Researchers behaving badly: (Unreported) misconduct in clinical trials

Charles Seife, Professor of Journalism
Arthur L. Carter Journalism Institute at NYU

Barriers to Evaluating Clinical Trials

- Missing studies
- Disappearing subjects
- Changing outcomes
- Misrepresentation of results
- Misconduct and fraud

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

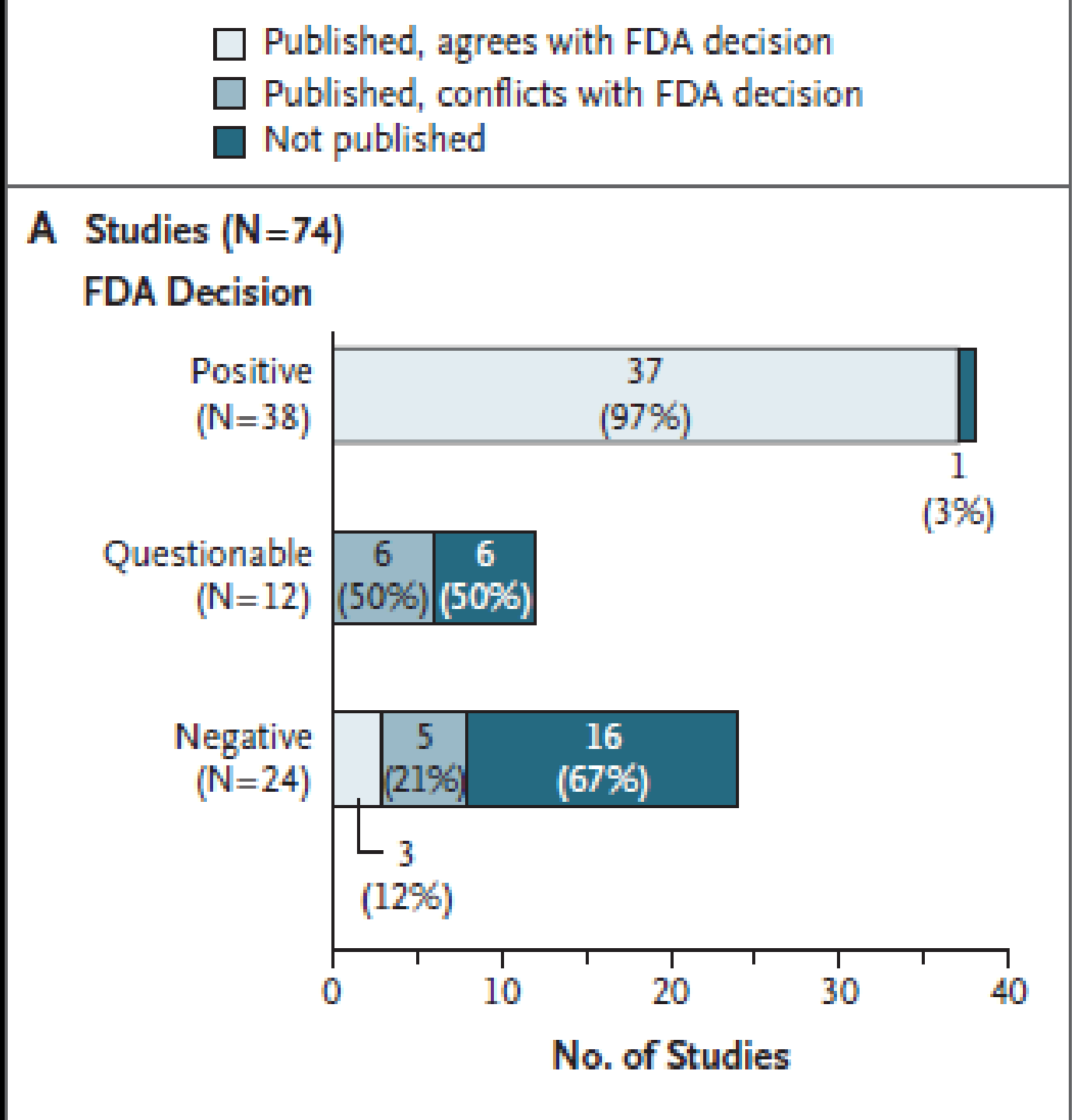
Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

ABSTRACT

BACKGROUND

Evidence-based medicine is valuable to the extent that the evidence base is complete and unbiased. Selective publication of clinical trials — and the outcomes within those trials — can lead to unrealistic estimates of drug effectiveness and alter the apparent risk–benefit ratio.

N Engl J Med 2008;358:252-60.

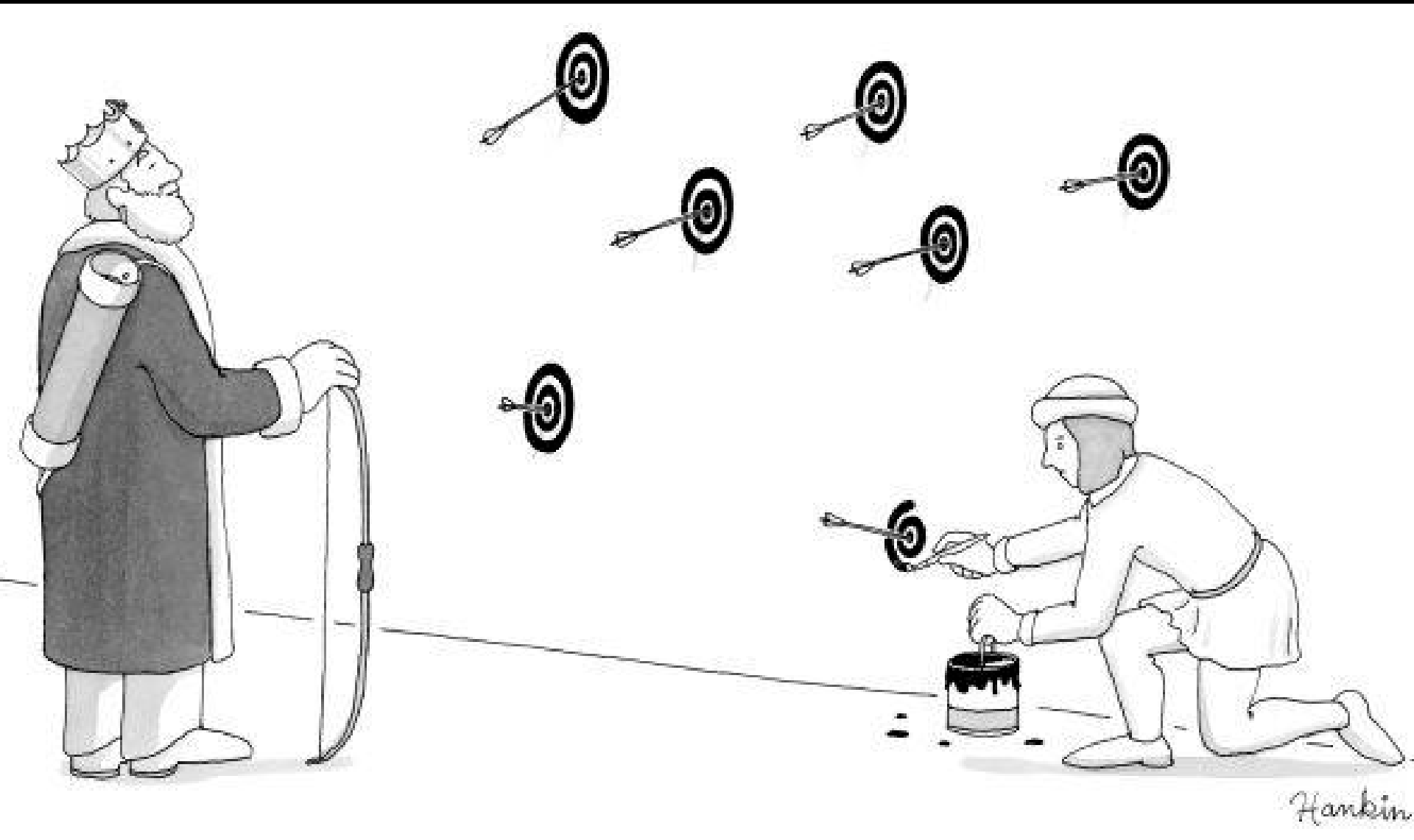

Published, agrees with FDA decision
Published, conflicts with FDA decision
Not published
A Studies (N=74)
FDA Decision
Positive (N=38)
37 (97%)
1 (3%)
Questionable (N=12)
6 (50%)
6 (50%)
Negative (N=24)
5 (21%)
16 (67%)
3 (12%)
0
10
20
30
40
No. of Studies

Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis

Joseph S Ross *assistant professor of medicine*[1 2], Tony Tse *program analyst at ClinicalTrials.gov*[3], Deborah A Zarin *director of ClinicalTrials.gov*[3], Hui Xu *postgraduate house staff trainee*[4], Lei Zhou *postgraduate house staff trainee*[4], Harlan M Krumholz *Harold H Hines Jr professor of medicine and professor of investigative medicine and of public health*[2 5 6]

[1]Section of General Internal Medicine, Department of Medicine, Yale University School of Medicine, New Haven, CT, USA; [2]Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, CT; [3]Lister Hill National Center for Biomedical Communications, National Library of Medicine, National Institutes of Health, Bethesda, MD, USA; [4]Fuwai Hospital and Cardiovascular Institute, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [5]Robert Wood Johnson Clinical Scholars Program and Section of Cardiovascular Medicine, Department of Medicine, Yale University School of Medicine, New Haven, CT; [6]Section of Health Policy and Administration, Yale University School of Epidemiology and Public Health, New Haven, CT

BMJ 2011;344:d7292 doi: 10.1136/bmj.d7292 (Published 3 January 2012)


Hankin

Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research

An-Wen Chan, Karmela Krleža-Jerić, Isabelle Schmid, Douglas G. Altman

CMAJ • SEPT. 28, 2004; 171 (7) 735

The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews

Jamie J Kirkham,[1] Kerry M Dwan,[1] Douglas G Altman,[2] Carrol Gamble,[1] Susanna Dodd,[1] Rebecca Smyth,[3] Paula R Williamson[1]

Cite this as: BMJ 2010;340:c365
doi: 10.1136/bmj.c365

Outcome Reporting in Industry-Sponsored Trials of Gabapentin for Off-Label Use

S. Swaroop Vedula, M.D., M.P.H., Lisa Bero, Ph.D., Roberta W. Scherer, Ph.D., and Kay Dickersin, Ph.D.

N Engl J Med 2009;361:1963-71.

Sexual Function in Men Receiving Dutasteride for Androgenetic Alopecia

This study is ongoing, but not recruiting participants.

Sponsor:
Stiefel, a GSK Company

Collaborator:
GlaxoSmithKline

Information provided by (Responsible Party):
GlaxoSmithKline (Stiefel, a GSK Company)

ClinicalTrials.gov Identifier:
NCT02014584

First received: **December 12, 2013**
Last updated: **February 4, 2016**
Last verified: January 2016
History of Changes

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History of Changes

Primary outcome	Measure: Proportion of subjects with a change in sexual function defined as a negative change from baseline in the IIEF-EF score of >=4 units or a score of <=25 on or before Week 24 Time Frame: Baseline and Weeks 4, 12 and 24. Safety Issue? No Description: International Index of Erectile Function (IIEF) questionnaire is used to assess erectile function. It is a 15-item questionnaire with individual items assigned to five separate domains of sexual function (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction). Erectile function domain of the IIEF (IIEF-EF) includes Questions 1 through 5 and Question 15 (maximum score of 30).
Enrollment	700 (Anticipated)

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ClinicalTrials.gov Identifier:
NCT02014584

First received: **December 12, 2013**
Last updated: **February 4, 2016**
Last verified: January 2016
History of Changes

Primary outcome	Measure: Occurrence of adverse events related to sexual dysfunction Time Frame: Up to 6 months after the last dose of study medication Safety Issue? No Description: Any adverse events related to sexual dysfunction will be carefully monitored during the study, and any such events ongoing at the end of treatment (Week 48) will be reassessed up to 6 months after the last dose of study medication

Enrollment	120 (Anticipated)

Special Communication | April 16, 2008

Reporting Mortality Findings in Trials of Rofecoxib for Alzheimer Disease or Cognitive Impairment

A Case Study Based on Documents From Rofecoxib Litigation

Bruce M. Psaty, MD, PhD; Richard A. Kronmal, PhD

JAMA. 2008;299(15):1813-1817. doi:10.1001/jama.299.15.1813.

Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence

Joanna Le Noury,[1] John M Nardo,[2] David Healy,[1] Jon Jureidini,[3] Melissa Raven,[3] Catalin Tufanaru,[4] Elia Abi-Jaoude[5]

ABSTRACT

OBJECTIVES

To reanalyse SmithKline Beecham's Study 329 (published by Keller and colleagues in 2001), the primary objective of which was to compare the efficacy and safety of paroxetine and imipramine with placebo in the treatment of adolescents with unipolar major depression. The reanalysis under the restoring invisible and abandoned trials (RIAT) initiative was done to see whether access to and reanalysis of a full dataset from a randomised controlled trial would have clinically relevant implications for evidence based medicine.

