

## The Physicians Payment Sunshine Act – casting a shadow over clinical research?

In October 2010, the American congress passed the Physicians Payment Sunshine Act, which will force drug and medical device manufacturers to disclose their payments to healthcare professionals (HCPs). Starting this year, drug makers are required to track all payments to HCPs and from September 2013 onwards, details of these payments will be made freely available on the Internet for all and sundry to analyse. In other countries too, for example the UK with the new Association of the British Pharmaceutical Industry (ABPI) code of practice update, drug companies will be forced into disclosure, though the requirements are usually somewhat less stringent. In response, pharmaceutical companies have been scrambling to become compliant. This is no mean feat, given the complexity and extent of the relationship between drug companies and HCPs. In particular, large drug companies operate in many different countries with many different business cultures and attitudes, and under many different legislative frameworks.

Ostensibly, the main target of these changes is the marketing end of the pharmaceutical business. Although the free gifts handed out to physicians by drug reps are already more tightly regulated, drug companies still spend large sums of money, for example, on key note speakers at satellite symposia in medical congresses (thereby obtaining an indirect form of endorsement) and other forms of promotional activity. The argument goes that these large budgets are ultimately passed on to the consumer in the form of higher drug prices. Aggressive marketing could also persuade doctors to prescribe expensive new proprietary medicines when a cheap generic alternative would be perfectly acceptable. The greater transparency and awareness of how much money is actually spent by the drug companies will, according to the advocates of the Sunshine Act at least, help reduce the marketing budget as pharmaceutical companies change their practices to enhance their corporate image.

The Sunshine Act applies to all HCPs who receive payments from the drug companies. Thus, payments to investigators in clinical trials will also have to be disclosed, as will payments to members of advisory boards and drug safety monitoring boards. The reasoning behind extending the reporting requirements to clinical research activities is that an HCP who receives payment for marketing activities may also be a principal investigator or a member of an advisory board. Complete transparency is intended to ensure that HCPs do not receive disproportionate remuneration for research activities to compensate for loss of income elsewhere.

To assuage corporate concerns about loss of confidentiality, a delay by up to 4 years will be allowed for disclosure of payments to HCPs involved in the clinical development programme of a new product. But it is the reaction of the HCPs themselves that some find most worrying. The drug industry is currently under very close scrutiny and HCPs will be aware that the general public could take a very negative view of an apparently cosy relationship between drug companies and HCPs and question the independence of the HCPs and their hospitals. In the face of negative public opinion, might those same HCPs reconsider their involvement in research? The potential image problem could be accentuated by disclosure without context. Clinical trials are complex and expensive undertakings (not least because of an increased regulatory burden in recent years), and not all the money will go to lining the pockets of the HCPs. Nevertheless, the public or lay press, in their enthusiasm to expose HCP enrichment at the perceived expense of patients' best interest, may just focus on a lump-sum payment to trial staff, without really caring where that money goes or what clinical research actually involves. Ultimately, this could have a negative impact on research.

In summary, although the intentions of this new disclosure legislation are laudable, and something had to be done to expose the potential conflicts of interest that arise wherever there is a free flow of money from drug companies to HCPs, we should also be aware of possible unintended consequences

(which can often arise when there is an attempt to engineer changes in ingrained behaviour).

### *Regulatory agencies and social media*

When it comes to social media and networking, I must admit that I am rather twentieth century in my outlook – I am happy to use a telephone and e-mail, have a static webpage, and maybe even dabble in LinkedIn, but for the most part the attraction of Twitter<sup>®</sup> has always been beyond me. I could grudgingly admit that *Tweets* from eye witnesses to breaking news stories could also be of interest, but who cares whether Stephen Fry was stuck in a lift for 40 minutes, right? And as for any offerings from the FDA and EMA, who would be interested in *Tweets* from monolithic institutions?

This suspicion of the whole Twitter<sup>®</sup> thing perhaps explains why I took so long to actually investigate the FDA and EMA Twitter<sup>®</sup> feeds (@FDA\_Drug\_Info and @EMA\_News). When I did, I was surprised. In contrast to my prejudice, the *Tweets* were not along the lines of ‘such and such a member of the committee couldn’t make it today because of inclement weather’ but instead read like news announcements. In fact, the

Twitter<sup>®</sup> feeds for the FDA and the EMA (and presumably for most large institutions and companies) are managed by a press department rather than an individual. The downside of this control over output is, I suppose, less spontaneity and you also probably have to be wary of spin. (The FDA in particular is coming up for some refinancing agreements this year and is therefore rather image conscious).

