

Analytical Methods in Quality Control of Scientific Publications Part IV: Fraud Ordered by the Pharmaceutical Industry

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Abstract

In a series of papers under the common title: "Analytical Methods in Quality Control of Scientific Publications," cases of undisputable breaches of publication ethics and breaches of acceptable rules in the publication of scientific information have been presented. Clear cases of fraud, falsification by some authors, and unqualified review of papers by reviewers and editors were presented in: Analytical Methods in Quality Control of Scientific Publications, (2012) American Journal of Analytical Chemistry, Vol. 3, No. 6, pp. 443-447 DOI:10.4236/ajac.2012.36058. The place of authors, reviewers, editors, and publisher was discussed in: Editorial: Analytical Methods in Quality Control of Scientific Publications Part II: The Authors', Reviewers', Editors' Responsibility, and the Publishers' Authority, (2013) International Journal of Analytical MassSpectrometry and Chromatography, Vol. 1, No. 2, pp. 81-89 http://dx.doi.org/10.4236/ijamsc.2013.12010, Analytical Methods in Quality Control of Scientific Publications Part III: Publishers' Ethics and Editors' Complicity, (2014) International Journal of Analytical Mass Spectrometry and Chromatography, Vol. 2, No. 3, pp. 77-102. DOI: 10.4236/ijamsc.2014.23008 and in the book Historical Overview of Chromatography and Related Techniques in Analysis of Antimalarial Drug Primaquine (Editor, Ilia Brondz) Nova Science Publishers, Inc., (2011) ISSN 978-1-61761-944-1. Here, the corrupting influence of the pharmaceutical industry as a customer and employer of pseudoresearchers and corrupt editors and even to corrupt journal publishers for publication of fraudulent information and pseudoscientific data will be discussed by identifying the authors of pseudoscientific publications, the editors who gave the green light for the fraudulent publication, and the pharmaceutical companies involved. Documentation will be given to support the accusations of fabricated fraudulent "scientific" data, and the publication of such data without sufficient revision and sufficient background for publication of papers will be illustrated by discussing the content of papers: "Determination of Quinocide as Impurityin Primaquine Tablets by Capillary Zone Electrophoresis," Abdalla A. Elbashir et al., (2009) Biomedical Chromatography, Vol. 23, pp. 464-471, published in Wiley Interscience, "Development of a Capillary Electrophoresis Method for the Enantioselective Estimation of

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Keywords

Pharmaceutical Industry, Corruptive Customer, Prefabricated Fraudulent Scientific Data, Pseudoscientific Publications, Breaches of Publication Ethics, Pseudoscientists, Primaquine, Quinocide

1. Introduction

The pharmaceutical industry is probably the most income-rich industry in the world, and the production of drugs and medical equipment may even be a more lucrative business than the production of guns and military ammunition. Because of the absence of reliable statistical information and because of the secrecy associated with these industries, the real income of these businesses is unknown. However, it is well known that the pharmaceutical industry is involved in many high-profile corruption scandals and is regarded as one of the most corrupt environments on the globe. Examples include the recent scandal connected to GSK in China (quotes are from these open sources as indicated in italic font): <u>http://www.rsc.org/chemistryworld/2014/09/gsk-fined-300million-china-corruption</u>, *In a statement*, *GSK admitted the bribery*, *expressed apologies*; and

http://www.nytimes.com/2014/09/20/business/international/gsk-china-fines.html, Glaxo said in a statement that it "fully accepts the facts and evidence of the investigation, and the verdict of the Chinese judicial authorities." "GSK P.L.C. sincerely apologizes to the Chinese patients, doctors and hospitals, and to the Chinese government and the Chinese people."

The scandal involving bribing the editors of Elsevier to publish spurious medical- and drug-related papers is well known: "*Elsevier published 6 fake journals*"

http://www.the-scientist.com/?articles.view/articleNo/27383/title/Elsevier-published-6-fake-journals/, and "Merck paid an undisclosed sum to Elsevier to produce several volumes of a publication that had the look of a peer-reviewed medical journal."

http://www.the-scientist.com/?articles.view/articleNo/27376/title/Merck-published-fake-journal/.