DESIGN

Double blind randomised placebo controlled trial.

SETTING

12 North American academic psychiatry centres, from 20 April 1994 to 15 February 1998.

PARTICIPANTS

275 adolescents with major depression of at least eight weeks in duration. Exclusion criteria included a range of comorbid psychiatric and medical disorders and suicidality.

(HAM-D score ≤8 or ≥50% reduction in baseline HAM-D) at acute endpoint. Prespecified secondary outcomes were changes from baseline to endpoint in depression items in K-SADS-L, clinical global impression, autonomous functioning checklist, self-perception profile, and sickness impact scale; predictors of response; and number of patients who relapse during the maintenance phase. Adverse experiences were to be compared primarily by using descriptive statistics. No coding dictionary was prespecified.

RESULTS

The efficacy of paroxetine and imipramine was not statistically or clinically significantly different from placebo for any prespecified primary or secondary efficacy outcome. HAM-D scores decreased by 10.7 (least squares mean) (95% confidence interval 9.1 to 12.3), 9.0 (7.4 to 10.5), and 9.1 (7.5 to 10.7) points, respectively, for the paroxetine, imipramine and placebo groups (P=0.20). There were clinically significant increases in harms, including suicidal ideation and behaviour and other serious adverse events in the paroxetine group and cardiovascular problems in the imipramine group.

Barriers to Evaluating Clinical Trials

- Missing studies
- Disappearing subjects
- Changing outcomes
- Misrepresentation of results
- Misconduct and fraud

33 Animals Who Are Extremely Disappointed in You

"…is a work of literature. I'm totally not joking…. [the author] spent like 15 hours finding images of animals that would express the particular palette of human emotion he was going for and wrote really witty captions for them." --Ben Smith, *Buzzfeed*

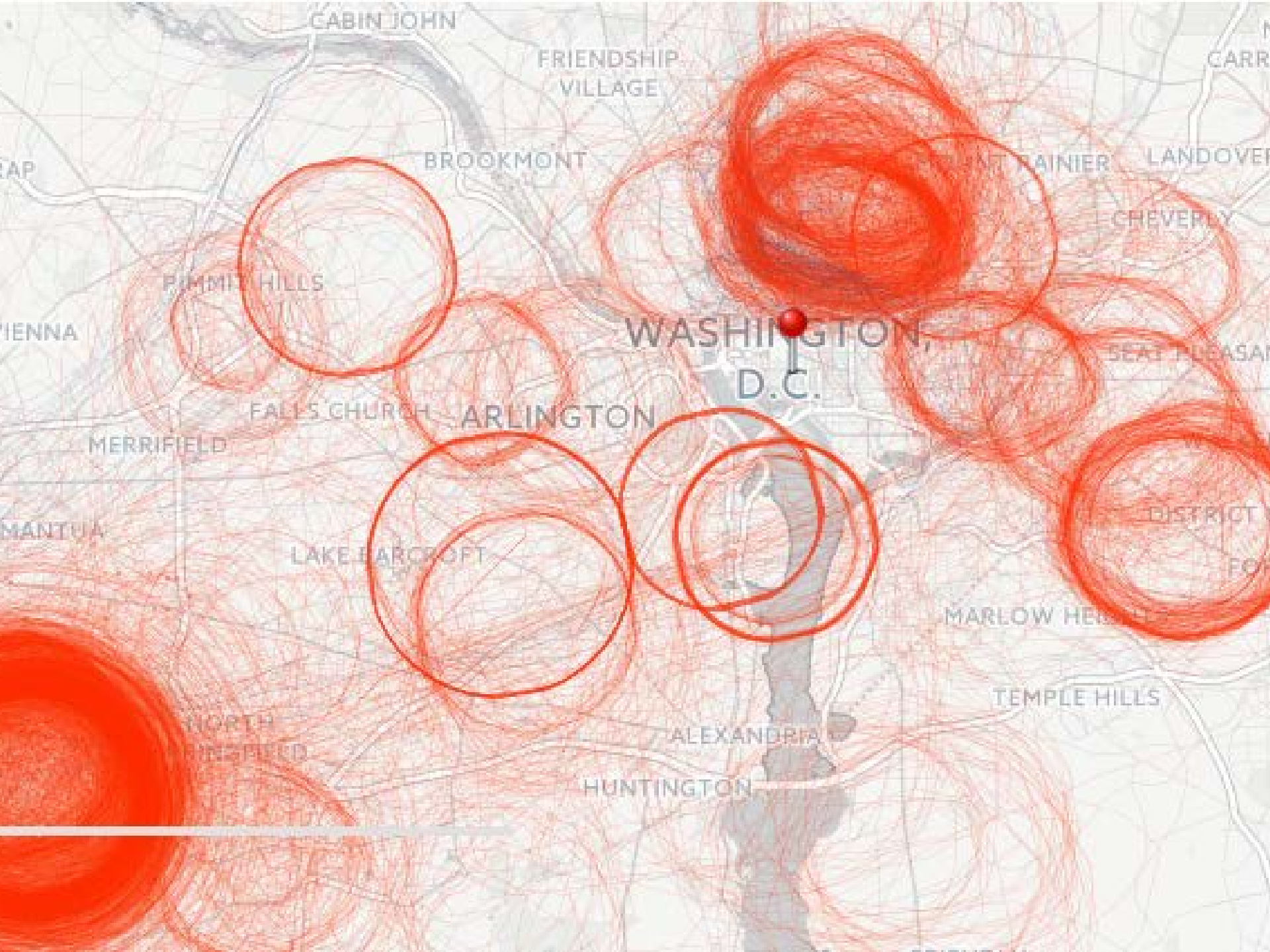
Daily Mail .com

'Vaccine' breakthrough may cure cancer - and stop it returning: How injecting two chemotherapy drugs into tumours can kick-start the immune system to fight back

- Scientists have successfully tested a new cancer 'vaccine' on mice
- The new approcach injects two chemotherapy drugs into tumours
- Researchers are to test it on people suffering from bowel and breast cancer

