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Harkonen Denied Rehearing on Conviction

A three-judge panel of the U.S. Court of Appeals for the Ninth Circuit denied a petition June 1 from W. Scott Harkonen for a rehearing en banc. Harkonen filed the appeal in January after the appeals court denied a writ of error in December 2017 upholding his wire fraud conviction in connection with a press release issued by InterMune Inc. concerning its drug Actimmune.

The panel noted "the full court has been advised of the petition for rehearing en banc, and no judge of the court has requested a vote on the petition for rehearing en banc."

Harkonen's appeal contended the denial "raises questions of exceptional importance regarding the judicial power to remedy on coram nobis the wrongful conviction of an innocent defendant. The panel ruled that coram nobis is not necessarily available to remedy claims of actual innocence. That ruling conflicts with Supreme Court precedent and the decisions of other circuits. Rehearing is required to conform this Court's case law with Supreme Court law, and also to resolve a question of exceptional importance." ❖

Arbitrator Rules in Favor of Trial Sponsor In Breach of Contract Case Against CRO

An arbitrator ruled June 25 that Clinical Research Organization inVentiv, which is now part of Syneos Health, breached a contract with CEL-SCI Corporation. CEL-SCI hired inVentiv to manage a global Phase 3 head and neck cancer study from 2011 to 2013.

"This is a final and binding decision and to CEL-SCI's knowledge, marks the first ever decision in favor of a pharmaceutical/biomedical company against a CRO for breach of contract," CEL-SCI said in announcing the decision.

CEL-SCI noted the arbitration and its findings are subject to confidentiality requirements; however, CEL-SCI disclosed the arbitrator found inVentiv materially breached its contract with CEL-SCI and that "inVentiv knowingly misled CEL-SCI with respect to 'enrollment projections,' which, in the arbitrator's opinion, was 'fraudulent,' but the arbitrator denied CEL-SCI's fraud claim as a result of certain legal 'roadblocks.'"

The arbitrator assessed inVentiv for all of the arbitrator's fees for the arbitration as a result of inVentiv's "scorched earth litigation tactics" and denied all but one of inVentiv's counterclaims against CEL-SCI ($429,649 for unpaid invoices). The arbitrator awarded CEL-SCI $2.9 million in damages.

"With this ruling against inVentiv, we have been vindicated. inVentiv's actions slowed down the clinical development process of our Phase 3 cancer immunotherapy Multikine. The delays in the study caused by inVentiv not only delayed the potential approval of this investigational cancer drug by years, but it caused investors to wonder about the utility of the drug, said CEL-SCI CEO Geert Kersten.

The arbitration ruling in favor of CEL-SCI was for breach of contract by inVentiv, which CEL-SCI said fewer than 100 subjects in CEL-SCI's Phase 3 cancer trial. CEL-SCI replaced inVentiv in March 2013 with Ergomed and ICON CROs, which "successfully completed enrollment of 928 patients in the world's largest Phase 3 study in head and neck cancer." The last subject was enrolled in September 2016 and the company is waiting for the required number of events to occur to determine survival outcomes, which was the Phase 3 study's primary goal.

"The arbitrator's decision against inVentiv provides further vindication of our long-standing contention that we were not dealt with in good faith and fairly, and that inVentiv improperly managed our Phase 3 clinical trial that resulted in crippling delays in recruiting patients," said John Cipriano, CEL-SCI's senior vice-president of regulatory affairs. "The CROs that CEL-SCI hired to replace inVentiv and who have completed enrollment in our study demonstrated that there is a great amount of interest in our investigational product and that when properly managed our Phase 3 trial could be enrolled and completed in a reasonable period of time."

CEL-SCI signed an agreement with the CRO Pharmanet in 2010 to run the its pivotal Phase 3 clinical trial in advanced primary (not yet treated) head and neck cancer. Under the agreement, the Phase 3 clinical trial of 880 head and neck cancer patients was to be enrolled within 15-to-18 months from the start of the clinical trial and was to end in late 2015. Enrollment was started in January 2011.

In the summer of 2011, Pharmanet was acquired by inVentiv, which itself had been purchased by a private equity firm in 2010 to create a "super-sized" CRO by acquiring other CROs. "In April 2013, CEL-SCI replaced inVentiv because enrollment in the study was far behind what been agreed to in its contract," CEL-SCI said. Between January 2011 and April 2013 only 117

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subjects were enrolled in the trial and they included the subjects enrolled by CEL-SCI's partners Teva and Orient Europharma, which for the purposes of activities associated with the Phase 3 clinical trial, were managed by inVentiv.

In October 2013, CEL-SCI filed the arbitration suit against inVentiv Health Clinical, LLC (f/k/a PharmaNet LLC) and PharmaNet GmbH (f/k/a PharmaNet AG). The arbitration hearing started in September 2016 and the last witness was called in November 2017. Closing arguments were presented this April.

