

# Fraud and misconduct – how pervasive in the world?

The EFGCP Annual Conference 2009 in Prague on 27-28 January 2009 is about the dark side of clinical research: when it goes wrong because of willful quality lapses.

**Not because of Murphy, who can be helpful or tricky. In science one sometimes finds what one is looking for. More often research means trial and error. But finding what one is not looking for is not an error. Many would consider serendipity favourably. Some would argue it is the motor of research. In clinical R&D, we are also familiar with failure or the mere absence of success. We set up a clinical trial with clear objectives and a solid design, and at the end of a long and difficult road, the results do not support the research hypothesis we were pursuing in good faith; or even more puzzling, the study is “inconclusive”. All this is still the domain of unbiased scientific experimentation, observation and reporting.**

When a researcher introduces bias voluntarily by design or by interfering with the experiment or the communication of results to tweak the conclusions in one way or another and serve partisan interests, we leave the domain of unbiased scientific research. The researcher becomes the demiurge who wishes us to believe his/her observations are caused by nature, and yet they are artifacts he/she created to deceive.

Why is fraud or misconduct practiced? Most research is paid for and there are many different types of additional rewards when the research is “successful” in our society. Some of these payments and rewards may – or may not, depending on the organisation in which the

researcher works – trickle to the individual researcher. The more the income and potential rewards can be significant for the researcher, the more this creates a situation of conflict of interest challenging the independence of a researcher. Unfortunately, there is practically no publicly available information on research grants from commercial sponsors of clinical trials, the internet included. Clinicaltrials.gov does not contain any information about research grant levels by therapeutic area and protocol complexity, despite abundant information about the latter. Research should be funded urgently into this subject, to better understand the motives behind fraud and misconduct in clinical research. Knowing the motives would facilitate preventive action.

What is the extent of fraud and misconduct? Fraud and misconduct is almost never self-reported. Even discovered, it is rarely admitted wholeheartedly or to its full extent. It tends to be repetitive within the same person or institution.

How pervasive willfully biased clinical research is can be judged from findings about the withholding of conflict-of-interest declarations as well as from public inspection statistics. As to the declaration of conflict-of-interest situations we know that they are grossly underreported by authors of clinical trial publications like presentations, articles, posters and abstracts. As to the findings from inspections of clinical trials, the density of inspections is very low in comparison with the number of trials and sites in the world, and the

outcomes are often not publicly available.

The US Food and Drug Administration (FDA) is the public authority with the largest experience of fraud and misconduct in clinical research, thanks to a global inspection programme. If one considers the 20 largest countries of the world in terms of population, Figure 1 shows that the FDA started inspecting sites in 1977 on its own territory, and moved to practically all parts of the world over the next 30 years, following a gradient of diminishing Gross Domestic Product (GDP) per capita. Sites in Bangladesh, Indonesia, Pakistan and Vietnam have not been inspected yet. These countries have a GDP per capita at or below \$3,000. The expansion of FDA inspections in the world is therefore not finished, as more emergent markets open up to clinical research with new drugs to be registered in the USA.

The absolute number of FDA inspections has increased gradually to reach a peak in the 2nd half of the nineties, and has been declining since (see Figure 2). The proportion of international audits by the FDA over the last 20 years shows a six-fold increase, from 5% to 31%. This underscores the growing importance of sites outside the USA in the development of drugs for the American market. The frequency of FDA audits in the European Union is small in comparison to the USA, and is also declining, to judge from the evolution in the Top 4 European Union (EU) countries, France, Germany, Italy and the United Kingdom. This may be related to a strong effort by the national authorities in the European Union to introduce local inspection programs since 2004, following the entry into effect of the Clinical Trial Directive. The frequency of FDA audits in the BRIC countries (Brazil, Russia, India and China), which together represent half the remaining population of the world, is even smaller, but catching up fast with the EU recently.

Table 1 shows the proportion of inspections which are sufficiently violative of Good Clinical Practice (GCP) to warrant a classification as OAI (Official Action Indicated) and all sub-categories (C, P, R, RR, W, WR). Before 2000, foreign sites performed distinctly worse than sites in the USA, but since then, foreign sites appear to perform better. Given the frequency of inspections in the USA, it is alarming to see that in the last few years one in every twenty inspected sites was found to have violated GCP significantly.