The companies in these examples and many other big and small pharmaceutical companies are bribing a broad range of authorities and authors of sources of scientific and technical information to present favorable data for their products and hold back unfavorable or harmful data, for example, the case of tafenoquine developed by GSK [1] [2]. In part, these actions can be understood to take place as a response to the highly competitive environment in which fraud and falsifications exist among the pharmaceutical companies. However, such actions can become criminal, especially when data concerning harmful or toxic drugs or contaminants in the drugs is withheld, removed, or even fabricated, and when the amounts of contaminants are underreported. These underreported data [3] [4] were published in comparison to the publication of accurate amounts of toxic contaminants in primaquine medical forms or the side effects of drugs, for example, when the side effects of thalidomide were published only after a big disaster.

1.1. Background of the Problem

In 1996-1997, the Therapeutic Goods Administration (TGA) of Australia became concerned with the high levels of unidentified contaminants in primaquine tablets. All Pharmacopeias at the time alluded to levels of contamination in primaquine of 6% "related substances"; however, all of the Pharmacopeia's committees obscured the nature of the impurities. At the time, the contaminants were variously presented under a perverse range of descriptions such as" related products" or "related substances" [2] [5]-[11] and later as the enantiomer. Such tendencies persisted long into the 20th century. In 1997, the Norwegian private pharmaceutical company Weifa AS (Norway) received a demand from the TGA to give clear account of the nature of the contaminant [2]. Dr.

Brondz from Jupiter AS Norway identified the so-called "related products" or "related substances" contaminant in primaquine as quinocide [2] [12] [13]. Resistance from members of Pharmacopeia's committees and the pharmaceutical industry, which have editors in all the leading pharmaceutical and related journals, prevented publication of this information in real time. This delay is described in [2]. Only in 2003 at the 3rd International Symposium on Separation in BioSciences SBS 2003 "100 Years of Chromatography," 13-18 May, (Moscow), in Russia, was it possible to bring this finding into the public domain [12]. The information on the real nature of the contaminant in primaquine and on the resultant enhanced toxicity of primaquine with quinocide in the mixture was first presented as a poster [12]. The information was published as a paper later in 2004 [13].

It is not a secret that bribery of medical personnel, editors, and publishers [14]-[17] is widespread among the pharmaceutical companies; only courageous reporters, journalists, and researchers curtail this criminal behavior by publishing their accusations about this criminal activity [14]-[20] and push the data into free and independent publications.

The presentation of high performance liquid chromatography-mass spectrometry (HPLC-MS) [12] [13] and gas chromatography-mass spectrometry (GC-MS) [21] [22] research results on primaquine contamination by quinocide and the associated enhanced toxicity of this mixture, led to some hard questions being asked of some manufactures of primaquine tablets. It was necessary to show that their products met the minimum standards required of Pharmacopeias. This required either production of tablets from high-quality primaquine, which involved higher production costs and a reduction in profit, or made it necessity for the manufactures to find tractable partners who were willing to publish false reports on the compliance of their products with Pharmacopeias' demands.

1.2. Tractable Partners

A paper was submitted to the Journal of Chromatography A in which the authors described a capillary electrophoretic (CE) method for separation, validation, and quantification of quinocide as a contaminant in primaquine tablets. This paper was transferred to reviewers. Surprisingly, the authors did not reveal the names of the two tablet manufacturers and validation of the nature of quinocide as a contaminant was based only on their intuitive assumption, without referring to the previous published papers on this aspect, and with no mass spectrometry analysis (connection of CE for separation of substances by using polymers to MS at the time was impossible and even today it remains challenging). Neither analytical nor technical grade standard quinocide had been used for the quantitative measurements. Many additional remarks were presented to the authors, and the recommendation to the editor was to reject the paper if clear answers were not provided. A short time after rejection of the manuscript in J. Chromatography A the author of the plagiaristic and fraudulent manuscript wrote an e-mail to Dr. Brondz. The text of the e-mail is presented in Figure 1. The arrival of this e-mail was not a surprise. The name of the owner of the company that manufactured primaquine tablets in Malaysia was known. The authors of the fraudulent manuscript submitted to J. Chromatography A were also from Malaysia, and the arrival of the e-mail was also expected. The supplier of unprocessed primaquine was also known. It was not a secret that this unprocessed raw primaquine did not comply with the Pharmacopeias' demands. Dr. Brondz was not interested in participating in the publication of the fabricated false data, especially because Mr. Baharuddin Saad already presented the data in his previous manuscript submitted to and rejected by J. Chromatography A.

