SALUD COLECTIVA, Buenos Aires, 9(1):5-10, January- April, 2013

The contribution of high-impact clinical journals to science: the case of *The Lancet*

La contribución de las revistas clínicas de alto impacto a la ciencia: el caso de *The Lancet*

***Ugalde**, Antonio[1]; **Homedes**, Núria[2]*

Digital technology allows a rapid exchange of ideas, almost in real time, among professionals of many countries. Present-day society is undergoing an IT explosion that permits an increasingly universalized access to scientific knowledge, but that also facilitates the disclosure of incomplete or incorrect information.

High-impact clinical journals know how hard it is to filter valid information from corrupted information, whether due to involuntary mistakes, data manipulation or fraud (1). In 2004, in order to minimize the bias in publications on clinical trials, high-impact clinical journals decided not to publish the results of any trial whose protocol had not been included in a public registry of clinical trials before starting patient recruitment. Although it is a step in the right direction, problems persist.

The owners of clinical trial protocols deem these protocols an industrial secret and as such unable to be shared. They are the only ones who know the quality of the collected data, the analysis to which they are subjected, and the authenticity of the published results. The possibility of manipulation is undeniable, especially if we recall that positive results open the door for multi-million dollar earnings. The inability of the great regulatory agencies to examine trials is well known. Eighty percent ot the new drug commercialization requests that are submitted to the US Food and Drug Administration (FDA) contain data from trials carried out in other countries, but the FDA is only able to examine less than 1% of the foreign centers where the trials are conducted (2).

This situation in turn makes the work of scientific journal editors more difficult and forces them to be attentive. It is difficult, if not impossible, to identify authors or professors who sign articles written by other individuals with conflicts of interest, and to assess the quality of the data or their manipulation. All of these situations change the meaning of what is published in journals or is submitted to regulatory agencies, as was seen in the Vioxx case (3).

The number of articles that scientific journals retract is increasing: 3 in 2000 and 180 in 2009 (4). However, many others that should have been withdrawn are still a source of information to investigators and doctors that provide medical care. For example, according to documents of the University of California, articles about Seroquel, Celebrex, Lyrica, Neurontin, and many articles about hormonal replacement therapy written by the staff of the marketing company Designwrite of Pfizer and published under the name of other authors have not yet been withdrawn from circulation (5,6).

[1]Professor Emeritus, Department of Sociology, University of Texas at Austin, USA. augalde@utexas.edu
[2]Professor, School of Public Health, Health Science Center at Houston, University of Texas, USA. nhomedes@utep.edu

SALUD COLECTIVA, Buenos Aires, 9(1):5-10, January - April, 2013

Some authors state that the readers of scientific journals have every day less certainty of the scientific veracity of what they read. There are "perverse incentives that lead scientists to cut corners" in order to publish as quickly as possible, "and, in some cases, commit acts of misconduct" unacceptable from a professional point of view (7).

The British journal *The Lancet* is considered one of the highest-impact journals. In February 2012, the journal published information about the irregularities commited during the implementation of the clinical trial *Clinical Otitis Media & Pneumonia Study* (COMPAS) of GlaxoSmithKline (GSK) in Argentina (8) that, as we will show, contains incorrect information. It is a short piece but, given the importance of the matter, the editor of *The Lancet* should have asked for the sources of the information presented, and should not have published the information without consulting with experts. Some fragments of the information published by *The Lancet* about the COMPAS clinical study are included below, and we compare them with the data that we have found about the same study, which may be verified in the documents of the Argentinian courts and in press articles.

> GlaxoSmithKline (GSK) was fined US$92 000 by Argentinian courts for administrative irregularities... (8)

1. GSK was not fined by the Argentinian courts. GSK was fined by the National Administration of Drugs, Food and Medical Technology [*Administración Nacional de Medicamentos, Alimentos y Tecnonlogía Médica*] (ANMAT), the Argentinian regulatory agency, due to serious regulatory violations.