Fraud and misconduct at investigative sites is certainly

preoccupying. However, fingers should not be pointed exclusively at investigators. Ethics committees, CROs and sponsors have been caught as well. Healthcare institutions have been blamed for a lack of oversight over clinical research conducted inside the institutions. Perhaps some of the extraordinary moneys invested in external monitoring by sponsors should be better invested in strengthening research oversight processes inside healthcare institutions? ■

#### Source of raw data:

- a) About FDA inspections: [www.accessdata.fda.gov](http://www.accessdata.fda.gov)
- b) About the population of countries and their GDP per capita: [www.cia.gov](http://www.cia.gov)

**Table 1.** OAI classification of audits by region and by period in proportion of FDA audits performed

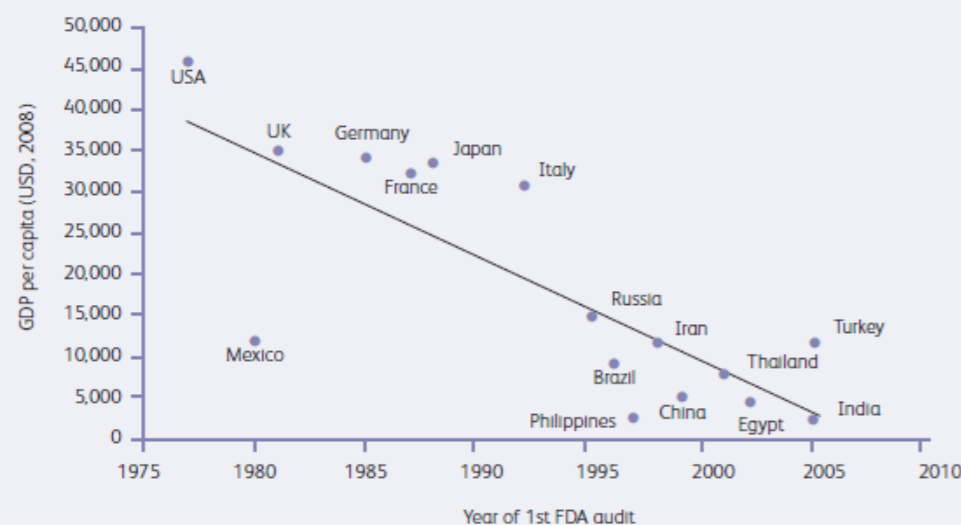
Country	Period				
	85-<90	90-<95	95-<00	00-<05	05-<10
USA	3%	2%	3%	3%	5%
Top 4 EU	0%	13%	7%	0%	2%
BRIC		0%	0%	0%	1%
ROW	6%	8%	8%	0%	1%



**Jean-Pierre Tassignon**  
 Jean-Pierre Tassignon, MD, PhD, FFPM, MBCPM  
 Chairman of the Board, European Forum for GCP,  
 Brussels. Lecturer and Examiner, Pharmed PG course  
 in Pharmaceutical Medicine, Université Libre de  
 Bruxelles, Visiting Professor, CHU Brugmann, Brussels,  
 Head of the Clinical Research Unit at CHU Brugmann  
 and HUDERF hospitals, Brussels, President & CEO,  
 Crossover CRI AG, Zug, Switzerland.

Email: [Jean-Pierre.Tassignon@efgcp.be](mailto:Jean-Pierre.Tassignon@efgcp.be)

**Figure 1.** Year of 1st FDA audit versus GDP per capita for the 20 most populous countries in the world (Bangladesh, Indonesia, Pakistan and Vietnam have not had a first FDA audit yet; their GDP per capita is \$1,400, \$3,600, \$2,400 and \$2,600 respectively)



**Figure 2.** Frequency of FDA audits by 5-year period between 1985 and 2008. (EU= European Union; Top 4 EU= France, Germany, Italy and the United Kingdom; BRIC= Brazil, Russia, India and China; ROW= rest of the world; percentages indicate the proportion of audits overseas as a function of total FDA audits during the period)

