Tamiflu: Full reports from trials should be public; regulators respond to recommendations

April 10 2012

The full clinical study reports of drugs that have been authorized for use in patients should be made publicly available in order to allow independent re-analysis of the benefits and risks of such drugs, according to leading international experts who base their assertions on their experience with Tamiflu (oseltamivir).

Tamiflu is classed by the World Health Organization as an essential drug and many countries have stockpiled the anti-influenza drug at great expense to taxpayers. But a recent Cochrane review on Tamiflu has shown that even more than ten thousand pages of regulatory evidence were not sufficient to clarify major discrepancies regarding the effects and mode of action of the drug.

Writing in this week's *PLoS Medicine*, Peter Doshi from Johns Hopkins University School of Medicine in Baltimore, USA, Tom Jefferson from the Cochrane Collaboration in Rome, Italy, and Chris Del Mar from Bond University in the Gold Coast, Australia say that there are strong ethical arguments for ensuring that all clinical study reports are publicly accessible. In the course of trying to get hold of the regulatory evidence, the authors received several explanations from Roche as to why it would not share its data. By publishing that correspondence and comment, the authors assert that experiments on humans should be made available, all the more so given the international public health nature of the drug.

They argue: "It is the public who take and pay for approved drugs, and therefore the public should have access to complete information about those drugs. We should also not lose sight of the fact that clinical trials are experiments conducted on humans that carry an assumption of contributing to medical knowledge. Non-disclosure of complete trial results undermines the philanthropy of human participants and sets back the pursuit of knowledge."

However, according to the authors, industry and regulators have historically treated clinical study reports as confidential documents, impeding additional scrutiny by independent researchers.

Using the example of Tamiflu, in which drug companies, drug regulators, and public health bodies such as the World Health Organization and the Center for Disease Control have made discrepant claims about its clinical effects, the authors argue that critical analysis by an independent group such as a Cochrane review group is essential. By recounting the details of an extended correspondence with Tamiflu's manufacturer Roche, the authors argue that the company provided no convincing reasons to refuse providing access to clinical study reports.

The authors challenge industry to either provide open access to clinical study reports or publically defend their current position of randomized controlled trial data secrecy.

They say: "we hope the debate may soon shift from one of whether to release regulatory data to the specifics of doing so. But until these policies go into effect—and perhaps even after they do—most drugs on the market will remain those approved in an era in which regulators protected industry's data."

Peter Doshi is funded by an institutional training grant from the Agency for Healthcare Research and Quality #T32HS019488. The funders had

no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

All review authors have applied for and received competitive research grants. All review authors are co-recipients of a UK National Institute for Health Research grant to carry out a Cochrane review of neuraminidase inhibitors (http://www.hta.ac.uk/2352). In addition: TJ was an ad hoc consultant for F.Hoffman-La Roche Ltd in 1998-1999. TJ receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore, none of which are on neuraminidase inhibitors. TJ is occasionally interviewed by market research companies for anonymous interviews about Phase 1 or 2 products unrelated to neuraminidase inhibitors. Since submission of this article, TJ has been retained as an expert consultant in a legal case involving Tamiflu. CDM provided expert advice to GlaxoSmithKline about vaccination against acute otitis media in 2008-2009. CDM receives royalties from books published through Blackwells, BMJ Books and Elsevier. PD declares no further conflicts of interest.

European regulators respond to the Tamiflu recommendations

In a Perspective article accompanying a new analysis by Peter Doshi and colleagues in PLoS Medicine that recommended full clinical study reports of authorized drugs be made publicly available in order to allow independent re-analysis of the benefits and risks of such drugs, four drug regulators (representing the European Medicines Agency, the French Agence Française de Sécurité Sanitaire des Produits de Santé, the UK's Medicines and Healthcare products Regulatory Agency, and the Medicines Evaluation Board in The Netherlands) respond.

The four regulators say: "We consider it neither desirable nor realistic to

maintain the status quo of limited availability of regulatory trials data," and suggest what they call a "three pronged approach", which includes establishing rules of engagement to follow the principle of maximum transparency whilst respecting the need to guarantee data privacy and to avert the potential for misuse.

The regulators say: "We welcome debate on these issues, and remain confident that satisfactory solutions can be found to make complete trial data available in a way that will be in the best interest of public health."

However, they also lay out arguments for why trial data should not be open for all: personal data protection; non-financial competing interests; and the risks of competition.

They conclude: "We welcome debate on these issues, and remain confident that satisfactory solutions can be found to make complete trial data available in a way that will be in the best interest of public health."

No specific funding was received for writing this article. All authors work for drug regulatory agencies. The authors have declared that no other competing interests exist. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies, or the committees or working parties of the regulatory agencies the authors work for.

More information: Doshi P, Jefferson T, Del Mar C (2012) The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience. PLoS Med 9(4): e1001201. doi:10.1371/journal.pmed.1001201

Eichler H-G, Abadie E, Breckenridge A, Leufkens H, Rasi G (2012) Open Clinical Trial Data for All? A View from Regulators. PLoS Med

9(4): e1001202. doi:10.1371/journal.pmed.1001202