By STEPHEN ADAMS HEALTH CORRESPONDENT FOR THE MAIL ON SUNDAY

PUBLISHED: 18:48 EST, 7 May 2016 | **UPDATED:** 00:07 EST, 8 May 2016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BROOKMONT
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WASHINGTON, D.C.
ARLINGTON
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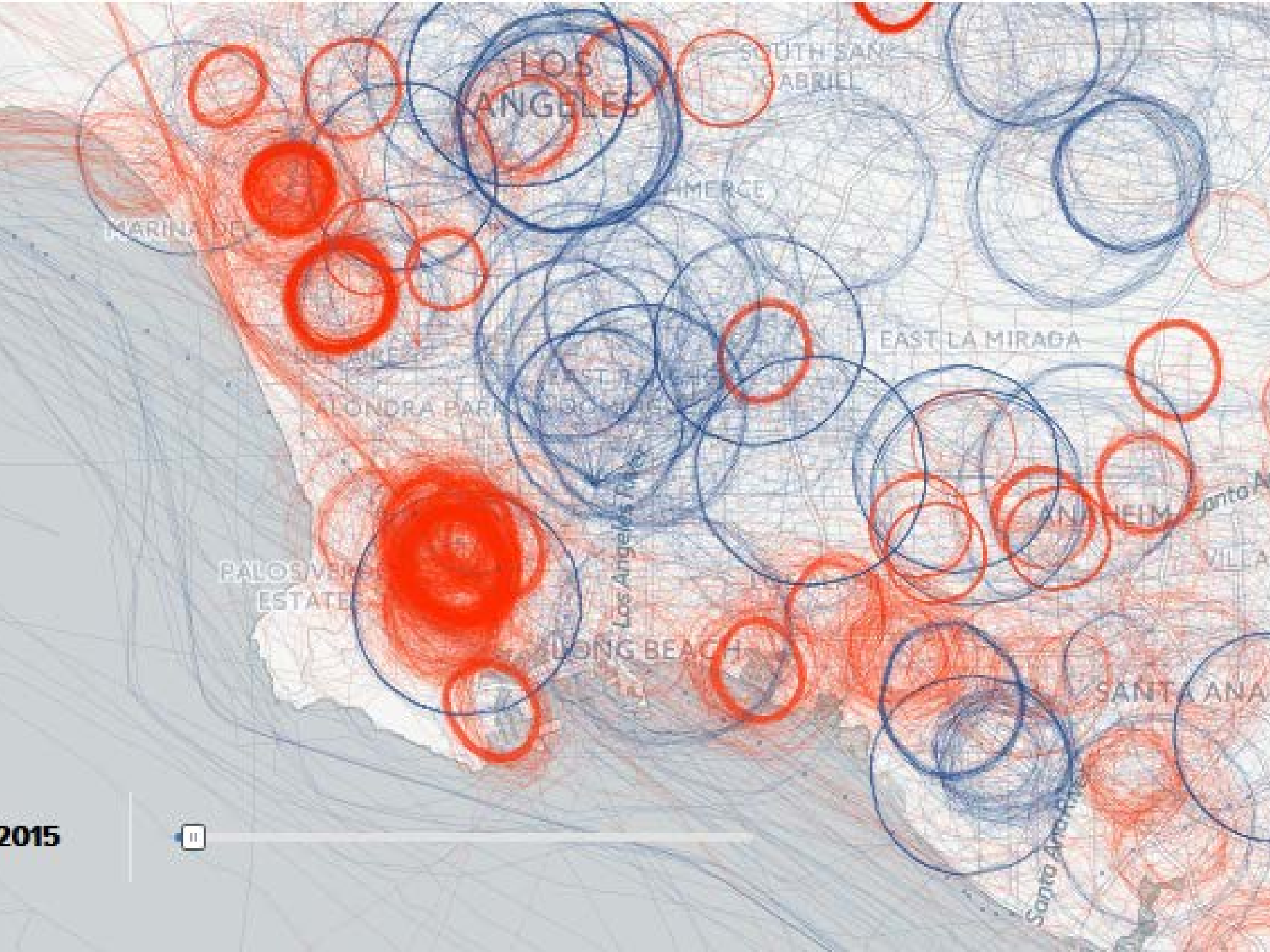
LAKE BARCROFT
ALEXANDRIA
HUNTINGTON
TEMPLE HILLS
LANDOVER
CHEVERLY
DISTRICT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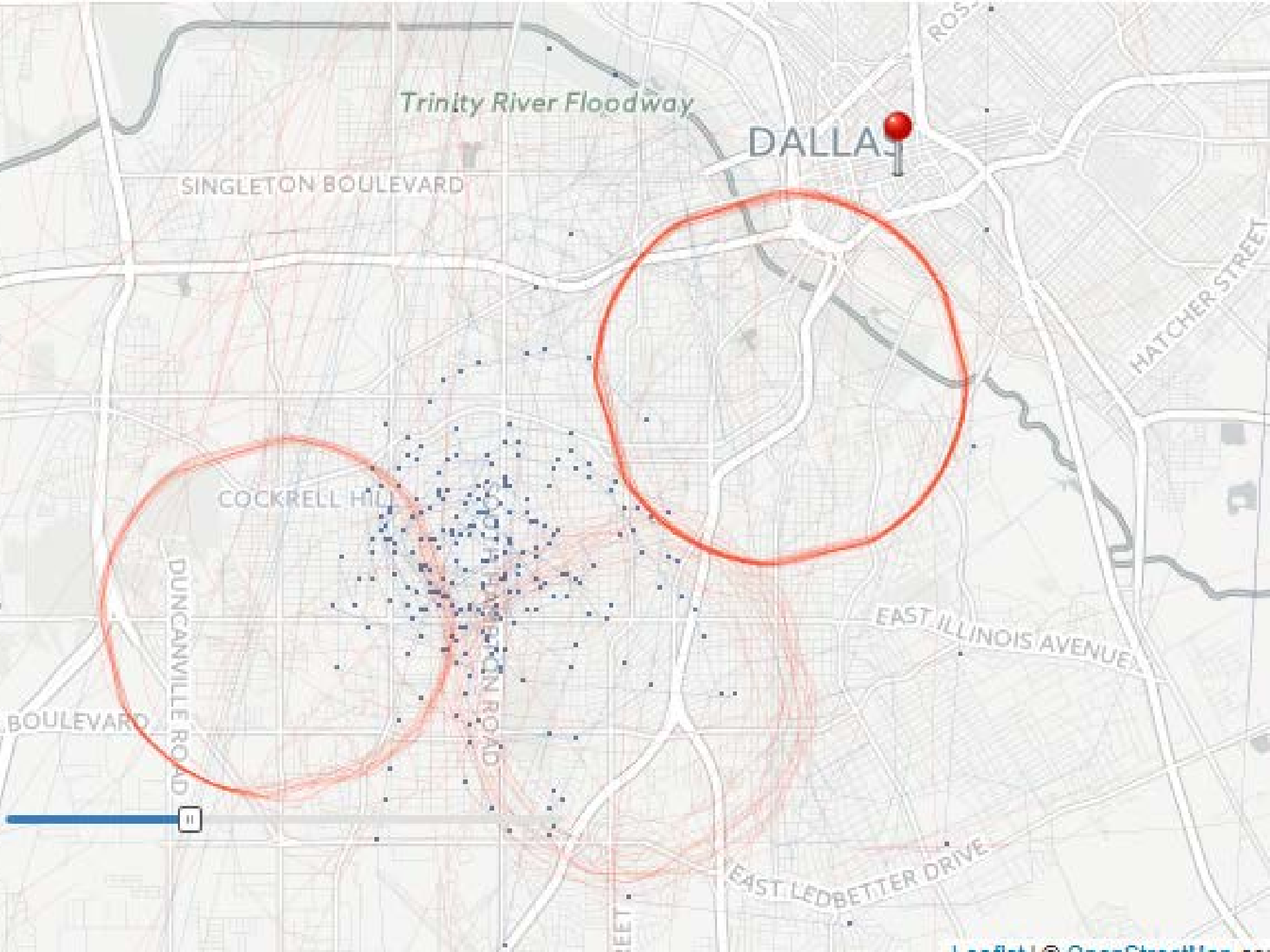
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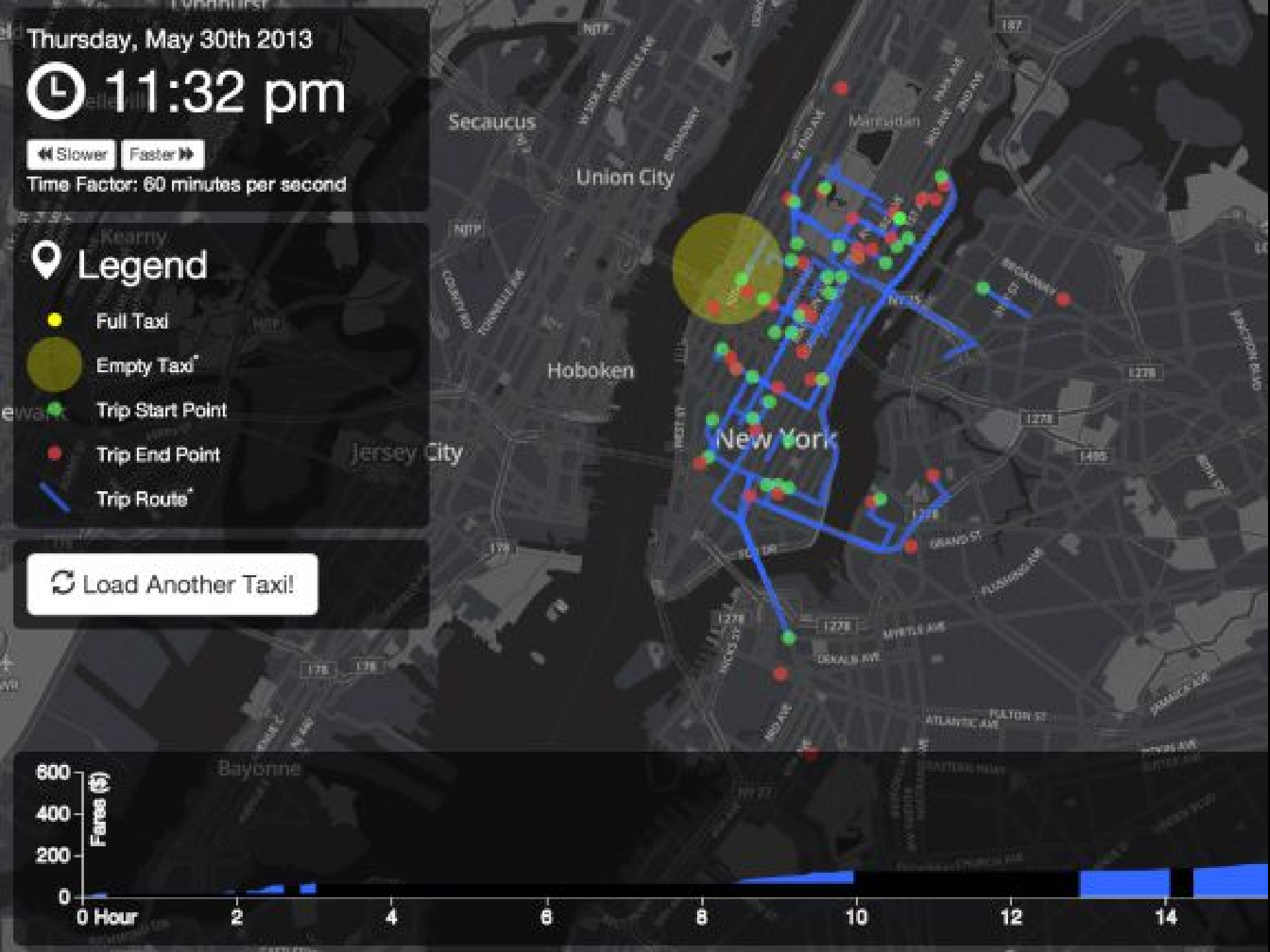
HATCHER STREET
COCKRELL HILL
DUNCANVILLE ROAD
EAST ILLINOIS AVENUE
EAST LEDBETTER DRIVE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Hoboken
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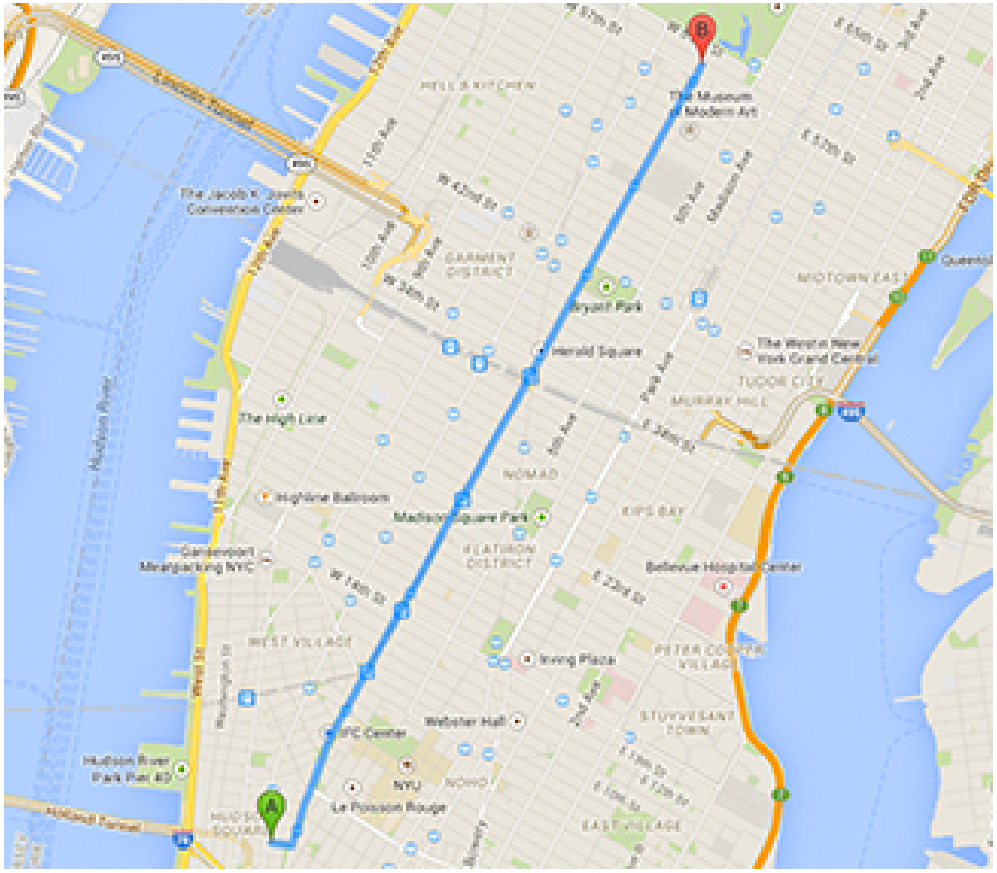

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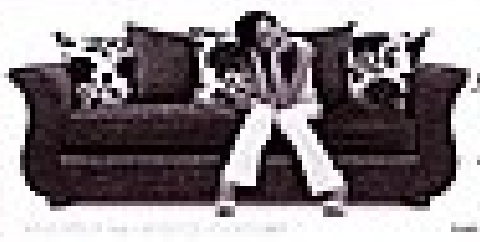
$16.50 FARE • $3.40 TIP • ©SPLASH

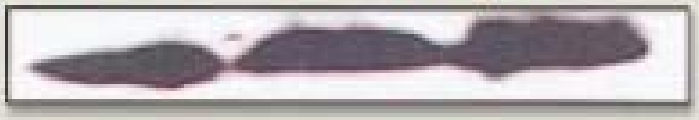
HIDDEN RECORDS SHOW MMR TRUTH



Fresh questions on stem cell findings

The discovery of more duplicated data is again casting a shadow over "versatile" adult stem cells

- First, an image of three bands on a gel is used to represent a control for an experiment in which stem cells are made to differentiate into bone cells (*Blood*, vol 98, p 2630)



- On the same page of the *Blood* paper, a reversed version of the same image, with some small modifications, is used to show the production of collagen II in stem cells made to differentiate into cartilage cells

- The same reversed image is used in US patent 7015037 to show the production of a bone-specific protein in stem cells made to differentiate into bone cells

By JIM EDWARDS / MONEYWATCH / *July 27, 2011, 4:58 PM*

FDA Finds Falsification of Drug Trial Results Affecting Dozens of Companies

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The FDA is writing to all pharmaceutical companies that have pending new drug applications to ask if they used Cetero to generate their test results. The reason: "widespread falsification" and "manipulation of equilibration samples" at the company from 2005 to 2010, the FDA says. The fallout from the Cetero scandal could affect dozens of drugs and companies.

U.S. Food and Drug Administration

Drugs

FDA Notifies Pharmaceutical Companies that Studies Conducted by Cetero Research May Require Reevaluation

The FDA is notifying pharmaceutical companies that bioanalytical studies conducted by Cetero Research, Houston, Texas (Cetero) between April 2005 and June 2010 in support of marketing applications may need to be repeated or confirmed. Cetero is a contract research organization (CRO) that performs bioequivalence and pharmacokinetic testing for a number of pharmaceutical companies.

The FDA is asking drug sponsors to identify those tests conducted by Cetero during the designated time frame that were used to support New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs). Drug sponsors will need to determine whether any of the testing performed by Cetero should be re-done.

Also, the FDA will send letters to drug sponsors with pending applications, requesting that they either repeat the bioequivalence testing done by Cetero or retest drug samples using a different test laboratory or contractor.

It is unlikely that these concerns relating to data integrity affect the overall safety and efficacy of drugs already on the market and, at this time, there is no evidence of problems with the safety, quality, purity or potency of drugs already approved. However, as a precautionary measure the FDA is asking drug sponsors to review the testing in question conducted by Cetero to make sure that data are completely reliable.

FDA is taking this action as a result of two inspections of Cetero's bioanalytical facility in Houston, Texas conducted in 2010, as well as the company's own investigation and third party audit. The inspections and audit identified significant instances of misconduct and violations of federal regulations, including falsification of documents and manipulation of samples.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Reference No.: 11-HFD-45-07-02

Roger N. Hayes, Ph.D.
President, Bioanalytical
Cetero Research
10550 Rockley Road, Suite 150
Houston, TX 77099

Dear Dr. Hayes:

This letter is to inform you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspections conducted at your bioanalytical facility, located in Houston, Texas, from May 3-7, 2010, by FDA investigators Mr. Patrick D. Stone, Dr. Jacqueline A. O'Shaughnessy, and Dr. Carol M. Rivera-Lopez; and from December 6-10, 2010, by FDA investigators Drs. Albert Peacock, Martin K. Yau, Sam H. Haidar, John Kadavil, and Xikui Chen. FDA investigators have identified significant violations of the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulations, Part 320. These violations include the widespread falsification of dates and times in laboratory records for subject sample extractions, and the apparent manipulation of equilibration samples to meet pre-determined acceptance criteria.

Cetero Research

Cetero Research Responds to FDA Untitled Letter

Cary, NC (July 27, 2011) - Cetero Research, the leading provider of early phase research services, remains fully committed to maintaining the quality and integrity of the data collected in each of its facilities, including the Houston, TX, bioanalytical laboratory. It is this commitment that makes the broad action announced publicly by FDA on July 26, 2011, even more difficult to understand.

Cetero initiated its own internal investigation of its Houston bioanalytical laboratory over two years ago when it discovered the recording of inaccurate day/time data by a small number of research chemists in its Houston facility. Cetero proactively contacted the FDA to self-report its preliminary findings, as well as seek agency feedback on its comprehensive investigation plan. At that time, Cetero clients were also contacted to make them aware of the situation. The Untitled Letter does not accept the results of our rigorous scientific analysis and discredits the Company's 1,200 dedicated and experienced employees. The research conducted on behalf of our pharmaceutical sponsors can be, and has been, properly validated.

Burning questions

- Who did the fabrication? Few bad eggs, or institutional?
- When did the fabrication happen? Why did it go on for so long?
- Where did the fabrication happen? Just Houston, or more widespread?
- Why did the fabrication happen?
- Which tests were affected?
- Which drug companies have to redo these tests?
- Which drugs were affected? Are they on the market?
- What did FDA do w/r/t affected drugs?