After a while, the manuscript previously submitted to *J. Chromatography A* by Mr. Saad was again submitted to the *Journal of Pharmaceutical and Biomedical Analysis (JPBA)* by Abdalla A. Elbashir *et al.* with the same analytical measurements that were previously submitted to *J. Chromatography A* by Mr. Saad; however, in this case, the use of standard quinocide received from Prof. William Y. Ellis, Walter Reed Army Institute of Research, Silver Spring, MD, USA, was acknowledged [3]. It was surprising that that there was no change in the data regarding the quantity of contaminant quinocide between the text of the manuscript previously submitted to *J. Chromatography A* and the text of the manuscript submitted to *JPBA*. The data were the same in both manuscripts. The use of a "standard sample" of quinocide apparently had no influence on the measurements. This new manuscript was sent for peer review. Several questions were asked by the reviewer for the authors to answer: 1) The names of the two manufacturers of the primaquine tablets; 2) The identity of the substance in the received standard sample with quinocide in the tablets; 3) The quality of the received standard sample; 4) Was the standard sample pro analysis grade or was it of technical grade?

Instead of answering these questions, the manuscript was again submitted by Elbashir et al. to the other editor

Subject:	Re: Quinocide standard
From:	"Baharuddin Saad" <bahrud@usm.my></bahrud@usm.my>
Date:	Thu, September 20, 2007 08:57
To:	ilia.brondz@bio.uio.no
Cc:	hajaae@yahoo.com
Create Filter:	Automatically From To Subject
Options:	View Full Header View Printable Version Download this as a file Add to Addressbook View Message details

Dear Prof Bronz

We are developing a capillary electrophoresis method for the separation of quinocide from the primaquine enantiomers. Three components were baseline separated and the method is more rapid than the LC methods reported. We have submitted the work to J. Chromatog A, but was not favoured as we need to conclusively show that the unknown peak is indeed quinocide. If we have a small quantity of the quinocide, then the issue can be settled. We will consider you as one of the coauthors for the paper if the quinocide standard can be made available to us.

I look forward to a positive response from you and with best regards from us in Penang, Malaysia.

```
Prof Bahruddin Saad
Deputy Dean (Research & Postgraduate Studies)
School of Chemical Sciences,
Universiti Sains Malaysia
11800 Penang, Malaysia
Fax: 04-6574854
----- Original Message -----
From: <u>ilia.brondz@bio.uio.no</u>
Date: Thursday, September 20, 2007 3:25 pm
Subject: Quinocide standard
```

Figure 1. The letter from Mr. Baharuddin Saad

in the same journal, possibly in the hope that the manuscript would be reviewed by a less-demanding reviewer.

A second submission of the same paper by the same team without answering questions asked by a peer reviewer is forbidden and is classed as fraud. The case was reported to the quality control body of Elsevier and the paper was withdrawn from consideration for publication.

The text of the manuscript presented by Elbashir *et al.* contained many fraudulent and plagiaristic sections. The specific details are not of great interest in the context of this paper; however, the main points have been described to illustrate the abominable behavior of some "scientists" and publishers to achieve the aim of presenting unusable quality chemicals as drugs of good quality.

1.3. Publishers and Editors as Tractable Partners

It is not difficult to find examples for publishers who are willing to publish papers that have been ordered by pharmaceutical industry, as described in [17], and examples of bribing publishers and editors, as described in [16].

Some starting "scientists" look to build up their career by servicing the demands of the pharmaceuticals industry by the fraudulent unethical publication of false data. In this particular case, it is difficult to trace in whose pocket the money landed, but strong suspicion exists about who was promoted by customers. A short time after the fraudulent paper submitted for consideration in *JPBA* by Elbashir *et al.* was rejected, the text of this pseudo research was finally published in the journal, *Biomedical Chromatography* [3]. The paper was published under interesting circumstances. The journal acknowledged arrival of the manuscript on August 5, 2008, as documented in Figure 2. Astoundingly, on August 6, 2008, the paper was accepted for publication, as documented in Figure 2. This must constitute the speediest acceptance of any paper in this particular journal and probably in all known independent peer-reviewed scientific publications. How, in less than 24 hours, was it possible to register



the manuscript, transfer it to reviewers, review the manuscript, transfer the recommendation of the reviewers to the editor, and for the editor to make their editorial decision? What prompted this hurry? The published paper was an exact blueprint of the manuscripts previously submitted to and rejected by *J. Chromatography A* and *JPBA*.

