute's plan for an expansion of the Community Clinical Oncology Program and the Minority-Based CCOPs, two longstanding grant programs that support community oncology participation in national clinical trials.

CCOP, begun in 1983, currently supports 47 community oncology sites as well as 12 research bases, which design and conduct cancer prevention and control clinical trials. NCI proposes to increase the number of CCOP sites to 50, and add one research base. The expansion would cost an estimated $13.6 million over five years for the four awards.

The MBCCOP, begun in 1990, currently funds 14 sites, and would be expanded to fund five new sites at a cost of $6.2 million over three years.

The NCI Board of Scientific Advisors voted unanimously (22 in favor and one abstention for conflict-of-interest) in support of expansion of the two programs at its meeting Nov. 4.

The board also voted unanimously in favor of reissuing a Request for Applications for the Blood and Bone Marrow Clinical Trials Network, a consortium of transplant centers funded jointly with the National Heart, Lung and Blood Institute.

The board voted 19-2 in favor of reissuing a Request for Proposals for preclinical pharmacokinetic and pharmacological studies of anticancer agents, costing $26.5 million over seven years. A similar RFP concept for preclinical toxicology studies was approved on a 19-1 vote.

Excerpts from the concept statements follow:

Community Clinical Oncology Program. Concept for an RFA reissue, first year set aside $3.3 million, total cost $13.6 million over five years, four awards (three to five years). The proposed budget includes funds to cover the total costs for three new CCOP applications, with recommended funding for a three-year project period and one new research base application with recommended funding for a five-year project period. Division of Cancer Prevention.

The CCOP RFA solicits applications to the network for both the community accruing sites and the CCOP research bases. The CCOP RFA is released annually. The fiscal year 2009 portfolio of CCOP network cooperative agreements includes 47 CCOPs in 28 states and 12 CCOP research bases.

Established in 1983, the CCOP network is a national program for conducting cancer clinical trials in community settings across the U.S. The network is a partnership involving NCI, peer-reviewed cancer centers, clinical cooperative groups (CCOP Research Bases), and local networks of community hospitals and physicians.

CCOP sites have successfully enrolled patients to cancer clinical trials for the past 26 years with over 235,500 patients enrolled to NCI trials since the program's inception. Approximately one-third of all patients accrued to NCI cooperative group trials come through CCOP sites. Community physicians participating in the CCOP network improve the quality of care for their patients and accelerate the diffusion of state-of-the-art treatment and prevention and control interventions to a wider segment of the U.S. population.

Recent accomplishments include several trials conceived and conducted through the CCOP program that have contributed to changes in clinical practice. Most notably, results from a Radiation Therapy Oncology Group trial (RTOG 97-14) demonstrated that single fraction radiotherapy is as effective as multi-fraction radiotherapy in relieving pain caused by bone metastasis. Consequently, patients and their families will now find it much easier to arrange for a single session of radiotherapy rather than 10 or more daily sessions. Also, this newer regimen will significantly reduce the impact on timing of other treatments. A University of Rochester trial (URCC-01-14), reported at ASCO in 2009, demonstrated that ginger significantly reduced chemotherapy-related nausea on the first day of chemotherapy, and reduced nausea overall. Another important study completed through the CCOP network was a prospective longitudinal study of the prevalence, severity, impact, and current treatment of common symptoms I the most frequently-occurring cancers. This study represents the first of its kind to be completed, with over 1,000 cancer patients responding to the survey. Data from this study, also reported at ASCO in 2009, will be used to inform future clinical trials, as well as current practice patterns in the community.

CCOP cancer control trials address a variety of issues related to side effects from cancer treatment or from the cancer itself. The current portfolio of protocols addresses issues that

include osteoporosis, altered cognitive function, fatigue, lymphedema, skin toxicities, radiation effects, neuropathies, and others. Patient quality of life during and after treatment continues to be a high priority research area. The development of new targeted therapies has resulted in new symptoms and toxicities, such as EGFR-inhibitor skin toxicities. These developments have contributed to a shift in the focus of cancer control research to mechanism-based interventions for cancer symptoms and toxicities.

Four large-scale prevention trials have been completed through the CCOP network over the past 17 years, as well as multiple other small to moderate size chemoprevention trials. To date, the major prevention trials have focused on breast and prostate cancer. However, plans to expand prevention trials research to other major cancers such as colon are part of future plans.