> On Dec 28, 2011, Marcelo Aguinsky, a judge in the province of Mendoza, found GSK guilty of irregularities in obtaining informed consent [...] GSK is currently [date of publication Febraury 11th, 2012] appealing the decision. (8)

2. Marcelo Aguinsky is not a judge in the province of Mendoza but in the National Court with jurisdiction over criminal-economic matters. In order to clarify the decision regarding the appeal, please see point 7 of this article. As explained further on in point 4, in addition to breaches related to informed consent, the courts make mention of many other serious violations.

> "GSK conducts clinical trials to the same high standards, irrespective of where in the world they are run", the company said in a statement. (8)

3. There is no need to reproduce this declaration in a scientific journal, as GSK could not have said anything else without falling into self-incrimination during criminal proceedings. Furthermore, this statement contradicts the fact that GSK admitted to the irregularities committed while COMPAS was carried out, as can be read in point 4.

> Problems in the GSK trial first came to light in 2007, when paediatrician Ana Marchese reported possible irregularities to FeSProSa (Syndicate Federation of Argentinian Health Professionals) after speaking to the trial participants' families. FeSProSa investigated the accusations and filed a report to the National Administration of Drugs, Food and Medical Technology (ANMAT) in December, 2007, declaring problems surrounding informed consent. GSK stated that it was the company that had identified the irregularities through self-monitoring and reported them straight to ANMAT. (8)

4. Natalia Fuertes, the author of the information published in *The Lancet*, only mentions that there had been irregularities regarding the obtention of informed consent, ignoring the information published in the court rulings (9,10), in the press, and in the statements of FeSProSa (11,12). In section 3 – subsections a, d and e – and sections 27, 29, 31, 32 and 33, the Argentinian Judicial Power (9) establishes the violation of the inclusion/exclusion criteria required by the trial protocol, the double

vulnerability of the participants, and the violation of other good clinical practices, even stating that "the apellants underestimate the Court." Therefore, Fuertes could have asked herself how, given the seriousness of the breaches, GSK did not stop the trial immediately when detecting the violations during its supervision. Furthermore, GSK was aware, because the problem was well known in Argentina, that since 2005 the Municipality of Córdoba had forbidden the principal investigator to carry out clinical trials in the Municipality due to ethical breaches during the implementation of trials (13).

> Roberto Lede, director of Planning and Institutional Relationships of ANMAT, states that "the intervention of the ANMAT was very opportune. The recruitment was stopped in the way it was being carried out and resumed with intensive control. It should be noted that the irregularities only affected less than 1% of the subjects." (8)

5. The auditor of ANMAT in 2008 confirmed that Roberto Lede was not holding this office when the irregularities took place. Quoting a statement claiming that the irregularities only affected 1% of the subjects is naive and belittles the violations committed by GSK. In order to know how many subjects had been affected, a random and representative sample of all recruited patients should have been researched (13,981 in total).

> COMPAS ended successfully in 2008, with only 18% fewer subjects than originally intended, and Synflorix was approved by ANMAT. (8)

6. Once again, the author belittles the consequences of GSK's behavior, in this case the impact on the protocol of reducing the number of subjects. Without analyzing the impact that the change could have on the statistic analysis, she states that the trial ended successfully with a reduction of "only" 18% subjects. Immediately afterwards, Fuertes claims that the ANMAT approved Synflorix, implying that there was a relation between the "success of the trial" and the approval of the vaccine in Argentina. Nothing is further from the truth. Synflorix was approved in the European Union in March 2009 (14) and in Argentina in July 2009, not because COMPAS ended successfully, but because ANMAT is able to approve any drug or vaccine that has been approved in a country with high health surveillance. In 2012, GSK claimed that the company "is now focusing its efforts on delivering the results of the study that assesses the effectiveness of the Synflorix vaccine in the prevention of pneumococcal diseases in children..." (15). That is to say, Synflorix could not have been approved due to COMPAS success in Argentina because, in April 2012, GSK had not yet finished evaluating the data.