1.4. The Fraud Imbedded in the Paper by Elbashir et al.

After receiving negative answers on their attempts to publish fraudulent data in *J. Chromatography A* and *JPBA*, Elbashir *et al.* published the same text in *Biomed. Chrom.* as [3] and continued to present this text as variations on the same theme in other publications published by the same publisher with acknowledgments to Dr. William Y. Ellis, Chief, Department of Chemical Information, Division of Experimental Therapeutics, Walter Reed Army Institute of Research, for providing the standard sample of quinocide.

Given that the capacity of the Walter Reed Army Institute of Research to synthesize quinocide was uncertain, the donation of analytical quality standard came under scrutiny. In the early 1950s, the Walter Reed Army Institute of Research requested a sample of quinocide for biological testing from the Martsinovsky Institute. At that time, only the Martsinovsky Institute of Medical Parasitology and Tropical Medicine in Moscow, Russia, had the knowledge and capability to synthesize quinocide. In [1] [2] [12] [13] [21]-[32] and in other publications, the analytical quality standard quinocide synthesized in the Martsinovsky Institute was used.

Under these circumstances, and because of the persistent refusal by Elbashir *et al.* to disclose information on the nature of the quinocide standard used, it was of interest to obtain the correct information from the source (Dr. William Y. Ellis, Chief, Department of Chemical Information, Division of Experimental Therapeutics, Walter Reed Army Institute of Research). The request to Dr. Ellis for information regarding the quinocide standard led to the response presented in Figure 3.

From the reply made by Dr. Ellis, it appears that the sample was more than 35 years old, and that the sample was kept under minimal protection from the elements for the whole period. It is beyond dispute by any analytical chemist or pharmaceutical analyst that this sample should not have been used as a standard for quantification of drugs. However, further questions remained unanswered. In additional correspondence with Dr. Ellis (see document in **Figure 4**), some clarification was obtained. Several facts were mentioned in this document (**Figure 4**), including 1) the sample was never intended to be an analytical standard and 2) the sample was of quinocide monophosphate, not quinocide diphosphate. To avoid any misunderstanding, Dr. Ellis also provided the data sheet for the compound (**Figure 5**).

Summarizing main facts concerning the publication of [3] and other "works of fiction" by Elbashir *et al.*, which were mainly published in *Biomed. Chrom.* and other journals of Wiley & Son Ltd., it should be noted that: 1) Preventing repetition of experiments to verify the results by other scientists or opponents, publications by Elbashir *et al.* consistently used vague definitions such as: "An amount of equivalent to 15 mg of the PQ was taken..." (why not 15 mg?) or "After appropriate dilution..." (why not *with* or *to* some exact volume?). Elbashir *et al.* are not alone in this respect: most "scientists" of this type use this formula. 2) It was clear that Elbashir *et al.* understood well that the substance they presented as standard could not qualify as a standard, and they tried to avoid answering reviewers' questions regarding the nature of the material. 3) Elbashir *et al.* understood that