Freedom of Information Act (5 USC §552)

Scope: executive branch (with some exceptions)

Exemptions cover:

- Ex 1: Classified material
- Ex 2: Internal personnel rules
- Ex 3: Protected by law
- Ex 4: Confidential commercial information
- Ex 5: Predecisional information
- Ex 6: Personal privacy
- Ex 7: Certain law-enforcement records
- Ex 8 & 9: Certain records pertaining to banks and oil wells

FDA and fraud

- FOIA documents

Subject of Request: Cetero

Dear Sir/Madam:

The Food and Drug Administration (FDA) has completed processing your request for records under the Freedom of Information Act (FOIA). I apologize for any delay in responding to you.

We have already released certain materials to you and are denying the remainder of your request. The estimated volume of the records we are denying is 41 pages.

The following exemption of FOIA, 5 U.S.C. 552, is the authority for denying you access to the non-disclosable material: Exemption (b)(4) Trade secret and confidential commercial information. We have included citations to the FOIA and regulations for your information.

Section 5.65(c) of the implementing regulations of the Department of Health and Human Services (DHHS) is applicable to this denial. The regulations are contained in the Code of Federal Regulations (CFR), Title 45.

The following sections of the implementing regulations of FDA and reasons applicable to this denial are contained in the CFR, Title 21

- 20.61(b)(c) and 314.430(d)(1) Trade secret and confidential commercial information, in general, and information, not previously publicly disclosed, in a pending Investigational New Drug Application (IND)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
4040 North Central Expressway, Suite 300 Dallas, Texas 75204 Tel: 214 253-5200	05/03-07/2010
	FEI NUMBER 1000117586

NAME OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Chinna Pamidi, Ph.D., President

FIRM NAME	STREET ADDRESS
Cetero Research	10550 Rockley Rd., Suite 150
CITY AND STATE *(Zip Code)* Houston TX 77099	TYPE OF ESTABLISHMENT INSPECTED Bioanalytical Laboratory

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

This document lists observations made by the FDA representative during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

The following observations 1 and 2 pertain to Cetero's internal investigation of complaint allegations initially reported to FDA in June 2009.

1. Falsified source records

Records for the extraction of subject samples in numerous studies were falsified. Specifically, laboratory technicians identified as conducting the work were not present in the facility at the documented time of the study event. Electronic records of card key building entry time indicate that laboratory technicians arrived onsite only after the documented start time of sample extraction in at least 1900 instances over the period of April 15, 2005 through June 30, 2009. The falsification involves data from multiple studies for multiple sponsors.

2. Failure to document procedures for and identity of "prep" run injections

Electronic records of chromatography acquisition for subject sample analysis include a "prep" folder in addition to the study folder of final results. Cetero's internal investigation reported more than (b)(4) "prep" runs for about (b)(4) studies over the period of April 2005 through June 2009. There are no written procedures to describe the selection, evaluation, and reporting of such sample "prep" injections. Aside from the details in the chromatography acquisition software, there is no documentation to confirm the actual identity of the samples saved in the "prep" folder and laboratory staff did not record the injection of "prep" runs in the instrument log book. Cetero's written correspondence to FDA for the "prep" runs does not reveal the lack of written procedures and documentation of the identity of the "prep" injections. Despite the above, the firm's investigation plan claims that the allegation of "fixing" runs to obtain a passing result can be addressed by reviewing the "prep" injections.

3. Study (b)(4) and the two related bioanalytical method validation projects: AP LC/MS/MS 305.100 ((b)(4)) and AP LC/MS/MS 168.100 ((b)(4) (b)(4)

May 2010 Inspection

- Study (b) (4) ((b) (4)), sponsored by (b) (4) .
- Study (b) (4) ((b) (4)), sponsored by (b) (4)
- Study (b) (4) ((b) (4)), sponsored by (b) (4)
- Study (b) (4) ((b) (4)), sponsored by (b) (4)
- Study (b) (4) ((b) (4)), sponsored by (b) (4)

December 2010 Inspection

- Study (b) (4) ((b) (4)), sponsored by (b) (4) .
- Study (b) (4) ((b) (4)), sponsored by (b) (4)
- Study (b) (4) ((b) (4)), sponsored by (b) (4) .
- Study (b) (4) ((b) (4)), sponsored by (b) (4)

These inspections are part of FDA's Bioresearch Monitoring (BIMO) Program, which includes inspections to evaluate the conduct of research, to confirm that data intended for submission to FDA are reliable as a basis for FDA approval and regulatory decisions, and to verify compliance with the bioavailability and bioequivalence requirements in 21 CFR Part 320.

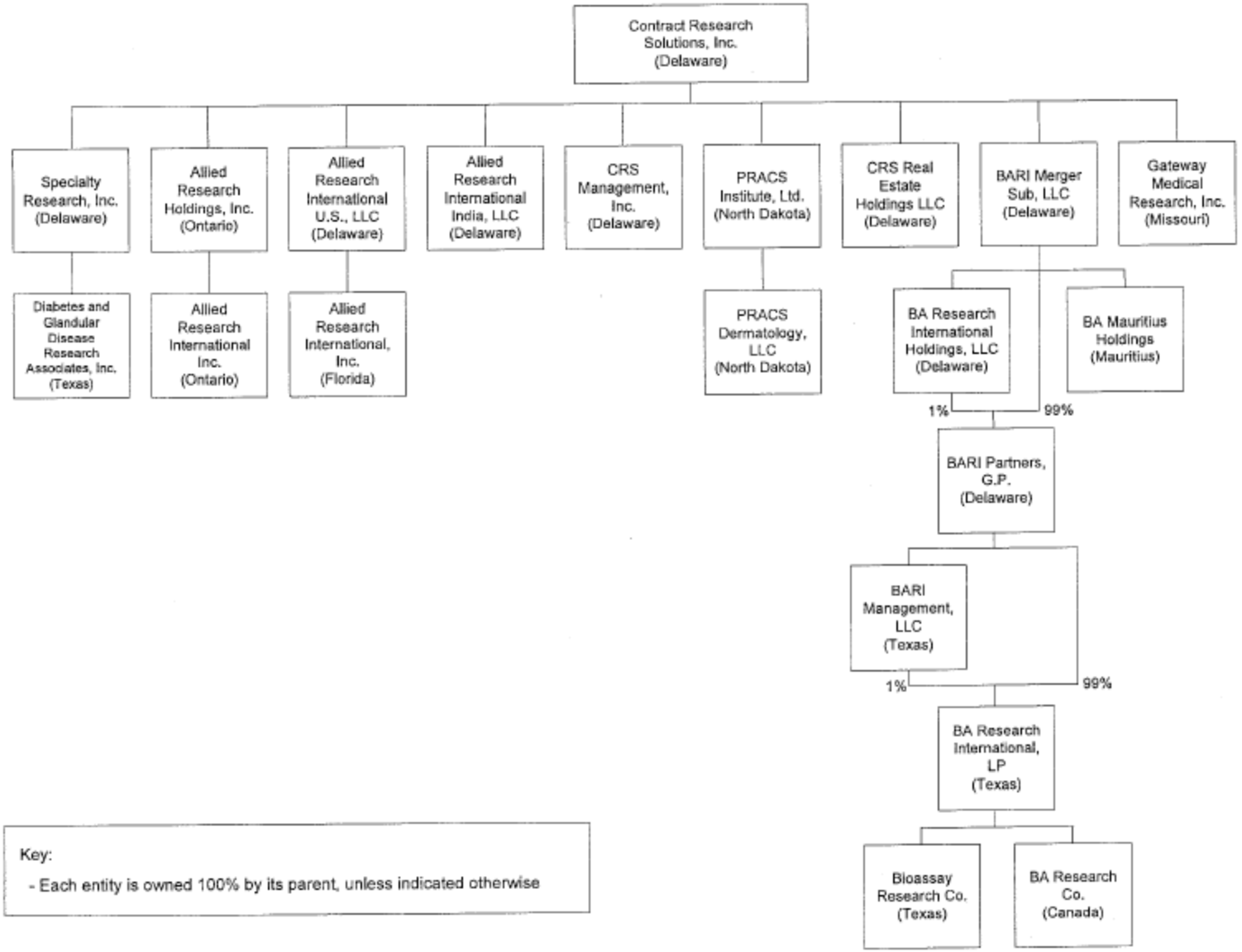
In a letter dated April 22, 2009, one of your employees (the complainant) brought formal allegations of regulatory violations and other misconduct to your firm's attention. In this letter, it was noted that as early as June 2007, the complainant "first raised certain issues in a supervisor's meeting in which the former CEO ... attended. During such meeting, [the

FDA and fraud

- FOIA documents X
- Court documents

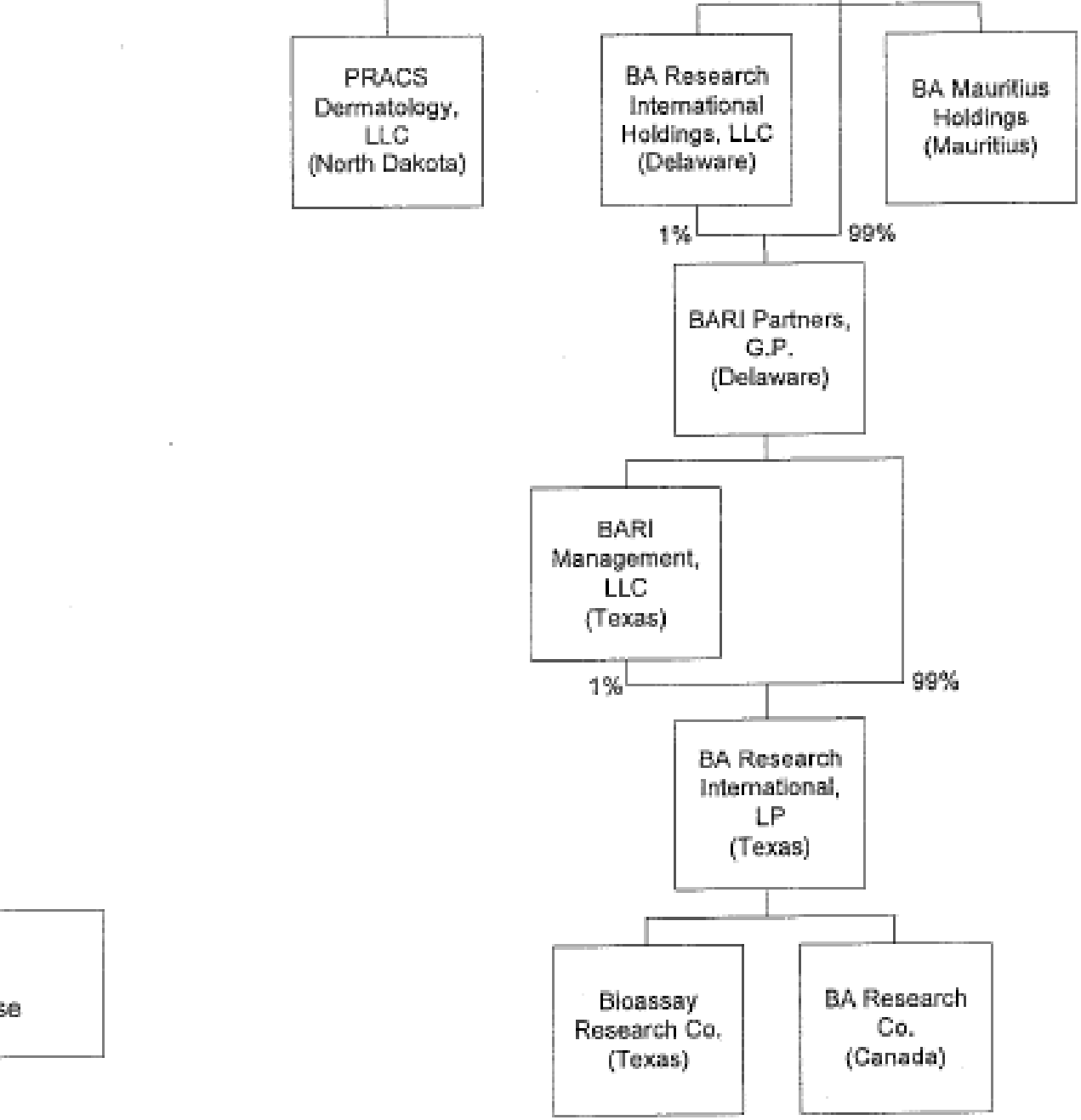
Counterparty	Address	Contract Description	Cure
Gilead	333 Lakeside Drive Foster City, CA 94404	CTA201110136661	
Gilead	333 Lakeside Drive Foster City, CA 94404	CTA201112216857	
Gilead	333 Lakeside Drive Foster City, CA 94404	CTA201201116899	
Gilead	333 Lakeside Drive Foster City, CA 94404	CTA201202087008	
GSK	7333 Mississauga Road North Mississauga, ON L5N 6L4	CTA201004304568	
GSK	7333 Mississauga Road North Mississauga, ON L5N 6L4	CTA201007144895/ CTA201007304965	
JOHNSON & JOHNSON	PO Box 16535 New Brunswick, NJ 08906-6500	CTA200910023837	
JOHNSON & JOHNSON	PO Box 16535 New Brunswick, NJ 08906-6500	CTA201106086201	

Corporate and Capital Structure Chart



Key:

- Each entity is owned 100% by its parent, unless indicated otherwise


PRACS Dermatology, LLC (North Dakota)
BA Research International Holdings, LLC (Delaware)
BA Mauritius Holdings (Mauritius)
1%
99%
BARI Partners, G.P. (Delaware)
BARI Management, LLC (Texas)
1%
99%
BA Research International, LP (Texas)
Bioassay Research Co. (Texas)
BA Research Co. (Canada)

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF MISSISSIPPI
JACKSON DIVISION

CYPRESS PHARMACEUTICALS, INC., and
HAWTHORN PHARMACEUTICALS, INC.