> While GSK are appealing the fine in Mendoza, in Santiago del Estero, their appeal to the Supreme Court was successful. In San Juan, the local courts have yet to rule. (8)

7. These statements are completely inaccurate. The history of GSK judicial confrontations is the following:

   a. ANMAT sequentially filed three administrative proceedings (one per province): the first in Santiago del Estero, the second in Mendoza, and the third in San Juan. As a result, GSK was fined for violating regulations during the implementation of COMPAS (ANMAT also imposed an administrative fine on two COMPAS investigators).
   b. GSK appealed the first fine imposed by ANMAT's administrative proceedings (Santiago del Estero) to the Argentinian Judicial Power (the National Court with jurisdiction over criminal-economic matters). It did the same as it heard about the administrative proceedings in the other two provinces. On April 8, 2010, the Argentinian Judicial Power dismissed the first appeal of GSK (Santiago del Estero), and later on the appeals of Mendoza and San Juan were also dismissed, that is to say, in the three provinces the fines imposed by ANMAT were validated.

SALUD COLECTIVA, Buenos Aires, 9(1):5-10, January - April, 2013

c. When GSK heard that the Argentinian Judicial Power had dismissed its appeal regarding the case in Santiago del Estero, it resorted to the Supreme Court, which rejected the appeal on July 5, 2011.
d. However, after learning the Argentinian Judicial Power's decision against GSK in the Mendoza case on December 28, 2011, GSK claimed in a press statement dated January 4, 2012 (16) that it would again appeal to the Supreme Court. This statement can only be understood as a provocation to the Argentinian judicial system in order to conceal the company's mistakes. Months later, GSK changed its mind and decided not to appeal (15).

> After the irregularities in the COMPAS trial were disclosed, the government decided to create a National Register of Trials. (8)

8. It cannot be claimed that Resolution 102/2009 of Argentina's National Department of Health (14), by which the Registry of Clinical Trials in Human Subjects is created, is an answer to COMPAS irregularities. In January 2007, through Resolution 35/2007, the Ministry of Health entrusted to the Commission of Applied Clinical Research on Human Subjects the creation of a National Registry of Clinical Research, and the project was thence developed (17). The registry was a response to the International Clinical Trials Registry Platform (ICTRP) that, as indicated by Resolution 102/2009, was developed with the backing of the World Health Assembly, and was replaced in 2011 by the National Registry of Health Research through the Resolution 1480/2011 (19).

The information disclosed by *The Lancet* contains a series of mistakes and misinformation that favors GSK. This is not what is expected from a high-impact scientific journal. The editor should have at least requested that the information presented be based in sources. That someone can write about the history of COMPAS in Argentina without having made a careful reading of the court rulings and without explaining the political and economic context in which trials are carried out in the country is unjustifiable. Readers unfamiliar with the events obtain a biased view of what occurred, and they may even think that COMPAS had a positive impact expediting regulatory changes and the responsibility for the creation of a registry of clinical trials.

In Argentina, it is legal to pay doctors a certain amount of money for every patient they recruit to participate in a clinical trial. However, we have to question if it is ethical for doctors to recruit their own patients in public facilities, most of whom are poor or indigent. In the case of COMPAS, US$350 were paid for every one of the 13,981 children recruited, that is to say, GSK paid almost five million dollars. With this attractive incentive, there is an obvious possibility that conflicts of interest may have interfered in the recruting, in the application of inclusion and exclusion criteria, and in accepting without argument the sponsors' demands. The information published about COMPAS by investigative journalists – and Argentina is characterized for having very good journalists – also questions the physical quality of the facilities, the training of staff and the lack of inspections. None of this is mentioned in the piece published by *The Lancet*.