Subject Request for information on quinocide (UNCLASSIFIED) Sender <u>Ellis, William Y Mr CIV USA MEDCOM WRAIR</u> 1 "Ellis, William Y Mr
CIV USA MEDCOM WRAIR" <bill.ellis@us.army.mil> Recipient <u>ilia.brondz@bio.uio.no</u></bill.ellis@us.army.mil>
• <u>BE66770.PDF</u>
To protect your privacy, remote images are blocked in this message. <u>Display images</u> Classification: UNCLASSIFIED Caveats: NONE
Dear Dr. Brondz,
My apologies for the tardy response but your letter of last December has only recently reached me. I hope that the following information may still be of use to you.
The quinocide you asked of was prepared for us in 1974 under contract with Park-Davis. It has been in our repository at ~22°C since that time. A copy of the data sheet is attached. Our experience with crystalline samples of this sort is that they are stable for decades when stored at room temperature in brown glass bottles.
We sent a sample of this material to Dr. Hassan Y. Aboul-Enein in December of 2007 when he was a visiting scientist in Malaysia. I assume that this is the reference referred to in the Elbashir paper cited in your letter.
If I can help further, please let me know.
Best Wishes,
Bill
William Y. Ellis Chief, Department of Chemical Information Division of Experimental Therapeutics Walter Reed Army Institute of Research
Classification: UNCLASSIFIED Caveats: NONE
Figure 3. Reply from Dr. Ellis, Chief, Department of Chemical Information, Division of Experimental Therapeutics, Walter Reed Army Institute of Research.
Classification: UNCLASSIFIED Caveats: NONE
Dear Dr. Brondz,
I sent your request to the library folks for response but they are distracted so I have retrieved your missive for personal response. The quinocide of your query was prepared for a project investigating radical cure in malaria. It

query was prepared for a project investigating radical cure in malaria. It is, therefore, of research quality but never intended as an analytical standard. The compound is reported as the monophosphate salt. The free base comprises 72.6% of the salt and phosphoric acid comprises 27.3% of the salt. The purity is reported as >95% based on mp, IR, elementals, and TLC. A recent ms implies a purity of not less than 98%.

I hope this is helpful.

Regards,

Bill

William Y. Ellis Chief, Department of Chemical Information Division of Experimental Therapeutics Walter Reed Army Institute of Research

Figure 4. Additional information about the sample of quinocide received from Dr. Ellis.

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APPEARANCE Dull vella	soli	1			ELEMENT	CALCULATED	FOUND	WR FOUND
QUANTITY /	-SVII	CODE NR. AM-16	79	-	с	50.42	50.38	1
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	-n2-n21	CH30		HNG	CH2CH2CH2CHCH			- Froduct HCHg Hg
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Figure 5. The data sheet for the compound demonstrates the nature of the "analytical standard" used by Elbashir *et al.* for quantification of contamination in primaquine diphosphate tablets.

the substance they claimed to be a standard for the determination of contamination in primaquine diphosphate tablets was not the diphosphate salt of quinocide, but was in fact the monophosphate salt of quinocide.

What does all this imply? It implies that the substance claimed to be a standard for contaminant determination was a monophosphate salt of quinocide, not the diphosphate salt of quinocide. This difference is crucial because the two materials are different substances with a different percentage of quinocide in the molecule. As a result, such a material cannot be used as a standard for quantitative determination.

The molecular weight for the monophosphate salt of quinocide is 357.35, but that of the diphosphate salt is 455.34. The quinocide content in the monophosphate salt is 72.58%, but the quinocide content is 56.96% for the diphosphate salt. The diphosphate salt of quinocide contains as much crystal water as diphosphate salt of primaquine and the amount is defined by the Pharmacopeia. The quinocide monophosphate received from Dr. Ellis did not contain crystal water.

Clearly, the substance received from Dr. Ellis, Chief, Department of Chemical Information, Division of Experimental Therapeutics, Walter Reed Army Institute of Research, could not and should not be used as an analytical standard. Elbashir *et al.* knew this.

The proclamation that the sample is a valid standard of quinocide under the cover of a donation received from a known and respected scientist and well-known research institute was unethical at best. The fact that Elbashir *et al.* avoided answering reviewers'questions regarding the nature and quality of the standard demonstrates good knowledge that they were using the chemical in name only, and not the real substance. It is (and was) possible to transform the sample of monophosphate salt of quinocide into the corresponding diphosphate salt with the required amount of crystal water. However, a lack of elementary knowledge prevented Elbashir *et al.* from performing this simple operation. It also was possible to convert the monophosphate salt into the free base of quinocide and to use this as a standard for calibration. This operation also involves the conversion of antimalarial tablets into free bases. Free bases are not stable and must be stabilized against rapid oxidation. Such an operation was, without doubt, beyond the abilities of Elbashir *et al.* The most natural and easiest way for Elbashir *et al.* to publish their work was to find tractable partners among the editors embedded in publishing companies by the pharmaceutical industry or by using colleagues and friends who were willing to turn a blind eye to the lack of analytical integrity and to the presence of elements of plagiarism and fraud in the manuscript and who will process the manuscript with unnatural haste for publication without even a review process.