Minority-Based Community Clinical Oncology Program. Concept for an RFA reissue, first year set aside $2 million, total $6.2 million over three years, five awards. Division of Cancer Prevention.

Increasing access of underserved populations to state-of-the-art clinical trials is a major goal of NCI and NIH. Begun in 1990, Minority-Based CCOPs are an important component to minority recruitment serving geographic regions where 40 percent or greater of their newly diagnosed cases of cancer are from minorities. These programs are commonly associated with academic centers in urban areas or free-standing community hospitals, operate in environments characterized by socioeconomic challenges and limited resources especially for involvement in clinical trials research, and increasingly serve new racial ethnic populations with varying experiences with cancer care.

The purpose of this program is to support physicians involved in the care of minority cancer patients and individuals at high risk of cancer who are eligible for treatment and cancer prevention and control clinical trial research. The linkage of minority cancer patients to the current clinical trials network will facilitate the transfer of new technology and the identification of etiological leads and biological characteristics and differences between different racial and ethnic populations.

The MBCCOP 1) provides support for expanded clinical research in minority communities; 2) brings the advantages of state-of-the-art treatment and cancer prevention and control research to minorities in their own communities; 3) increases the involvement of primary health care providers and their specialists in cancer prevention and control studies; 4) establishes an operational base for extending cancer prevention and control and reducing health disparities by reducing cancer incidence, morbidity, and mortality in minority populations; 5) examines select issues of MBCCOP performance (contributions to cooperative group research bases; national minority accrual and identification of successful approaches of recruitment); and 6) serves as a training ground for scientists interested in research among special populations.

The proposed budget includes funds to cover the total costs for five new MBCCOP applications, with recommended funding for a three-year project period.

The Blood and Bone Marrow Clinical Trials Network. Concept for RFA reissue, first year set aside $3.5 million, total cost $18.5 million over five years, 17 awards. Division of Cancer Treatment and Diagnosis.

The National Heart, Lung and Blood Institute and NCI jointly established the BMT CTN in 2001 with a second five-year budget period awarded in 2006. The goal of the network is to efficiently compare novel HCT methods and management strategies derived from single center studies to existing treatments, in a multi-center setting, to improve the safety and efficacy of the transplantation procedure and improve successful therapy of specific diseases. The purpose of this RFA concept is to seek approval to renew the network. The network has been a dynamic and successful enterprise focused on improving survival for patients undergoing hematopoietic stem cell transplantation, and thus improving successful therapy for both malignant and nonmalignant diseases. The network continues to be successful in advancing research on the most promising HCT therapies and evaluating them in high quality trials. Another project period is sought to allow completion of ongoing trials, new trials planned based on recently completed phase II studies, as well as to initiate high priority new trials based on recommendations from the 2007 State-of-the-Science symposium.

For the current funding period, NCI has been providing $3.2 million each year with the NHLBI initially providing somewhat more than that amount. NHLBI has provided increases each year as cost of living adjustments, resulting in an overall reduced NCI percentage (to 30 percent). The proposed 2011 budget for NCI provides an increase, to $3.5 million a year and a 3 percent cost of living increased is proposed for each of the out years of a five-year budget. The 3 percent increase over 2010 and the cost of living increases in the out years are justifiable due to the number of current and planned trials in hematology/oncology and the increased cooperation of the BMT CTN with the NCI cooperative groups. Since NHLBI is proposing an increase from $7.2 million to $8.4 million in 2011 with no cost of living increases for the duration of the award, increasing the NCI budget maintains a 30 percent share in the costs of the BMT CTN for the award over the five-year award duration (however, since NHLBI is planning a seven-year award, if approved this will need to be addressed by NCI at a later time).

With a total cost per year to the NCI of that of a medium-sized P01, the BMT CTN has: 1) built a network of 16 core and more than 60 additional participating transplant centers in a national research effort to evaluate and treat patients using BMT; 2) opened 18 trials in five and a half years (an average of about three per year) with accrual of more than 2,600 patients to these trials, with five more trials undergoing final approvals or protocol development; and 3) joined with the

NCI cooperative groups to enhance accrual to open trials and develop new trials, bringing additional focus to the transplant activities of the groups. An external review of the network in 2008 was quite favorable.