Importantly, when the EMA tweets about, for example, new guidelines for advanced therapies, there is usually a link to the news story on the agency website, which gives more detail than is possible in *Tweets* (which are limited to 140 characters). These news stories then provide a link to the actual guidelines (or whatever the *Tweet* was about). Why, you might ask, can’t you just go to the news sections of the EMA and FDA website? Well yes, of course you can, but I still found that the Twitter<sup>®</sup> format seems excellent at giving you a very succinct overview of what is going on. What is also interesting is that you can quickly see what news stories are generating most attention (as measured by the number of *Retweets*). And this is not to mention the networking potential of Twitter<sup>®</sup> that I have yet to investigate or comprehend.

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## **Indian Government gives green light to cheap Nexavar copy**

In a ruling with major implications, the Controller General of Patents, Designs, and Trade Marks of the Government of India on the 12th of March granted domestic company Natco Pharma a licence to manufacture and sell a generic version of Bayer Corporation’s anticancer drug Nexavar at a knockdown price that ‘shall not exceed (8800 rupees) for a pack of 120 tablets’ (a month’s supply).<sup>1</sup> This represents a massive 97% saving on the current cost of Nexavar (about 280,000 rupees per month).

In arriving at his decision, the Controller General invoked the 1970 Patents Act, according to which any interested party may apply for a compulsory licence after 3 years have expired since the granting of a patent if ‘the reasonable requirements of the public with respect to the patented invention have not been satisfied’.

Natco produced figures, broadly accepted by the Controller General, showing that the amount of Nexavar Bayer imported into India fell way short of what was needed to meet the demand of patients. The Controller General further accepted Natco’s assertion that the drug was unaffordable to the public.

Under the conditions of the licence, Natco must pay a royalty amounting to 6% of net sales to Bayer and provide the product free of charge to ‘atleast (sic) 600 needy and deserving patients per year’.

At the time of writing, Bayer was considering its next move. Keeping its legal team busy is a second case, this one involving Cipla Ltd, which has been selling a generic form of Nexavar in India since 2010. Bayer is currently pursuing the matter through the courts.

While India has modest health expenditure per capita, its population is expected to become the world’s largest within the next few decades.<sup>2</sup>

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## Tamiflu research leaves more publication questions than answers

Tamiflu is the brand name for the drug oseltamivir and is an antiviral used to treat infections caused by viruses, particularly influenza. Tamiflu first came to prominence in the general media in May 2009 after the WHO requested stockpiles of Tamiflu to tackle what it termed a global pandemic of the H1N1 swine flu. This of course had a large impact on sales of Tamiflu, which reached 3.2 billion Swiss Francs in 2009.<sup>1</sup>

The Swiss newspaper, *Neue Zürcher Zeitung*, recently published a very interesting interview with Gerd Antes, director of the German Cochrane Centre.<sup>2</sup> In particular the focus was on the Tamiflu vaccine and the non-publication of research results. Antes notes that over 50% of the results of Tamiflu studies have not been made public, making a proper evaluation of the vaccine nigh on impossible, despite the fact it has been on the market since 1999. The Tamiflu manufacturer counters this accusation saying, 'Roche provided the Cochrane group with access to 3,200 pages of very detailed information, enabling their questions to be answered'.<sup>3</sup>

Critically, Tamiflu's use in a pandemic was evaluated in a 2003 meta-analysis of 10 studies sponsored by Roche.<sup>4</sup> However, of these 10 studies, 8 were unpublished.

Cochrane has been pressing Roche for several years to release all study data and although some information has been forthcoming, the amount of detail remains unsatisfactory to Cochrane, particularly the data relating to side effects. Antes notes that one published study is seven pages long, yet the clinical study report for it is over 2000 pages long.<sup>2</sup> Cochrane suspects a lot of information relating to that study has not been made public.

What role are the authorities playing in all of this? The FDA in the USA sent Roche a warning letter in 2000 instructing Roche to desist from claiming that Tamiflu reduces complications. In order to comply with this until recently Roche ran 2 Tamiflu websites –

one for US residents, and one for the rest of the world (which did not follow the FDA's instruction).

That the European authority (European Medicines Agency (EMA)) came to a different conclusion than the FDA is worrying according to Antes who questions if both authorities were presented with the same information. Dr Fiona Godlee, Editor-in-Chief of the *British Medical Journal*, also picked up on this point and wrote, 'The discrepancies between the conclusions reached by different regulators around the world highlights the absurd situation we find ourselves in. In a globalised world, regulators should cooperate and pool their limited resources. Otherwise we will continue to waste money and risk people's health on drugs that don't work'.<sup>5</sup>

Antes also notes the much better resources at the disposal of the FDA compared to Europe.<sup>2</sup> The FDA employs 170 biostatisticians, a number that European agencies can only dream of.