In July 2017, inVentiv Health, Inc., the ultimate parent company of the respondents in the arbitration, merged with INC Research Holdings, Inc., a company of about equal size. The combined entity was named INC Research. In January 2018 INC Research changed its name to Syneos Health. ❖

CDER Sends Untitled Letter To Israeli Company Over Missing PMR Study

An Israeli company received a June 15 Untitled Letter from the Center for Drug Evaluation and Research's Office of Scientific Investigations after the company failed to conduct a study, which was a postmarketing requirement (PMR) for Testosterone Gel 1%.

"Failure to conduct the PMR impedes the evaluation of important information regarding the serious safety risk of major adverse cardiovascular events (MACE) associated with the use of your drug for testosterone replacement therapy (TRT) in men," the letter said.

The letter noted that the FDA notified Perrigo Israel Pharmaceuticals Ltd on Feb. 9, 2015, of the requirement for a postmarket clinical trial to complete study with final protocol submission due in June 2016, trial completion in June 2021 and final report submission in June 2022. "FDA encouraged Perrigo to work with other holders of NDAs for TRT products to complete this required clinical trial/PMR," the letter said.

Perrigo conveyed its commitment to complete the postmarketing requirement in April 2015. "In September 2017, FDA became aware of Perrigo's decision not to join the TRT Consortium. And in October 2017, FDA notified Perrigo of its failure to comply with the Final Study Protocol Submission date; requested an explanation for Perrigo's noncompliance with the PMR timetable for completion; and reminded the company of its responsibility to complete the PMR, whether independent of the TRT Consortium or as part of the Consortium.

In November 2017, the company requested the FDA "waive" its responsibility for its PMR because:

- Membership in the TRT Consortium would pose an undue financial burden on Perrigo;
- Completion of the PMR independent of the TRT Consortium would pose an undue financial burden on Perrigo;
- Testosterone Gel is an AB-rated product and is equivalent to a generic and is not subject to the PMR requirement; and that the company only should be responsible for labeling changes once the PMR is fulfilled by the TRT Consortium.

In January, FDA notified Perrigo of its failure to demonstrate good cause for noncompliance with the timetable because the circumstance for the delay was under its control, and the circumstance underlying the PMR noncompliance was not directly related to the milestone that was missed.

"As the NDA holder of Testosterone Gel, your firm is subject to PMR, including each of the milestones that constitute a timetable for completion, until a formal request to withdraw your NDA has been submitted and withdrawal of the NDA is published in the *Federal Register*," the Untitled Letter said. "Your firm has failed to comply with the timetable for completion under section 505(o)(3)(E)(ii) of the Act and has failed to demonstrate good cause for noncompliance with PMR."

The FDA said the company's Testosterone Gel was considered misbranded and the required postmarketing trial was in delayed status.

Editor's Note: All FDA Warning and Untitled Letters are available in Thompson Information Services' FDA Enforcement Letter Database, which is available to subscribers of Thompson's electronic service fda.complianceexpert.com. ❖

Recommendations Developed for Expanding Lung Cancer Trial Eligibility Criteria

The LUNGevity Working Group developed recommendations for expanding lung cancer clinical trial eligibility criteria.

The group used recently published recommendations from the American Society of Clinical Oncology and Friends of Cancer Research to examine eligibility criteria involving brain metastases, history of previous malignancy and reduced performance status. "When defined as exclusion criteria, these three conditions in aggregate could exclude as many as 50 percent of lung cancer patients from participating in clinical trials," the

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group said in a June 18 *Journal of Thoracic Oncology* article detailing the recommendations.

"We have been working with multiple stakeholders to create clinical trials that are effective and accessible to more patients," said Andrea Ferris, president and CEO of the LUNGevity Foundation. "New options in lung cancer treatment are evolving rapidly, and patients need to be able to access them. The publication is a big step toward our goal of expanding clinical trial eligibility, and one that can potentially benefit a lot of lung cancer patients."

The group said allowing patients with untreated, asymptomatic brain metastases to participate in clinical trials would provide "an opportunity to identify potentially effective systemic treatments for intracranial disease and could reduce the need for whole brain radiation, while providing important safety information in the patient population that will inevitably be seen in clinical practice."

The article added that "exclusions of patients with brain metastases continue to appear in lung cancer clinical trials despite evidence that the relative impact of brain metastases on overall survival is modest after accounting for other factors such as number of metastatic sites. In addition, response rates of untreated lung cancer brain metastases to systemic therapies are not substantially different than response rates at extracranial sites."

The group noted that "although excluding prior malignancy in the prior five years might make sense in the curative setting where the time horizon to outcome is long, these exclusions make little sense in the palliative setting where median survival historically has been less than 15 to 18 months and where the likelihood of death from a pre-existing cancer is extraordinarily unlikely." The group also said the restriction of individuals with poor performance status "may be unnecessary with new, less toxic targeted and immunotherapeutic agents and with improved supportive care. The Working Group recommends that sponsors consider feasibility of expansion cohorts or separate safety studies specifically targeting [poor performance status] patients who are analyzed separately from the trials conducted for regulatory purposes."