Preclinical Pharmacokinetic and Pharmacological Studies with Anticancer and Other Therapeutic Agents. Concept for an RFP reissue, $26,576,971 over seven years, seven awards. Division of Cancer Treatment and Diagnosis.

The contracts resulting from this procurement will provide a continuing resource for conducting the following types of studies with agents selected for preclinical development through NCI programs: 1) development o sensitive analytical methods to quantify compounds in plasma, urine, tissues, and other biological matrices; 2) plasma stability and protein binding studies, which are conducted at an early stage of compound development to ensure proper sample handling and to aid in the interpretation of in vivo studies; 3) pharmacokinetic evaluation of test compounds following administration to animals by various routes and schedules, including a determination of bioavailability by various routes; 4) quantification and identification of drug metabolites generated in vivo and in various in vitro systems (S9 fractions, microsomes, hepatocytes, P450 isoforms, liver slices); and 5) assessment of agent effects on putative molecular targets (pharmacodynamic studies) and correlation of the response with drug levels and/or total exposures.

Contract resources for preclinical development studies have existed in DTP continuously since the late 1970s. Numerous compounds have advanced to clinical trial through the years and pharmacology information obtained through these contracts has been included in many Investigational New Drug Applications. Since the seven current contracts were awarded in 2004, analytical method development, pharmacokinetic studies, and other evaluations (protein binding, metabolism, pharmacodynamics, etc.) were conducted on a total 51 compounds. Of these, 16 were developed under the auspices of the NCI Joint Development Committee and 12 were Rapid Access to Intervention Development compounds. The remaining compounds were approved through the NIH-RAID, DDG, and other programs. The compounds were of diverse chemical structure and the drug development goals of the projects were varied, thus requiring a variety of different approaches for development of analytical methods and the selection of drug formulations, routes of administration, and preclinical species evaluated.

These contracts will be managed using a work assignment system, in which projects are assigned to a contractor by the project officer, with subsequent approval by the contracting officer. Each WA is written for a particular drug development project and both estimated and final itemized costs for the project are obtained from the contractor. Awards arising from the solicitation will be completion contracts. The work assignment mechanism effectively divides the contract into discrete phases of performance with defined deliverables (WA Final Reports).

The current preclinical pharmacology portfolio was last recompeted in 2004, resulting in seven awards, each with a period of five years plus two option years. The FY09 negotiated amount for all awards is $2,887,174. It is anticipated that monies will be available to fund these contracts as needed in FY09 and that the first option year, FY10, will be exercised and also funded as needed. It is the choice of the program to recompete these contracts now and not exercise the second option year, FY11. This will allow for competitive refreshment of the portfolio and also slight modifications to the Statement of Work and other contract terms.

The current contracts were competed at two levels of work, with Level B providing twice as much capacity as Level A. A mixture of four Level A and three Level B awards were made. However, it is now evident that actual productivity vs. costs may not always be proportional to these levels, particularly for academic contractors. Therefore, it is proposed that the competition go forward at a single level, intermediate between the previous levels. Thus, the estimated budget is based on 5,000 total productive labor hours (not proposal-restrictive for a completion contract) with labor costs based on current average contractor salaries and appropriate cost of living escalations.

Preclinical Toxicology of Drugs Developed for Cancer and Other Diseases. Concept for an RFP reissue, total $76,024,216 over seven years, six awards. Division of Cancer Treatment and Diagnosis.

Toxicology studies conducted under these contracts include: maximum tolerated dose; dose limiting toxicities; schedule-dependent toxicity; reversibility of adverse effects; safe clinical starting dose. Historically, agents approved for evaluation under these contract arise from a variety of sources through NCI and NIH programs.

Since 1996, the Toxicology and Pharmacology Branch has supported the development of numerous agents for NCI and NIH programs. Between 2004 and 2008, resources obtained via the contracts derived from this concept supported 37 NCI RAID projects and 18 DDG and JDC programs. For NIH-RAID programs from 2006 to the present, eight of 13 approved projects utilized these contracts to support IND filing. Work done under the current contracts supported the filing of 21 INDs. There is expected to be an increased need for these resources.

The use of the Work Assignment Managed Contract to perform toxicology studies allows the TPB to modify the study design as the study is in progress with relative ease so that the opportunity to collect important toxicological or plasma drug level data is not missed.

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