Plaintiffs,

v.

CRS MANAGEMENT, INC.,
PRACS INSTITUTE, LTD.,
GATEWAY MEDICAL RESEARCH, INC., and
BA RESEARCH INTERNATIONAL, L.P.,

Defendants.

Civil Action No. 3:10CV691 TSL-FKB

COMPLAINT

JURY TRIAL REQUESTED

FACTS

CYPRESS ENGAGES CETERO TO CONDUCT BIOEQUIVALENCE TESTING

18. In early 2008, Cypress sought to conduct bioequivalence testing for two prescription drug products it developed to treat cough and cold symptoms. The first contains active ingredients "A" and "B" (the "AB product"). The second contains active ingredients "A," "B," and "C" (the "ABC product").[2]

19. On April 14, 2008, Cypress entered into an agreement with CRS Management, Inc., pursuant to which Cetero would conduct bioequivalence testing for the AB product and the ABC product, pursuant to Study Protocol S08-0179, referred to in the agreement as "the Protocol." The bioequivalence testing that Cetero was engaged to conduct pursuant to Study Protocol S08-0179 is referred to herein as "Study S08-0179."

FACTS

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19. On April 14, 2008, Cypress entered into an agreement with CRS Management, Inc., pursuant to which Cetero would conduct bioequivalence testing for the AB product and the ABC product, pursuant to Study Protocol S08-0179, referred to in the agreement as "the Protocol." The bioequivalence testing that Cetero was engaged to conduct pursuant to Study Protocol S08-0179 is referred to herein as "Study S08-0179."

8.2 Drug-Drug Interactions

There is no drug-drug interaction study conducted in this NDA submission. The result of the clinical pharmacology study S08-0179 in the original NDA submission (NDA 22-439/22-442 N-000) showed that the subjects' exposure for hydrocodone in the proposed drug hydrocodone, chlorpheniramine, and pseudoephedrine oral solution was lower that that in the reference drug product Hycodan. This suggests that there may be drug-drug interaction between hydrocodone and chlorpheniramine and/or pseudoephedrine in the proposed drug formulation. However, the result of the clinical pharmacology study 11058503 in current complete response submission, the exposure of hydrocodone is within the bioequivalence range compared to the RLD. There were no differences in pseudoephedrine exposure between the test drug and the OTC monograph pseudoephedrine solution. More information regarding possible drug-drug interaction affecting the hydrocodone exposure in the Rezira™ Oral Solution may be found in the Clinical Pharmacology Review. [NDA 22-439/NDA 22-442, Clinical Pharmacology Review, Elizabeth Shang, Ph. D., R. Ph.]

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FDA and fraud

- FOIA documents
- Court documents with FDA approval docs

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF TEXAS
HOUSTON DIVISION

RACHID CHAKIR; DAVID GRAHAM; CHRISTOPHER HARRISON; TANYA KALIS; CHARLENE REED; ALBERT NGUYEN; and IKENNA OFOMA, on Behalf of Themselves and All Other Plaintiffs Similarly Situated,	)	
Plaintiffs,	)	
v.	)	Case No. 4:10-CV-2850
BA RESEARCH INTERNATIONAL, L.P.,	)	
Defendant.	)	

CPS Research
Houston, TX, USA
International Group

ALL TIMESHEETS D
07/24/0

PAY PERIOD: 7/12/08 to 7/26/08
PAYDAY: Thursday, July 31, 2008

EMPLOYEE: ALBERT NGUYEN

Study Name	Study Number	Client Code	12	13	14	15	16	17	18
Tolterodine	TOLT101	100							4
Letrozole	10845603				8				
Darifenacin	R071248	80				8		8	
Pseudoephedrine	S080179P	159					4		
Darifenacin	R071248	80							

DRUG	STUDYNUMBER	CLIENTCODE	TIMESHEET	DATE	NOTES	Company
tacrolimus	C117TAC01MR	65	NGUYEN, ALBERT	Jun-08	Client from Graham	
tacrolimus	C117TAC02MR	65	NGUYEN, ALBERT	Jun-08		
fentanyl	C004807001		NGUYEN, ALBERT	Jun-08	Archimedes PecFent	
tolterodine	TOLT101	100	NGUYEN, ALBERT	Jun-08		
letrozole	l0845603	148	NGUYEN, ALBERT	Jul-08	Client from Ofoma	
darifenacin	r071248	80	NGUYEN, ALBERT	Jul-08	Implies client code 80 :	
pseudoephedri	s080179p	159	NGUYEN, ALBERT	Jul-08	w/hydrocodone??? CY	
darifenacin	r071249	80	NGUYEN, ALBERT	Jul-08	drug name from Ofom	
quetiapine	OS122pkp03		NGUYEN, ALBERT	Jul-08		
metformin	S08-144	69	NGUYEN, ALBERT	Jul-08	note: +pioglitazone	
olmesartan	CRI00013450	65	NGUYEN, ALBERT	Aug-08	note: + amlodipine?	
hydrocodone			NGUYEN, ALBERT	Aug-08		
naproxen	CRI-00014160	65	NGUYEN, ALBERT	Aug-08		

FDA and fraud

- FOIA documents
- Court documents with FDA approval docs
  Clinicaltrials.gov
  EMA approval docs
  published protocols

9 January 2013

To whom it may concern:

This is a request for documents pursuant to EC Regulation 1049/2001 of the European Parliament and Council.

We are journalists (Seife is also a professor of journalism) who are investigating inaccurate and possibly fabricated data in US clinical trials for ProPublica.

We are currently looking into the Cetero scandal, and its implications for drugs on the US (and European) markets.

To assist in that pursuit, we request the following documents:

Any documents that discuss protocols, studies, or trials that were conducted by CRO/Cetero Research, Houston between April 2005 and July 2010. Of particular interest would be documents that identify specific protocols/studies by number or by title. Also of particular interest would be documents that provide the reasoning for conducting reviews of various formulations of Conbriza, PecFent, Torisel, Ribavirin, Temodal, Tygacil, Cilazapril, Fenofibrato, and Leflunomide, and/or provide the reasoning for suspending marketing authorizations for various

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

To all marketing authorisation holders for authorised medicinal products for which studies have been carried out or analysed by Cetero Research, during the time period April 2005 to June 2010

2 August 2012
EMA/505039/2012
Patient Health Protection

Subject: Referral under Article 31 of Directive 2001/83/EC
For authorised medicinal products for which studies have been carried out or analysed by Cetero Research, during the time period April 2005 to June 2010
Procedure number: EMEA/H/A-31/1340

Dear Sir or Madam

We hereby inform you that a procedure under Article 31 of Directive 2001/83/EC has been initiated for authorised medicinal products for which studies have been carried out or analysed by Cetero Research,

FDA and fraud

- FOIA documents
- Court documents with FDA approval docs
  - Clinicaltrials.gov
  - EMA approval docs
  - published protocols
- EMA documents with FDA documents

Six Drugs the FDA Doesn't Want You to Know Relied on Tainted Data

In 2011, the Food and Drug Administration determined that a major laboratory, the Houston facility of the now-defunct Cetero Research firm, had committed such "egregious" and pervasive research violations that years of its tests were potentially worthless. About 100 drugs were affected, but the FDA has declined to name them, saying to do so would reveal confidential commercial information. ProPublica was able to pinpoint six drugs whose approval rested, at least in part, upon data from the Cetero studies. Related Story »

	Temodar IV *Injection*	**Torisel** *Injection*	**Lazanda** *Nasal spray*	**Generic Ibuprofen** *Gelatin Capsules*	**Generic Tramadol** *Extended-release capsules*	**Generic Hydrocodone polistirex/ chlorpheniramine polistirex** *Liquid*
GENERIC NAME	Temozolomide	Temsirolimus	Fentanyl			
OTHER NAMES	Temodal (in Europe)	Torisel	PecFent (in Europe)			
DRUG COMPANY	Merck & Co	Pfizer Inc.	Archimedes Pharma	Banner Pharmacaps	Cipher Pharmaceuticals	Tris Pharma
WHAT IT IS	A chemotherapy drug aimed at difficult-to-treat brain cancers	A drug used to treat renal cell carcinoma, a type of kidney cancer	An extremely potent painkiller	A popular over-the-counter painkiller	A powerful painkiller	A narcotic cough suppressant and anti-allergy medication
WHAT WE KNOW ABOUT CETERO'S ROLE	Cetero Houston analyzed the "pivotal" trial that formed the basis for the	Cetero analyzed a component of a study to test the drug's effect on heart	Cetero analyzed a clinical trial that tested how the drug behaved when paired	Cetero analyzed one of the trials to establish the capsule's	Cetero performed three clinical trials meant to prove the drug's equivalence to	Cetero analyzed both of the clinical trials used to show that the generic was

FDA Let Drugs Approved on Fraudulent Research Stay on the Market

by Rob Garver and Charles Seife, Special to ProPublica, April 15, 2013, 9:17 a.m.

On the morning of May 3, 2010, three agents of the Food and Drug Administration descended upon the Houston office of Cetero Research, a firm that conducted research for drug companies worldwide.

Retired FDA investigator Patrick Stone (Katie Hayes Luke for ProPublica)

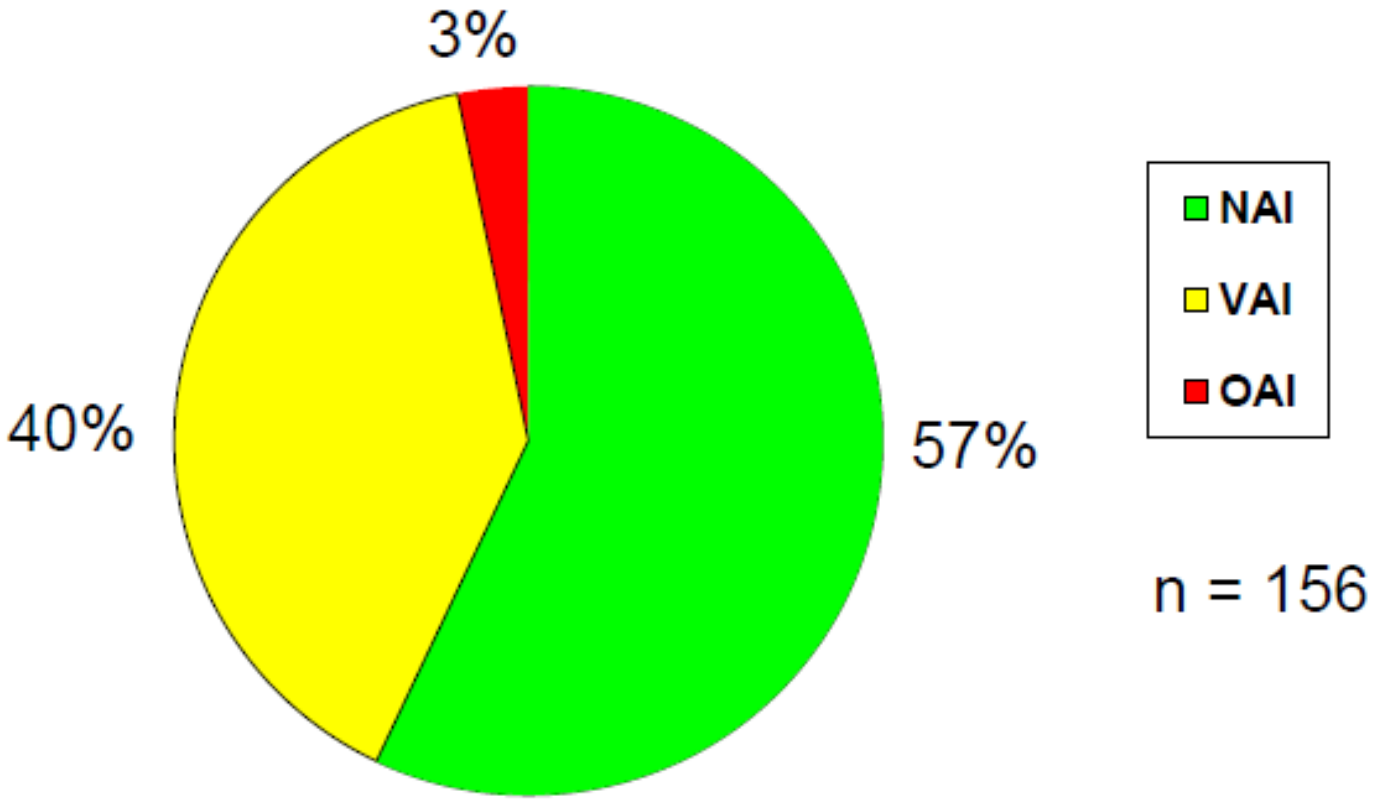
Lead agent Patrick Stone, now retired from the FDA, had visited the Houston lab many times over the previous decade for routine inspections. This time was different. His team was there to investigate a former employee's allegation that the company had tampered with records and manipulated test data.

