

Brussels, 11 October 2013

**Joint letter to Member States' Ministers of Health
and Permanent Representatives (CoRePers)**

**EU Regulation on clinical trials:
further enhance clinical data transparency**

- ***A clear stance by the Council in favour of freedom of information for European citizens and of public access to clinical trial data is needed.***

Selective publication of only those results which favour the drug in question biases scientific analysis, Medicines Agencies' decisions and clinical decision making, therefore putting public health at risk and wasting resources of Member States' healthcare systems (a). Moreover, it is an unethical practice contrary to the Helsinki Declaration and to the basic scientific and political principle of transparency, and it calls for a political answer (b).

On 29 May 2013, the Environment, Public Health and Food Safety (ENVI) Committee adopted a perfectly reasonable demand in order to finally allow for independent analysis of clinical trials: that clinical data contained in clinical study reports (CSRs) *"should not be considered commercially confidential once a marketing authorisation has been granted or the decision-making process on an application for marketing has been completed"* (amendment 30, creating a new recital).

This demand is in line with the European Medicines Agency policy on access to documents (1) and with the position of the European Ombudsman who found that clinical study reports (CSRs) do not contain commercially confidential information or personal data (participants' clinical data are previously anonymised) (2). This was confirmed by an in-depth analysis of 78 clinical trials by two researchers from the Cochrane Collaboration in early 2013 (3) (c).

However, since the beginning of the discussions, the pharmaceutical industry has been fighting heavily against citizens' freedom of information right:

- In March 2013, two pharmaceutical companies, AbbVie and InterMune, supported by European and US pharmaceutical industries trade associations (EFPIA and PhRMA), brought cases against the EMA and its 2010 access to document policy at the European Court of Justice (d) (4);
- In July 2013, EFPIA and PhRMA proposed deficient and non-binding self-regulation principles that would maintain the *status quo* and are unlikely to be implemented by their members (no access to clinical study reports, demands for applications to be reviewed by a "scientific board" to be appointed by the company in question);
- In addition, in July 2013, EFPIA and PhRMA have made concrete proposals for a lobbying strategy that entailed "mobilising patient groups to express concern about the risk to public health by non-scientific re-use of data" (5).

a- In Europe, in 2009, several EU governments stockpiled millions of doses of Tamiflu® to combat A/H1N1 influenza, even though the effectiveness of Tamiflu® in the prevention of influenza complications was unproven, so wasting billions of euros. Health authorities made decisions without seeing the full data set (ref. 2).

b- See the AllTrials Campaign (<http://www.alltrials.net>), as well as other campaigns (<http://wp.rxisk.org/sign-the-rxisk-drug-safety-petition>) calling for access to clinical trials results. Clinical trials data are scientific data and should be open to scrutiny by independent parties (for more information, read "Debunking 4 secrecy myths which hinder transparency" here: <http://www.prescrire.org/Docu/DOCSEUROPE/20130400DebunkingSecrecyMyths.pdf>).

c- Moreover, in a recent study, the German health technology agency IQWiG showed that in contrast to CSRs, publicly available sources provide insufficient information on patient-relevant outcomes of clinical trials, and called for CSRs to be made publicly available (ref. 7).

d- In an intervention in August 2013, an AbbVie representative explained its opposition to transparency asserting that some adverse drug reaction data should be considered commercially confidential (ref. 8). At the end of September, the media reported that the former CEO of InterMune is in home detention as part of a six-month penalty for exaggerating the benefits of one of the firm's product... (ref. 9).

Throughout the trilogue negotiations, **a clear stance must be adopted by the Council, in favour of freedom of information for European citizens.** This is necessary in order to ensure that the new Regulation on clinical trials will **advance public access to clinical trial data, and will be of benefit to the public at large.**

- ▶ We therefore ask you to **support Amendment 30 of the ENVI report**, and also to **add this requirement to the Regulation, in the form of an article.** This would also enable the European Medicines Agency to defend itself in the procedure brought before the EU Court of Justice by the two companies challenging its 2010 policy on access to documents.
- ▶ We also moreover ask you to **further strengthen transparency requirements by demanding the publication of clinical study reports (CSRs) (e), within 1 year from the end of the clinical trial, and at the latest within 3 years if the company has not by then applied for marketing authorisation**, to ensure that these results are not forever lost to science should the company decide in the end not to seek marketing authorisation.

Clinical trials should also aim to determine how well patients tolerate new medicines. The Regulation only requires the reporting of serious adverse drug reactions by the trial sponsor to the Agency if they are "unexpected". Yet recent evidence suggests companies are reluctant to their drugs' adverse reactions to health authorities (6).

- ▶ **We urge you to demand reporting by the investigator (the clinician) of all serious adverse reactions, whether "expected" or not, via the centralised portal**, in order to avoid harmful delays in the decision-making process, especially when urgent measures are needed to protect participants.

We would be happy to further discuss this issue with you, as well as that of participants' protection (read in annex 1), and hope that you will be able to take our recommendations into account.