This is not the first time that we have detected bias in *The Lancet*'s publications. Interestingly, on October 28, 2006, six articles on the pilot health reform plan in Mexico were published and, more recently (August 16, 2012), a 22-page article about this reform was also published. This case is surprising because the articles were written by those who took part in designing the reform and in its implementation, and they are all close collaborators of a specific health minister. It is known that at least once *The Lancet* censored critical information regarding the reform by not responding to two letters sent by Dr. Asa Cristina Laurell, well-known for her professional prestige in Latin America. As Health Secretary in Mexico City, in her letters she identified inaccuracies/errors in the series of articles *The Lancet* published in 2006. All of this took place precisely when the minister was on the short list of candidates for director of the World Health Organization (WHO) and therefore needed to demonstrate the success of his policies. Dr. Laurell's criticisms were later published in another journal (20). On another occasion, the associate editors of *The Lancet* rejected, based on the comments of external reviewers, an article about Mexico.

SALUD COLECTIVA, Buenos Aires, 9(1):5-10, January - April, 2013

The reviewers received official notice from *The Lancet* stating that, according to their evaluations, the article had been rejected. The reviewers were surprised to see that the article was published afterwards without having been given any explanation from *The Lancet*'s editors. The minister of health appeared as one of the authors of the article, which incorporated some of the reviewer's comments without making any mention of the fact.

All of the matters discussed above lead us to think that *The Lancet* helps to increase doubts about the scientific value of what is published in high-impact medical journals; or that, perhaps, if it continues along this path, it will no longer be a high-impact journal at all.

BIBLIOGRAPHIC REFERENCES

1. Casadevall A, Fang FC. Reforming Science: Methodological and Cultural Reforms. Infection and Immunity [Internet] 2012 [cited 7 Mar 2013];80(3):891-896. Available from: http://iai.asm.org/content/80/3/891.full.

2. Department of Health and Human Services. Office of Inspector General: Semiannual Report to Congress, April 1- September 30, 2010 [Internet]. Washington DC: OIG; 2010 [cited 8 Mar 2013]. Available from: https://oig.hhs.gov/publications/sar/2010/fall2010_semiannual.pdf.

3. Cañás M, Ugalde A, Orchuela J, Homedes N. Las secuelas del rofecoxib. Boletín Fármacos [Internet] 2005 [cited 7 Mar 2013];8(2):58-70. Available from: http://www.saludyfarmacos.org/wp-content/files/apr05.pdf.

4. Steen RG. Retractions in the scientific literature: is the incidence of research fraud increasing? Journal of Medical Ethics. 2011;37(4):249-253.

5. Rosenberg M. Big Pharma's ghostwriters: Why are these fraudulent papers unretracted? Counterpunch [internet]. 2012 [cited 7 Mar 2013]. Available from: http://www.counterpunch.org/2012/04/27/why-are-these-fraudulent-papers-unretracted.

6. Rosenberg M. Los escritores fantasmas de las farmacéuticas innovadoras transnacionales: ¿Por qué no se han retirado los artículos fraudulentos que escribieron? Boletín Fármacos [Internet]. 2012 [cited 7 Mar 2013]. Available from: http://www.saludyfarmacos.org/boletin-farmacos/boletines/feb2013.

7. Simmer C. A sharp rise in retractions prompts calls for reform. The New York Times [Internet]. 16 abr 2012 [cited 7 Mar 2013]. Available from: http://www.nytimes.com/2012/04/17/science/rise-in-scientific-journal-retractions-prompts-calls-for-reform.html?_r=2&pagewanted=all&.

8. Fuertes N. GSK malpractice case raises questions about trial standards. The Lancet [Internet]. 2012 [cited 7 Mar 2013];379(9815):508. Available from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60217-7/fulltext.

9. Poder Judicial de la Nación, Juzgado Nacional en lo Penal Económico No 4, Secretaría No 7. Causa 13.617/2010: ANMAT c/ GlaxoSmithKline Argentina S.A. y Otros S/INF Ley 16.463. [signed by Judge Alejandro J. Catania]. Buenos Aires; 8 Apr 2010.

10. Poder Judicial de la Nación, Juzgado Nacional en lo Penal Económico No 2 Secretaría No 4. Causa 925/2011: GlaxoSmithKline Argentina S.A. – Abate Héctor – Tregnaghi Miguel S/Infracción Ley 16.463. Buenos Aires: 28 Dec 2011.