When Stone explained the gravity of the inquiry to Chinna Pamidi, the testing facility's president, the Cetero executive made a brief phone call. Moments later, employees rolled in eight flatbed carts, each double-stacked with file boxes. The documents represented five years of data from some 1,400 drug trials.

Pamidi bluntly acknowledged that much of the lab's work was fraudulent, Stone said. "You got us," Stone recalled him saying.


FDA
INVESTIGATOR
ADMINISTRATION
SERVICE
DA
FDA

FY'14 International CI Inspections Classified All Centers*



*Inspections classified in FY'14 by CBER, CDER, and CDRH. Some inspections may have occurred in a different FY.

From inspections to literature

1: find OAI-rated inspections

2: figure out which trials were associated with those OAI-rated inspections

3: find which publications were based upon those trials

4: determine the degree to which the literature reflects the problems that led to the OAI rating

In your response, you explained that the (b)(4)

(b)(4)

FDA does not accept your explanation. (b)(4)

(b)(4)

(b)(4) These issues were brought to your attention numerous times by study monitors and (b)(4) (b)(4), yet you did not implement corrections. Your repeated failure to adhere to the protocol precluded the (b)(4)

(b)(4)

(b)(4) therefore exposed subjects to increased and unreasonable risk.

You did not conduct the (b)(4)

(b)(4)

FDA and fraud

- Insp. Documents with FDA approval docs
  - clinicaltrials.gov
  - peer-reviewed lit.
  - published protocols
  - CVs
  - EMA docs

Therapeutic angiogenesis in patients with severe limb ischemia by transplantation of a combination stem cell product

The Journal of Thoracic and Cardiovascular Surgery
v. 144, no. 2, pp. 377-382.

F. You failed to promptly report to the IRB all unanticipated problems involving risk to human subjects and others, in that you failed to report to the IRB that (in Study 2B) Subject **(b)(6)** was amputated on **(b)(6)**, fourteen days after administration of the investigational stem cell product **(b)(6)** in Study 2B. The protocol requires that amputation within 30 days of cell implantation be reviewed by the Investigator and reported to the IRB. See item 1.D. above.

1. **You submitted false information to the sponsor or FDA in a required report [21 CFR 312.70(a)].**

   a. The sinus X-ray assessments for subjects enrolled in Protocol [ ] and Protocol [ ] which were used, in Case Report Forms or other documents you submitted to the sponsor, to confirm that the subjects met the inclusion criteria, were false. These false x-ray assessments provided the basis for the submission of false information to the sponsor or FDA in a required report.

ELSEVIER

International Journal of Antimicrobial Agents 20 (2002) 235–247

INTERNATIONAL JOURNAL OF Antimicrobial Agents

www.isochem.org

Original article

Outcome of treatment of respiratory tract infections due to *Streptococcus pneumoniae*, including drug-resistant strains, with pharmacokinetically enhanced amoxycillin/clavulanate

You indicate in your August 19, 2010, affidavit that one of your responsibilities as clinica
to double-check the OCT scans necessary for each subject. You also acknowledged in you
affidavit that "this substitution or manipulation [of the OCT scans and fundus photograph
allowed them [the subjects] to have been falsely qualified for the study." Your failure to a
supervise the individuals to whom you delegated study tasks resulted in these discrepanc
records, as well as the enrollment of subjects who may not have met the eligibility criteri
subjects who may not meet eligibility criteria raises concerns about the extent to which s
safety, and welfare were protected, and about the reliability and integrity of the data cap

Clinical Trials

Comparison of Film and Digital Fundus Photographs in Eyes of Individuals with Diabetes Mellitus

Investigative Ophthalmology & Visual Science, August 2001, v.52, no.9, pp. 616--6173

to be enrolled persons as study subjects who did not qualify under particular study protocols. In addition to other specific acts cited in the plea agreement, you admitted to:

- Submitting a case report form with regard to a study subject knowing the document contained materially false laboratory entries and altered information from a radiology display report, which were critical factors i determining whether the individual was eligible to participate in the Tax 325 study (violation of 18 U.S.C. § 1001(1)(3)).

- Knowingly and willfully misrepresenting the results of a blood chemistry analysis related to the participation of a Tax 325 study subject who would not otherwise have met the criteria for that study. The subject was administered the chemotherapeutic drugs docetaxel, cisplatin, and 5-FU in connection with Tax 325 and died as a result thereof. Your failure to perceive a substantial and unjustifiable risk that death would occur when you knowingly and willfully made and used such false documents constituted a gross deviation from the standard of care that a reasonable person would observe in the situation (violation of 18 U.S.C. §§ 1001(a)(3)and 13, and New York Penal Law § 125.10)).

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF NEW YORK

****

UNITED STATES OF AMERICA

v.

PAUL H. KORNAK,

Defendant.

Criminal Action No.
03-CR-436 (FJS)

PLEA (AND COOPERATION)
AGREEMENT

****

From: **Research Misconduct Identified by the US Food and Drug Administration: Out of Sight, Out of Mind, Out of the Peer-Reviewed Literature**

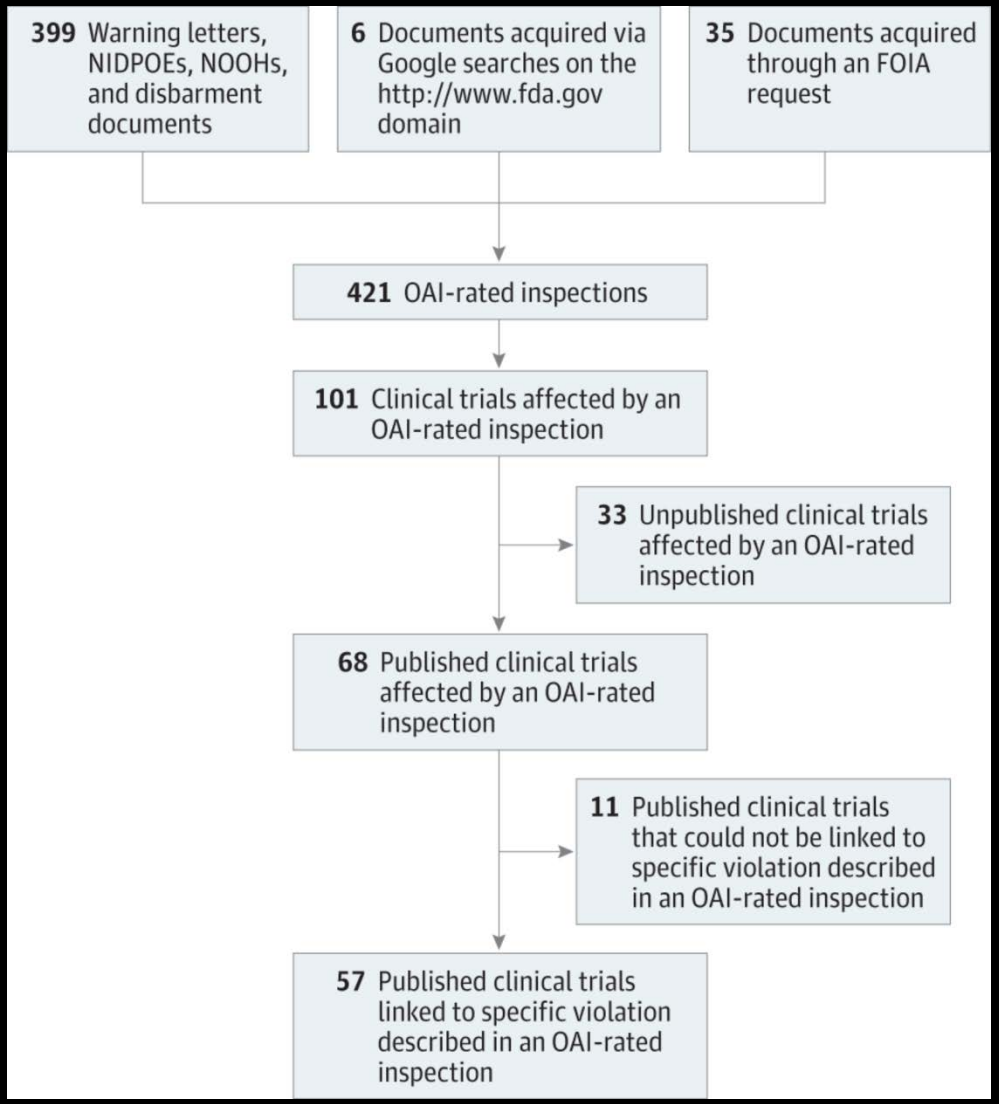


Table 2. Clinical Trials and Publications Affected by Official Action Indicated–Rated Inspections

No.	Drug/Biologic/ Procedure	Clinical Trial No.	Other Protocol Name(s)	Source Document No./ Publication Affected[a]	Falsification[b]	ADE Reporting[c]	Protocol[d]	Record-keeping[e]	Safety[f]	Other[g]
1[h]	Alogliptin	NCT00707993	SYR-322_303	Clinical inspection summary[42]/ Rosenstock et al[43]	...	—	Y	Y	Y	...
2	Amoxicillin/ clavulanic acid extended-release	—	25000/592	NIDPOE,[44] NOOH,[45] debarment order[46]/ File et al[47]	Y	—	Y	...	...	...
3	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Granger et al[50]	Y	Y	...	...	...	...
4[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Lopes et al[50]	Y	Y	Y	Y	Y	
5[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/McMurray et al[51]	Y	Y	Y	Y	Y	
6[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Wallentin et al[52]	Y	Y	Y	Y	Y	
7[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Garcia et al[53]	Y	Y	Y	Y	Y	
8[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Alexander et al[54]	Y	Y	Y	Y	Y	
9[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Alexander et al[55]	Y	Y	Y	Y	Y	
10[h]	Asenapine	NCT00145470	A7501008, P05844	Warning letter[56]/Szegedi et al[57]	...	—	Y	Y	...	...
11[h]	Autologous dendritic cells	—	1997-064	NOOH[58]/Redman et al[59]	...	—	Y	Y	...	...
12	Autologous stem cells	NCT00518401	2007-01-I	NIDPOE,[8] warning letter[9]/ Lasala et al[35]	...	—	...	...	Y	Y
13[h]	Autologous stem cells	NCT00721006	2008-01-II	NIDPOE,[8] warning letter[9]/ Lasala et al[37]	...	Y	...	...	Y	Y
14	Autologous stem cells	NCT00643981	2007-03-I	NIDPOE,[8] warning letter[9]/ Lasala et al[38]	...	—	Y	...	Y	Y
15	Autologous tumor cells	—	1995-243	NOOH[58]/Chang et al[60]	...	—	Y	Y	...	...
16[h]	Budesonide/ formoterol	NCT00206167	D5899C00001	NIDPOE[61]/Bleecker et al[62]	...	—	—	Y	...	...

	formoterol								
18[n]	Cd34+ cells	NCT00300053	ACT34-CMI	NIDPOE[64]/Losordo et al[65]	Y	Y	Y	Y	...	Y
19[n]	Cd34+ cells	NCT00300053	ACT34-CMI	NIDPOE[64]/Povsic et al[66]	Y	Y	Y	Y	...	Y
20[n]	Dfmo	NCT00003814	ILEX-DFMO341	NIDPOE,[67] NOOH[11]/Messing[68]	Y	—	Y	P	P	Y
21	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH[69]/ Ajani[70]	Y	—	Y	Y	Y	...
22	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH[69]/ Ajani[70]	Y	—	Y	Y	Y	...
23[n]	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH[69]/ Ajani et al[71]	Y	—	Y	Y	Y	...
24[n]	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH[69]/ Van Cutsem et al[72]	Y	—	Y	Y	Y	...
25[n]	Docetaxel	—	TAX327	NIDPOE,[11] NOOH,[67] NOOH[69]/ Tannock et al[73]	Y	—	Y	Y	Y	...
26	Erlotinib	NCT00081614	AVF2938	Warning letter[74]/ Bukowski et al[75]	...	—	Y	...	Y	...
27[n]	Esomeprazole/ naproxen	NCT00527787	PN400-301	NIDPOE,[12] form 483[76]/ Goldstein et al[76]	Y	P	P	Y	...	...
28	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Gibofsky et al[18]	...	—	Y	Y	Y	...
29	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Weaver et al[19]	...	—	Y	Y	Y	...
30[n]	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Markenson et al[20]	...	—	Y	Y	Y	...
31[n]	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Gibofsky et al[21]	...	—	Y	Y	Y	...
32	Faropenem daloxate	—	100288	Form 483 and EIR,[77] warning letter,[78] warning letter[79]/ Upchurch et al[80]	...	—	Y	Y	P	...
33[n]	Ferric carboxymaltose	NCT00982007	1VIT09031	Warning letter[81]/ Onken et al[82]	...	—	Y	...	...	...
34[n]	Fondaparinux	NCT00038961	APOLLO	NIDPOE[83]/Turpie et al[84]	...	—	Y	Y	Y	Y
35	Ibuprofen	NCT00225732	008a, CPI-CL-008	Warning letter,[85] clinical inspection summary[86]/ Southworth et al[87]	...	Y	Y	Y	...	Y
36[n]	Ibuprofen	NCT00225732	008b, CPI-CL-008	Warning letter,[85] clinical inspection summary[86]/ Kroll et al[88]	...	—	Y	Y	...	Y
37[n]	Indiplon	—	NBI34060-MR-0212	NIDPOE[89]/Lydiard et al[90]	Y	—	Y	Y	...	...