The Cochrane Collaboration and *BMJ* have been at loggerheads with Roche over full disclosure of Tamiflu results for quite some time. This current spat has been unleashed by the January 2012 issue of *The Cochrane Library* which published an updated Cochrane Review of the neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir (Relenza), antivirals used to treat and prevent influenza.<sup>6</sup>

Of particular interest to EMWA members is the criticism of the role that ghostwriters have played in some of the Tamiflu studies, writing according to Roche's instructions. The *BMJ* has also tackled Roche on this issue in a series of short 'Rapid Responses' and the answers hopefully serve as a barometer to show progress made in the area of ghostwriting over the past decade or so.

Specifically, the *BMJ* alleges that a paper by Treanor *et al.*,<sup>7</sup> published in 2000 in *JAMA* used ghostwriters.<sup>8</sup> Roche's response deserves to be republished in full. 'Roche confirms that medical writers were used to help draft some of the above papers. This is neither unusual nor secretive, and is common practice in the scientific community. At

the time of writing and submission (2002) (*sic*), it was not standard practice for professional medical writers to be named on manuscripts'.<sup>8</sup> Interestingly, this is at odds with the statement by Treanor *et al.*<sup>9</sup> that, 'the pivotal adult treatment trial published in *JAMA* in 2000 was not ghost-written'. The *BMJ* responded, 'While we are prepared to accept Dr Treanor's assurances that he was unaware that his paper was ghostwritten, this of course does not mean that it was not. Roche's evasive answers when asked about this matter only serve to reinforce our concerns'.<sup>8</sup>

Roche further refuted the influence of the marketing department in inserting key messages and had the following to say about ghostwriting at that time. 'During the period of time in question (1999–2002) it was common practice for scientific medical writers to provide writing support for publications with the authors having full access to data and full and final review of the publications. Since the introduction in 2003 of the Good Publication Practice guidelines for Pharmaceutical Companies (GPP), Roche has complied with the practice to acknowledge the involvement of professional medical writers'.<sup>3</sup>

With so many organizations involved and the whole controversy being played out over several years, the Tamiflu publication saga looks set to continue.

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## A new website for reporting and researching drug side effects

David Healy, a professor of psychiatry in Wales, is not much loved by the pharmaceutical industry. EMWA members might remember that he gave a presentation titled 'Ghostwriting: What's the Problem?' at the ICR-EMWA Joint Symposium on Publishing Clinical Trials: Ethics and the Pharmaceutical Industry on 27th February 2008. But what David Healy wants is to make medicines safer for us all – and sometime or other we all become 'patients'. To this end he has founded Data Based Medicine Limited which operates through its website RxISK.org. This is the first free

website (not sponsored by the pharmaceutical industry or advertising) for patients and their doctors to research, and easily report drug side effects. The website is still under construction but states that it will offer a medical timeline chart that captures essential information on treatment-induced problems, tag clouds that help convey the impact of problems on people's lives, and free access to FDA's database of adverse events.

David quotes others when he writes 'the greatest public health benefit would come from getting the greatest number of people on the greatest amount of medications to ward off all conceivable risks' (<http://davidhealy.org/>). He says this target is not

going to work out well. His article on the site titled 'Pills and the Man' explains the obstacles in terms of financial and political interests and concludes that 'It's difficult to avoid the impression that it's the

health of drug companies that regulators and others have been most concerned about'. However, much of your livelihood depends on the industry this article and others on his website give cause for thought.

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## Therapy Limericks, By Graham Guest

I wanted to rapidly fit  
Some new parts to my car bit by bit  
Then I thought of the fact  
While my car was intact  
My infinitive's definitely split  
Prepositions were dear to old Matt  
Whose sentences never were flat  
His rule did not bend  
They'd be put at the end  
So he always knew where they were at

The proofreaders job can be tuff  
When the client's right terrible stuff  
They do just as they pleeze  
Like put two e's in hee's  
When just one e is reely e-nuff  
An unknown young fellow called Hound  
Was upset by his name and its sound

He changed it to Getty  
And his girlfriend, Betty  
Said, 'Now you are truly re-nouned'

Clive wanting a life with more glamour  
Established himself as a spammer  
Police came one day  
'What gived me away?'  
'We're afraid, Sir, it was your bad grammar'

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