11. Calvo P. Santiago: cuestionan la captación de niños para ensayos de vacuna. Clarín [Internet]. 23 Dec 2007 [cited 7 Mar 2013]. Available from: http://edant.clarin.com/suplementos/zona/2007/12/23/z-04015.htm.

12. Seeger M. La muerte de 14 bebés desata una polémica sobre ensayos de una vacuna. El Litoral [Internet] 13 Aug 2008 [cited 7 Mar 2013]. Available from: http://www.ellitoral.com/index.php/id_um/32857.

13. Municipalidad de Córdoba, Dirección de Sumarios e Investigaciones Administrativas. Expediente 942.681/03. Informe No 03/05 [Internet]. 23 Aug 2005 [cited 7 Mar 2013]. Available from: http://www.cordoba.gov.ar/cordobaciudad/principal2/default.asp?ir=42_4.

14. GlaxoSmithKline. Synflorix™, GlaxoSmithKline's pneumococcal vaccine, receives European authorization [Internet]. 31 Mar 2009 [cited 7 Mar 2013]. Available from: http://www.gsk.com/media/press-releases/2009/synflorix-glaxosmithklines-pneumococcal-vaccine-receives-european-authorisation.html.

SALUD COLECTIVA, Buenos Aires, 9(1):5-10, January - April, 2013

15. La Voz. Glaxo pagará multa por realizar pruebas médicas irregulares. La Voz [Internet] 14 Apr 2012 [cited 6 Mar 2013]. Available from: http://www.lavoz.com.ar/print.php?site=lavoz&nid=567901.

16. Magnani R. El laboratorio apelará ante la Corte. Página/12 [Internet]. 4 Jan 2012 [cited 10 Mar 2013]. Available from: http://www.pagina12.com.ar/diario/sociedad/3-184730-2012-01-04.html.

17. Ministerio de Salud. Resolución 102/2009: Créase el Registro de Ensayos Clínicos en Seres Humanos [Internet]. 2 Feb 2009 [cited 7 Mar 2013]. Available from: http://test.e-legis-ar.msal.gov.ar/leisref/public/showAct.php?id=12916&word=registro%20de%20ensayos%20cl%C3%ADnicos.

18. Ministerio de Salud, Secretaría de Políticas, Regulación y Relaciones Sanitarias. Resolución 35/2007: Creación de la Comisión de Investigaciones Clínicas Aplicadas en Seres Humanos [Internet] 16 Jan 2007 [cited 7 Mar 2013]. Available from: http://test.e-legis-ar.msal.gov.ar/leisref/public/showAct.php?id=7087&word=registro%20de%20ensayos%20cl%C3%ADnicos.

19. Ministerio de Salud. Resolución 1480/2011: Guía para Investigaciones con Seres Humanos, Deroga las resoluciones 1490/07 y 102/09 [Internet] 13 Sep 2011 [cited 7 Mar 2013]. Available from: http://test.e-legis-ar.msal.gov.ar/leisref/public/showAct.php?id=18264&word=registro%20de%20ensayos%20cl%C3%ADnicos.

20. Laurell AC. Health system reform in Mexico: a critical review. International Journal of Health Services [Internet] 2007 [cited 8 Mar 2013];37(3):515–535. Available from: http://www.salud.gob.mx/unidades/pediatria/refo_mex.pdf.

CITATION
Ugalde A, Homedes N. The contribution of high-impact clinical journals to science: the case of *The Lancet*. Salud Colectiva. 2013;9(1):5-10.

The translation of this article is part of an interdepartmental collaboration between the Undergraduate Program in Sworn Translation Studies (English < > Spanish) and the Institute of Collective Health at the Universidad Nacional de Lanús. This article was translated by Giuliana Riveira and Waldo Terluk, reviewed by Pamela Vietri and modified for publication by Vanessa Di Cecco.