		MR-0212							
38[n] Leuprolide acetate	—	...	Form 483,[91] EIR,[92] letter,[93] NIDPOE[94]/ Crawford et al[95]	Y	—	Y	Y	Y	Y
39[n] Ly518674	NCT00133380	H8D-MC-EMBF	Warning letter[96]/ Nissen et al[97]	...	—	Y	P	P	Y
40[n] Modified lymphocytes	—	1990-489	NOOH[98]/Chang et al[98]	...	—	Y	Y	Y	...
41 Modified lymphocytes	—	1995-318	NOOH[98]/DeBruyne et al[99]	...	—	Y	Y	...	...
42[n] Nebivolol	NCT00200460	NEB302	NIDPOE[100]/Weiss et al[101]	Y	Y	Y	Y	...	Y
43 Ofloxacin	—	PRT002/ PRT003	NIDPOE,[102] NOOH,[103] proposal to debar/ NOOH,[104] debarment,[105] warning letter,[106] warning letter[107]/ Jones et al[108]	Y	—	Y	Y	Y	...
44[n] Olanzapine	—	FID-US-HGGD/ 2325	NIDPOE,[109] Proposal to debar/ NOOH[110]/Tunis et al[111]	...	—	Y	—	P	...
45[n] Olanzapine	—	FID-US-HGGD/ 2325	NIDPOE,[109] Proposal to debar/ NOOH[110]/ Ascher-Svanum et al[112]	...	—	Y	—	P	...
46[n] Olanzapine	—	FID-US-HGGD/ 2325	NIDPOE,[109] Proposal to debar/ NOOH[110]/Faries et al[113]	...	—	Y	—	P	...
47[n] Olanzapine	NCT00103571	F1D-US-HGLS	Warning letter[114]/Kinon et al[115]	...	—	Y	P	Y	...
48[n] Oxycontin extended-release	NCT01559701	PTI-821-CM	NIDPOE[116]/Friedmann et al[117]	P	—	Y	Y	Y	...
49[n] Paliperidone palmitate	NCT00111189	CR004198, R092670 PSY300	Warning letter[59]/ Kozma et al[118]	...	Y	Y	Y	Y	...
50[n] Paliperidone palmitate	NCT00111189	CR004198, R092670 PSY300	Warning letter[59]/ Hough et al[119]	...	Y	Y	Y	Y	...
51[n] Paroxetine	—	704	NIDPOE,[109] proposal to debar, NOOH[110]/Geller et al[120]	Y	—	Y	Y	Y	...
52[n] Phlebotomy for atherosclerosis	NCT00032357	FeAST	NIDPOE,[11] NOOH,[67] NOOH[69]/ Zacharski et al[121]	Y	—	....	...	...	...
53[n] Pomalidomide	NCT00072722	...	Warning letter,[122]/ Amato et al[123]	...	—	P	P	Y	...
54[n] Ranibizumab	NCT00445003	LRTforDME	Warning letter,[124] form 483	Y	—	Y	—	...	Y

		+PRP	and EIR,[125] warning letter[126]/ Googe et al[127]						
55[n] Ranibizumab	NCT00445003	LRTforDME +PRP	Warning letter,[124] form 483 and EIR,[125] warning letter[126]/ Gangaputra et al[128]	Y	—	Y	…	…	Y
56 Ranibizumab	NCT00445003	LRTforDME +PRP	Warning letter,[124] form 483 and EIR,[125] warning letter[126]/ Bhavsar et al[129]	Y	—	Y	…	…	Y
57[n] Ranibizumab	NCT00891735	HARBOR	Warning letter[130]/ Bushee et al[131]	…	—	Y	Y	Y	…
58[n] Reduced glutathione	—	…	Warning letter[132]/ Bishop et al[133]	…	—	—	…	Y	Y
59 Rivaroxaban	NCT00329628	RECORD 1	Compliance review,[134] medical review,[135] other review[136]/ Eriksson et al[137]	…	Y	Y	Y	…	…
60[n] Rivaroxaban	NCT00332020	RECORD 2	NIDPOE,[48] Compliance review,[134] medical review,[135] other review[136]/ Kakkar et al[138]	Y	Y	Y	Y	Y	…
61 Rivaroxaban	NCT00361894	RECORD 3	Compliance review,[134] medical review,[135] other review[136]/ Lassen et al[139]	…	Y		Y	Y	…
62[n] Rivaroxaban	NCT00362232	RECORD 4	Compliance review,[134] medical review,[135] other review,[136] form 483,[140] EIR[141]/ Turpie et al[142]	Y	Y	Y	Y	Y	Y
63[n] Rivaroxaban	NCT00329628/ NCT00332020/ NCT00361894	RECORD 1, 2, 3	Compliance review,[134] medical review,[135] other review[136]/ Eriksson et al[143]	Y	Y	Y	Y	Y	…
64[n] Rivaroxaban	NCT00329628/ NCT00332020/ NCT00361894/ NCT00329628	RECORD 1, 2, 3, 4	NIDPOE,[48] compliance review,[144] medical review,[145] other review,[146] form 483,[140] EIR[141]/ Eriksson et al[144]	Y	Y	Y	Y	Y	Y
65[n] Rivaroxaban	NCT00329628/ NCT00332020/ NCT00361894/	RECORD 1, 2, 3, 4	NIDPOE,[48] compliance review,[144] medical review,[145] other review,[146]	Y	Y	Y	Y	Y	Y

	NCT00361894/ NCT00329628		other review,[136] form 483,[140] EIR[141]/ Lassen et al[142]						
66[f] Rocuronium	NCT00124722	P05797	Warning letter,[146] letter[147]/ Pirotta et al[5]	...	—	—	P	Y	Y
67[f] Rofecoxib	NCT00060476	2006_414, Formally P30A03LD, MK0966-201	NIDPOE[83]/ van Adelsberg et al[148]	...	—	P	...	...	Y
68[f] Roflumilast	NCT00297102	BY217/M2-124	NIDPOE[61]/Calverley et al[149]	...	—	Y	Y	Y	Y
69[f] Ropinirole	—	SKF-101468/ 191	NIDPOE[89]/Allen et al[150]	Y	—	Y	Y	...	...
70 Sodium oxybate	—	OMC-GHB-2	Form 483 and EIR,[151] NIDPOE,[152] medical review[153]/ US Xyrem Multicenter Study Group[154]	P	P	...	P	P	Y
71[f] Sodium oxybate	—	OMC-GHB-3	Form 483 and EIR,[151] NIDPOE,[152] medical review[153]/ US Xyrem Multicenter Study Group[155]	P	P	...	P	P	Y
72[f] Sodium oxybate	—	OMC-SXB-21	Form 483 and EIR,[151] NIDPOE,[152] medical review[153]/ US Xyrem Multicenter Study Group[156]	P	P	...	P	P	Y
73[f] Thrombospondin-1	NCT00073125	...	Warning letter[123]/ Ebbinghaus et al[157]	...	—	P	P	Y	...
74[f] Tramadol extended-release	NCT00348010	...	NIDPOE,[158] NDOH[159]/ Babul et al[160]	Y	Y	Y	Y	Y	...
75[f] Tramadol extended-release	NCT00347685	...	NIDPOE,[158] NDOH[159]/ Pascual et al[161]	Y	Y	Y	Y	Y	...
76[f] Valsartan	NCT00154271	CVAH631DUS02	NIDPOE[162]/ Everett et al[163]	Y	Y	Y	Y	Y	...
77[f] Velimogene aliplasmid	NCT00044356	VCL-1005-208	Warning letter[164]/ Bedikian[165]	...	Y	Y	...	Y	...
78[f] Zolpidem modified-release	—	EFC4529/ ZOLADULT	NIDPOE,[89] medical review[166]/ Roth et al[167]	Y	—	Y	Y	...	...

Fraud in published clinical trials?

- We found hundreds of OAI inspections, and hundreds of cases of fraud in clinical trials
- We identified 78 publications associated with those clinical trials
- Of those 78 publications, 3 had any mention of the fraud in the text, as a retraction, a correction, or an expression of concern

Novel anticoagulants

Rivaroxaban (Xarelto)

- RECORD 1: 3 of 13 (23%) audited sites OAI/unreliable
- RECORD 2: 4 of 10 (40%)
- RECORD 3: 1 of 5 (20%)
- RECORD 4: 8 of 16 (50%)
  - (Entire RECORD 4 study deemed unreliable by FDA)

Novel anticoagulants

Apixaban (Eliquis)

ARISTOTLE

Fraud in China; suspected widespread

Site 1200: evidence of alteration of records prior to inspection

FDA recommended exclusion of 24 of 36 Chinese sites from analysis

With exclusion of site 1200, improvement in all-cause mortality not statistically significant.

Novel anticoagulants

Dabigatran (Pradaxa)

RE-LY:

DSI requested additional information from the sponsor, with respect to the above findings. In a letter dated June 30, 2010, the sponsor provided the following:

1. the date of the qualifying ECG of Subject 009 was retrospectively changed to make the subject eligible for the study. Specifically, the baseline ECG obtained during the baseline visit on July 21, 2006, did not show AF, therefore, an ECG showing AF within the last 6 months was needed to fulfill the inclusion criteria. The site used an ECG showing AF, taken December 1[illegible], 2006, backdated the date (which was still readable) and recorded a date of February [illegible], 2006, to make this subject eligible to participate in the study.

2. Sub-Investigator (b) (6) authorized colleagues to use his name and signature for study-related activities. By doing this it was not possible to identify the individuals who actually performed an examination or approved a document.

3. Source documents were found to be incomplete or retrospectively completed. CRF entries/changes were not supported by adequate source documentation. For example, for Subject 026, the source data worksheet was not completed until Visit 6, whereas the CRF was completed at Visit 13. For visits 7-13, no source documentation was available for the data documented in the CRF. The sponsor noted similar findings for multiple other subjects.

ACCEPTABLE

Fraud in published clinical trials?

- We found hundreds of OAI inspections, and hundreds of cases of fraud in clinical trials
- We identified 78 publications associated with those clinical trials
- Of those 78 publications, 3 had any mention of the fraud in the text, as a retraction, a correction, or an expression of concern
- Serious, **known,** misconduct is usually going unreported in the literature!

15 months later: How many corrections/EoCs/retractions?

0

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For Sale: "Your Name Here" in a Prestigious Science Journal

An investigation into some scientific papers finds worrying irregularities

By Charles Seife | December 17, 2014 | Véalo en español | 0

Klaus Kayser has been publishing electronic journals for so long he can remember mailing them to subscribers on floppy disks. His 19 years of experience have made him keenly aware of the problem of scientific fraud. In his view, he takes extraordinary measures to protect the journal he currently edits, *Diagnostic Pathology*. For instance, to prevent authors from trying to pass off microscope images from the Internet as their own, he requires them to send along the original glass slides.

In the past few years signs of foul play in the peer-reviewed literature have cropped up across the scientific publishing world
Credit: Mike Watson Images/Thinkstock

Despite his vigilance, however, signs of possible research misconduct have crept into some articles published in *Diagnostic Pathology*. Six of the 16 articles in the May 2014 issue, for instance, contain suspicious repetitions of phrases and other irregularities.* When *Scientific American* informed Kayser, he was apparently unaware of the problem. "Nobody told this to me," he says. "I'm very grateful to you."

First author	Citation	SearchPhrase	LikeEarlier
Shu-Li Fan	Ann. Hum. Genet. 2014 Jul;78(4):264-76.	CISCOM, CINAHL, Web of Science,	Mol Biol Rep (2014) 41:4481–4492
Ling Xu	Arch Med Sci. 2014 Jun 29;10(3):419-24.	standardized unbiased genotyping methods, homogeneous	*European Journal of Human Genetics (2009) 17, 244–249*
Jian-Yong Gu	Archives of Medical Research 45 (2014) 76e83	Begger's funnel plot	BMC Cancer 2010, 10:575
Yan-Song Xu	Asian Pac J Cancer Prev, 15 (11), 4563-4566	there are still some limitations in this meta-analysis	World J Gastroenterol 2011 March 7; 17(9): 1211-1218
Xin Zhou	Asian Pacific J Cancer Prev, 13 (10), 4909-4914	Begger's funnel plot	BMC Cancer 2010, 10:575
Zhen Yang	Asian Pacific J Cancer Prev, 13, 1203-1208	despite of those limitations, this meta-analysis suggests	Asian Pacific J Cancer Prev, 13, 111-115
Min Lu	Asian Pacific J Cancer Prev, 13, 2605-2610	despite of those limitations, this meta-analysis suggests	Asian Pacific J Cancer Prev, 13, 111-115
Zhao-Jun Pan	Asian Pacific J Cancer Prev, 13, 2635-2638	despite of those limitations, this meta-analysis suggests	Asian Pacific J Cancer Prev, 13, 111-115
Hong-Bo Ma	Asian Pacific J Cancer Prev, 13, 2841-2846	despite of those limitations, this meta-analysis suggests	Asian Pacific J Cancer Prev, 13, 111-115
Li-Ping Zhou	Asian Pacific J Cancer Prev, 13, 3165-3172	Begger's funnel plot	BMC Cancer 2010, 10:575
Li-Ping Zhou	Asian Pacific J Cancer Prev, 13, 3417-3422	Begger's funnel plot	BMC Cancer 2010, 10:575
Lu Xu	Asian Pacific J Cancer Prev, 13, 683-687	Begger's funnel plot	BMC Cancer 2010, 10:575
Xiu-Li Sun	Asian Pacific J Cancer Prev, 13, 915-921	despite of those limitations, this meta-analysis suggests	Asian Pacific J Cancer Prev, 13, 111-115

17 months later: How many corrections/EoCs/retractions

0

For every fraud action, there is an equal and inapposite inaction….