However, to illustrate the extent of the fraud in full, it is necessary to model the experiment as it was described by Elbashir *et al.* in [3]. Real standard solutions were prepared by dissolving 1000 μ g/mL primaquine diphosphate and 100 μ g/mL quinocide monophosphate. To simplify the task, we will not take into account the crystal water in primaquine diphosphate and quinocide diphosphate, despite there being a significant amount present in antimalarial tablets according to Pharmacopeias.

It should be recognized that the amount of quinocide in the analyzed tabletswas found to be underestimated by a factor of 1.35 by using the monophosphate salt as standard for calibration instead of the diphosphate salt. This means that "manufacturer 2" delivered tablets with 3.6% or 3.7% quinocide contamination; "manufacturer 1" was much better. However, a question arises. How could "manufacturer 1" be better than "manufacturer 2" when the same manufacturer of raw primaquine and the same batch of primaquine and the same percentage of contamination of quinocide was used for production? Simple "brit heads" of "scientists" missed this point from account. The fraud is obvious and it is more shameful in this case, because the authors tried to use the name of a respectable scientist and the name of an authoritative institute to conceal their fraud.

2. Discussion and Conclusions

It should be clearly acknowledged that Elbashir *et al.* were well aware of the difference between quinocide diphosphate presented in the tablets and the material they used as a standard. In publication [3] on p. 465 in Reagents, the authors declared that they used: primaquine diphosphate from Sigma-Aldrich and quinocide phosphate donated by Dr. William Y. Ellis. If the authors (Elbashir *et al.*) did not understand that primaquine diphosphate in tablets was contaminated with quinocide diphosphate from the synthetic procedure, even after they have read and referred to [13] and other papers published by the same team, and did not understand that quinocide diphosphate from the synthetic procedure and quinocide phosphate donated by Dr. Ellis are different substances, then they should not be accepted as qualified scientists. All the publications produced by Elbashir *et al.* involving the use of the material donated by Dr. Ellis must be withdrawn from circulation.

However, if the authors (Elbashir *et al.*) were well aware of the differences between quinocide diphosphate in tablets generated from the synthetic procedure and quinocide phosphate donated by Dr. Ellis, they should openly and clearly admit their fraud.

From the text of publication [3], it appears that Elbashir *et al.* were indeed well aware of the differences between quinocide diphosphate from the synthetic procedure in tablets and quinocide phosphate donated by Dr. Ellis.

The authors' awareness of their fraud was demonstrated in this way. How were the analytical data in this fraudulent paper produced? And how was it allowed to be published? Without doubt, the paper was not submitted to a normal review process by two independent reviewers, indeed it was not even reviewed by a single reviewer. The Editor in Chief of *Biomed. Chrom.*, by single decision, transferred the paper to publication. This clearly raises a number of questions: Is the Editor in Chief of *Biomed. Chrom.* an expert in pharmaceutical analytical chemistry? Is the Editor in Chief of *Biomed. Chrom.* an expert in analytical chemistry at all? Did the Editor in Chief of *Biomed. Chrom.* read the text of this paper at all? What was the background for the decision to publish?

The best way to curb this kind of fraudulent publication is to point out the authors of such articles by name together with reviewers and editors. The use of nonanonymous academic editors or reviewers and inclusion of the name of the Editor in Chief responsible for acceptance of the paper can help to clean the literary environment of unethical creations and respect the intelligence of scientists.

It should also be recognized that although Mr. Elbashir was the first author and the corresponding author was named as Mr. Aboul-Enein, they could not be the primary driver of this fraudulent project and might only be partly responsible for the fraud. It looks as if Mr. Baharuddin Saad, Deputy Dean (Research & Postgraduate Studies) from the School of Chemical Sciences, Universiti Sains Malaysia, 11800 Penang, Malaysia, e-mail: <u>bahrud@usm.my</u> is the real driving force behind this fraudulent project. It looks as though only Mr. Saad had the possibility and the authority to be in contact with the pharmaceutical industry. It looks as though only Mr. Saad had the capacity and the connections to push through publication of this unreviewed and fraudulent manuscript.

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