Specifically, the Working Group recommended to include untreated asymptomatic brain metastases (except brain stem metastases) and stable, previously radiated or resected brain metastases (not requiring corticosteroids) and exclude or limit pre-treatment requirements to symptomatic brain metastases, lesions larger than 1 cm, large posterior fossa metastases, and solitary brain metastasis with no other sites of metastatic disease or no secure diagnosis.

The group also recommended including subjects with any history of prior malignancy (regardless of time interval) except for invasive, active malignancy requiring ongoing therapy.

The group said poor performance status was not suggested for Phase 1 or registrational studies but to consider including poor performance status patients when the drug has been well-studied and safety has been established in a different tumor type, in studies for different disease states (such as stage 3 lung cancer with radiotherapy), in selected investigator-initiated trials, and in combination studies, when both agents have well-established safety.

They also recommended using poor performance status as a stratification factor for trials with randomization, or, in the context of Phase 2 trials, as "expansion cohorts." ❖

Michigan Medicine Reports Data Breach

Michigan Medicine notified 870 research subjects June 25 of a data breach after the theft of a laptop computer.

The data stored on the laptop, which was stolen in a car break-in June 3, was from several research studies and could have included patient names, birthdates, medical record numbers, gender, race, diagnosis and other treatment-related information.

The University of Michigan medical center said the employee violated the studies' institutional review board approvals and Michigan Medicine policies by downloading and storing the research data on a personal laptop. In addition, while center policy requires patient information to be stored on an encrypted device, the employee's laptop was password-protected, but not encrypted.

Affected subjects were advised to monitor their medical insurance statements for any potential evidence of fraudulent transactions using their information. "Michigan Medicine believes the risk of this occurring is low, partly because the data on the electronic device does not include any health plan information or other identifying information that could lead to medical identity theft or financial identity theft," the center said.

"Michigan Medicine continues to educate our entire workforce on the importance of following our patient

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privacy policies. In response to this incident, educational materials will be improved to further enhance key messages about the prohibited use of personal, unencrypted devices for storage of research data," a center statement said.

The theft was immediately reported to the police, and Michigan Medicine was notified on June 4. Michigan Medicine also notified Department of Health and Human Services' Office for Civil Rights. ❖

ACRP to Develop CRC Hiring Guidelines

The Association of Clinical Research Professionals (ACRP) announced a new initiative June 13 to create a comprehensive set of competency-based guidelines for hiring clinical research coordinators (CRCs).

"Variance is the enemy of quality. The ad hoc manner in which we hire and train CRCs is failing to improve quality in clinical research conduct," said ACRP Executive Director Jim Kremidas in announcing the initiative. "By providing industry with standardized hiring guidelines, we hope to equip hiring managers with the resources necessary to more efficiently and effectively build tomorrow's workforce, reduce turnover, and improve clinical trial quality."

The hiring guidelines will be based on ACRP's Core Competency Guidelines for Clinical Research Coordinators, which were developed earlier this year.

"This new initiative is a natural extension of our work in defining competency standards for CRCs," said Beth Harper, ACRP's Workforce Innovation Officer. "By equipping site leadership with hiring guidelines for entry-level CRCs, we are continuing to improve the efficiency and effectiveness of clinical trials by moving competency in our industry from theory to practice."

Development of the hiring guidelines will be conducted by a task force of the multi-stakeholder ACRP Workforce Innovation Steering Committee. The task force will:

- create job profiles based on the prioritized competencies required of entry-level CRCs;
- determine methods, such as behavioral and structured interviews, tests, simulation or organizational activities, and objective scoring criteria to evaluate prioritized competencies; and
- create behavioral interview questions based on a competency-based question bank.

If interested in contributing to this initiative and joining the task force, contact Harper at beth.harper@acrpnet.org. ❖

FDA Sets Public Docket on Data Standards

The FDA established a public docket June 18 on the use of data standards in new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), and certain investigational new drug applications (INDs).

The docket (FDA-2018-D-1216) is intended for general comments related to technical specifications that are not specific to documents or issues that are the subject of other dockets, or for comments specific to electronic submission guidance.

Electronic submissions are required two years after the FDA issues final guidance specifying an electronic submission format. "The agency has concluded it is not feasible to describe and implement the electronic format or formats that would apply to all the submissions covered in one guidance document," an announcement of the docket said.

Instead, the FDA issued guidance that described how the agency interprets the electronic submission requirements of the Food, Drug, and Cosmetic Act.

"To assist sponsors in the submission of data in standardized electronic format in NDAs, ANDAs, BLAs, and certain INDs, CBER and CDER have developed technical specifications guidances which provide useful technical specifications, recommendations, and general considerations for submitting standardized data and related information in electronic format." The guidances explain, clarify, and define the specific use of data standards in regulatory submissions.

The FDA plans to use the public docket to gather "information, comments, and ideas on any matters related to the use of technical specifications that are not specific to the documents or issues addressed in other dockets. This information will give the Agency insight into stakeholders' experiences and views regarding the use of technical specifications guidances and the data standards they contain," the FDA said. ❖