Journals ~~Researchers~~ behaving badly: (Unreported) misconduct in clinical trials

Charles Seife, Professor of Journalism
Arthur L. Carter Journalism Institute at NYU

FDA Let Drugs Approved on Fraudulent Research Stay on the Market

by Rob Garver and Charles Seife, Special to ProPublica, April 15, 2013, 9:17 a.m.

On the morning of May 3, 2010, three agents of the Food and Drug Administration descended upon the Houston office of Cetero Research, a firm that conducted research for drug companies worldwide.

Retired FDA investigator Patrick Stone (Katie Hayes Luke for ProPublica)

Lead agent Patrick Stone, now retired from the FDA, had visited the Houston lab many times over the previous decade for routine inspections. This time was different. His team was there to investigate a former employee's allegation that the company had tampered with records and manipulated test data.

When Stone explained the gravity of the inquiry to Chinna Pamidi, the testing facility's president, the Cetero executive made a brief phone call. Moments later, employees rolled in eight flatbed carts, each double-stacked with file boxes. The documents represented five years of data from some 1,400 drug trials.

Pamidi bluntly acknowledged that much of the lab's work was fraudulent, Stone said. "You got us," Stone recalled him saying.

Six Drugs the FDA Doesn't Want You to Know Relied on Tainted Data

In 2011, the Food and Drug Administration determined that a major laboratory, the Houston facility of the now-defunct Cetero Research firm, had committed such "egregious" and pervasive research violations that years of its tests were potentially worthless. About 100 drugs were affected, but the FDA has declined to name them, saying to do so would reveal confidential commercial information. ProPublica was able to pinpoint six drugs whose approval rested, at least in part, upon data from the Cetero studies. Related Story »

	Temodar IV *Injection*	**Torisel** *Injection*	**Lazanda** *Nasal spray*	**Generic Ibuprofen** *Gelatin Capsules*	**Generic Tramadol** *Extended-release capsules*	**Generic Hydrocodone polistirex/ chlorpheniramine polistirex** *Liquid*
GENERIC NAME	Temozolomide	Temsirolimus	Fentanyl			
OTHER NAMES	Temodal (in Europe)	Torisel	PecFent (in Europe)			
DRUG COMPANY	Merck & Co	Pfizer Inc.	Archimedes Pharma	Banner Pharmacaps	Cipher Pharmaceuticals	Tris Pharma
WHAT IT IS	A chemotherapy drug aimed at difficult-to-treat brain cancers	A drug used to treat renal cell carcinoma, a type of kidney cancer	An extremely potent painkiller	A popular over-the-counter painkiller	A powerful painkiller	A narcotic cough suppressant and anti-allergy medication
WHAT WE KNOW ABOUT CETERO'S ROLE	Cetero Houston analyzed the "pivotal" trial that formed the basis for the	Cetero analyzed a component of a study to test the drug's effect on heart	Cetero analyzed a clinical trial that tested how the drug behaved when paired	Cetero analyzed one of the trials to establish the capsule's	Cetero performed three clinical trials meant to prove the drug's equivalence to	Cetero analyzed both of the clinical trials used to show that the generic was

Fraud on the label

The Applicant did not conduct any efficacy and/or safety clinical studies in support of TEMODAR (b) (4) for Injection. The decision for the approval of this NDA submission is solely based on the results obtained from the pivotal bioequivalence Study P02467.

The MAH stated that the two pivotal studies supporting the line extension EMEA/H/C/229/X/35 which granted the additional powder for infusion formulations were study P02466 "*A Pilot Comparative Bioavailability Study of Oral and Intravenously Administered Temozolomide in Patients With Primary CNS Malignancies*" (initiated on 10th December 2004 and completed on 30th August 2005) and study P02467 "*A Bioequivalence Trial of Oral and Intravenously Administered Temozolomide in Patients with Primary CNS Malignancies*" (initiated on 29th September 2006 and completed on 18th October 2007). The scope of both trials was to show a 100% oral bioavailability of the capsules and consequently implement identical posology for the capsules and the powder for infusion for each individual indication respectively. Both studies were analysed by Cetero Research during the identified period of concern.

A pharmacokinetic study comparing oral and intravenous temozolomide in 19 patients with primary CNS malignancies showed that 150 mg/m^2 TEMODAR for injection administered over 90 minutes is bioequivalent to 150 mg/m^2 TEMODAR oral capsules with respect to both C_{max} and AUC of temozolomide and MTIC. Following a single 90-minute intravenous infusion of 150 mg/m^2, the geometric mean C_{max} values for temozolomide and MTIC were 7.3 mcg/mL and 276 ng/mL, respectively. Following a single oral dose of 150 mg/m^2, the geometric mean C_{max} values for temozolomide and MTIC were 7.5 mcg/mL and 282 ng/mL, respectively. Following a single 90-minute intravenous infusion of 150 mg/m^2, the geometric mean AUC values for temozolomide and MTIC were 24.6 mcg·hr/mL and 891 ng·hr/mL, respectively. Following a single oral dose of 150 mg/m^2, the geometric mean AUC values for temozolomide and MTIC were 23.4 mcg·hr/mL and 864 ng·hr/mL, respectively.

Fraud on the label

Apixaban (Eliquis)

All-cause mortality:

All sites included: **p = 0.0465**

Site 1200 excluded: **p = 0.0565**

W/O 24 China sites: **p = 0.0379**

All-cause death was assessed using a sequential testing strategy that allowed testing for superiority if effects on earlier endpoints (stroke plus systemic embolus and major bleeding) were demonstrated. ELIQUIS treatment resulted in a significantly lower rate of all-cause death ($p = 0.046$) than did treatment with warfarin, primarily because of a reduction in cardiovascular death, particularly stroke deaths. Non-vascular death rates were similar in the treatment arms.

Double Dose: In Second Case of Flawed Drug Research, FDA Response Was Slow and Secretive

by Rob Garver and Charles Seife, Special to ProPublica, April 17, 2013, 9:41 a.m.

This week, we reported [1] that the Food and Drug Administration left medicines on the market for years after discovering they were approved based on fraudulent studies by Cetero Research, which did testing for drug companies worldwide.

(©iStockphoto.com/DavidBGray)

Turns out that wasn't an anomaly: The agency's slow, secretive response in the Cetero case mirrors how it handled an earlier instance of scientific misconduct at another contract research organization, MDS Pharma Services.

The FDA found that data produced from 2000 through 2004 at two MDS facilities in Quebec, Canada, were questionable.

As it would do with Cetero, the FDA announced it was requiring drug manufacturers to redo many of the MDS studies conducted during the five-year problem period. And, just as in the Cetero case, the agency declined to make public a list of the 217 generic drugs, both on the shelves and awaiting approval, that it said could be affected by MDS' potentially faulty research.

Instead, the FDA assured the public that all affected drugs were safe and effective, even as it was requiring re-testing of many of those medicines.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Via FedEx

AUG 3 1 2006

Stephen P. DeFalco
President and Chief Executive Officer
MDS Inc.
100 International Blvd.
Toronto, Ontario
M9W 6J6 Canada

Dear Mr. DeFalco:

Between March 6 and 24, 2006, Barbara J. Breithaupt, Sriram Subramaniam, Ph.D., Martin K. Yau, Ph.D., Michael F. Skelly, Ph.D., Nilufer M. Tampal, Ph.D., John A. Kadavil, Ph.D., and Jacqueline A. O'Shaughnessy, Ph.D., representing the Food and Drug Administration (FDA), conducted a follow up inspection of several bioequivalence studies performed by MDS Pharma Services (MDS) in Saint Laurent (Montréal), Québec Canada, including the following:

Study [ ]Tablets
Study [ ] Patch
Study [ ]Tablets

Also, between March 13 and 24, 2006, Ms. Breithaupt and Drs. Skelly and Tampal inspected several studies that measured plasma concentrations of the drug [ ]that MDS performed at its analytical laboratory in Blainville, Québec Canada, including the following:

Studies [ ]and [ ]Tablets

L'ANSM lance une procédure de suspension, à compter du 18 décembre, de 25 médicaments commercialisés en France - Point d'Information

05/12/2014

Med

- Liste des spécialités commercialisées en France dont les AMM sont suspendues à compter du 18 décembre 2014 (05/12/2014) (46 ko)
- Suspension des AMM de 25 médicaments commercialisés en France à compter du 18 décembre 2014 - Questions/Réponses (10/12/2014) (51 ko)

Lire aussi

- Médicaments génériques : des médicaments à part entière - Rapport de l'ANSM (14/12/2012) (1430 ko)
- Médicaments génériques : lever l'opacité - Questions / Réponses (17/12/2012) (147 ko)

Une inspection par l'ANSM d'un site de la société GVK Bio qui réalise des essais cliniques parmi lesquels des essais de bioéquivalence en Inde, a mis en évidence des irrégularités dans des documents associés à ces essais sur lesquels s'appuient les AMM (autorisation de mise sur le marché) de plusieurs médicaments. Même si ces documents ne sont pas indispensables à la démonstration de la bioéquivalence, l'ANSM a décidé, par mesure de précaution, de suspendre les AMM de 25 médicaments génériques commercialisés.

GVK Biosciences: European Medicines Agency recommends suspending medicines over flawed studies

23/01/2015

GVK Biosciences: European Medicines Agency recommends suspending medicines over flawed studies

Medicines considered critically important for patients to remain available

A number of medicines for which authorisation in the European Union (EU) was primarily based on clinical studies conducted at GVK Biosciences in Hyderabad, India should be suspended, says the European Medicines Agency (EMA). The recommendation is based on findings from an inspection that raised concerns about how GVK conducted studies at the Hyderabad site on behalf of marketing authorisation holders.

What has FDA said about drugs tested by GVK Biosciences?

“ ”

...

Prescription and Over-the-Counter Drug Product List

34TH EDITION

Cumulative Supplement Number 11 : November 2014

ADDITIONS/DELETIONS FOR PRESCRIPTION DRUG PRODUCT LIST

	FELODIPINE			
	TABLET, EXTENDED RELEASE;ORAL			
	FELODIPINE			
>D>	AB	WOCKHARDT LTD	2.5MG	A091484
>A>		@	2.5MG	A091484
>D>	AB		5MG	A091484
>A>		@	5MG	A091484
>D>	AB		10MG	A091484
>A>		@	10MG	A091484

~~Journals~~

~~Researchers~~ behaving badly: (Unreported) misconduct in clinical trials

Charles Seife, Professor of Journalism

Arthur L. Carter Journalism Institute at NYU

The citalopram CIT-MD-18 pediatric depression trial: Deconstruction of medical ghostwriting, data mischaracterisation and academic malfeasance

Article type: Research Article

Authors: Jureidini, Jon N.[a] | Amsterdam, Jay D.[b;*] | McHenry, Leemon B.[c]

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Abstract: OBJECTIVE:Deconstruction of a ghostwritten report of a randomized, double-blind, placebo-controlled efficacy and safety trial of citalopram in depressed children and adolescents conducted in the United States. METHODS:Approximately 750 documents from the Celexa and Lexapro Marketing and Sales Practices Litigation: Master Docket 09-MD-2067-(NMG) were deconstructed. RESULTS:The published article contained efficacy and safety data inconsistent with the protocol criteria. Procedural deviations went unreported imparting statistical significance to the primary outcome, and an implausible effect size was claimed; positive post hoc measures were introduced and negative secondary outcomes were not reported; and adverse events were misleadingly analysed. Manuscript drafts were prepared by company employees and outside ghostwriters with academic researchers solicited as 'authors'. CONCLUSION:Deconstruction of court documents revealed that protocol-specified outcome measures showed no statistically significant difference between citalopram and placebo. However, the published article concluded that citalopram was safe and significantly more efficacious than placebo for children and adolescents, with possible adverse effects on patient safety.

David A. Bahr (Oregon Bar No. 90199)
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Plaintiff's Attorney

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

CHARLES SEIFE,

Plaintiff,

vs.

UNITED STATES FOOD AND DRUG ADMINISTRATION,

Defendant.

Case No. 1:15-cv-5487

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

Freedom of Information Act
Administrative Procedure Act

Plaintiff, Charles Seife, ("Plaintiff" or "Seife"), alleges as follows:

INTRODUCTION

1. This action is premised upon, and consequent to, violations of both the Freedom of In-