**Association Internationale de la Mutualité (AIM)
Nordic Cochrane Centre
Health Action International (HAI) Europe
International Society of Drug Bulletins (ISDB)**

**Medicines in Europe Forum (MIEF)
TransAtlantic Consumer Dialogue (TACD)
WEMOS**

References :

- 1- "[Draft policy 70: Publication and access to clinical-trial data](#)" 24.06.2013. www.ema.europa.eu
- 2- Gøtzsche PC. "Opening up data at the European Medicines Agency" *BMJ* 2011, **342**:d2686
- 3- Doshi P et Jefferson T "Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports" *BMJ Open* 2013;3:e 002496.
- 4- Dyer C "European drug agency's attempts to improve transparency stalled by legal action from two US drug companies" *BMJ* 2013; 346:f3588.
- 5- Sample I "Big pharma mobilising patients in battle over drugs trials data - Leaked memo from industry bodies reveals strategy to combat calls by regulators to force companies to publish results" [The Guardian](#), Sunday 21 July 2013.
- 6- There are many examples, well documented, e.g.:
 - Healy D "Let them eat Prozac" New York: New York University Press, 2004.
 - Gøtzsche PC. *Deadly medicines and organised crime: How big pharma has corrupted health care*. London: Radcliffe Publications, 2013.
 - "GlaxoSmithKline to plead guilty and pay \$3 billion to resolve fraud allegations and failure to report safety data". July 2012. www.justice.gov: 3 pages.
 - "European Medicines Agency acts on deficiencies in Roche medicine-safety reporting". July 2012. www.ema.europa.eu: 2 pages.
- 7- Wieseler B et coll. "Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data" *PLoS Med* 2013; 10(10): e1001526. doi:10.1371/journal.pmed.1001526. www.plosmedicine.org
- 8- Hawkes N "Industry and Drug regulators disagree on which data should remain confidential" *BMJ* 2013 ; 347: f5390.
- 9- Brown D "The press-release conviction of a biotech CEO and its impact on scientific research" washingtonpost.com 23 September 2013.

e- Clinical study reports are comprehensive documents containing the following sections: report synopses (about 5 pages), efficacy evaluation (about 13 pages), safety evaluation (17 pages), trial protocol (about 60 pages), and the remaining pages are attached tables and anonymised individual efficacy and safety listings (ref. 8).

Annex:

Recommendations in order to avoid undermining protection of participants of clinical trials

The draft Regulation on clinical trials prepared by the European Commission is primarily aimed at “*fostering EU's attractiveness in clinical research*”. However, it undermines the protection of trial participants (f).

We call on the Council to:

1. Re-establish the role of Ethics Committees to guarantee the protection of trial participants

With its proposal to disconnect “scientific” assessment (by a “reporting Member State”, whose findings are binding on the other Member States concerned) from “ethical” assessment (made by each Member State, but limited in practice to verifying compliance with the consent procedure), the European Commission proposes in effect to deprive Member States of their sovereignty over the acceptability of a clinical trial.

► **We urge you to:**

- Secure ethical improvements put forward by MEPs: **restoring the role of Ethics Committees and also authorising them to comment on the “scientific” assessment** (an ethical assessment also involves an assessment of the methodology and the two issues cannot be assessed separately) (*amendments 2, 64, 77 and 79*); **moreover, the Council must clarify the fact that Ethics Committees’ opinions are binding (g)**;
- **Refuse the generalisation of a tacit approval procedure**, to ensure that no trial can be authorised without an Ethics Committee opinion (this would contravene the Charter of Fundamental Rights of the European Union).

2. Clarification of definitions, including “low-risk clinical trials”

MEPs wish to support the Commission’s proposal to create a new category of “low-intervention trials” for drugs already on the market. However, MEPs understand the dangers of the recent trend to accelerate marketing authorisation procedures before gathering sufficient data on the efficacy and safety of the drugs concerned (h). MEPs therefore supported only “low-risk trials”, which differ from “low-intervention trials” because post-approval efficacy and safety studies of medicinal products authorised within the previous 10 years are excluded from “low-risk trials” (*amendment 57* explicitly included trials involving recent medicinal products in the definition of “standard” clinical trials, so they cannot be categorized as “low-risk”).

- **We urge you to support the clarification of definitions requested by MEPs**, particularly to avoid the risk that some clinical trials will be considered, by default, “non-interventional studies”;
- **We call on you to be particularly cautious with “low-risk trials”**, particularly in order to **ensure** that:
 - **participants in “low-risk clinical trials” will be eligible for compensation** in case of damages, as requested by MEPs (*amendment 235*) (i);
 - **“low-risk trials” cannot cover off-label indications**, even if they are based on “*sufficient published evidence and/or standard treatment guidelines*” (refuse *amendments 56 and 60*), **and cannot be conducted without seeking patients’ informed consent** (refuse *amendments 17, 34 and 167*).

f- For more details, read our joint analysis (“[New Proposal for a Regulation on Clinical Trials – Joint analysis](#)” 5 February 2013 : 12 pages.) and Kuhrt N “Unwitting Guinea Pigs: EU Seeks To Reduce Patient Protection in Medical Trials” 24 juin 2013 (www.spiegel.de).

g- According to Article 9(1) of Directive 2001/20/EC, “*the sponsor may not start a clinical trial until the ethics committee has issued a favourable opinion and inasmuch as the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance*”. Recital 11 of Directive 2001/20/EC confirms that a “tacit” administrative authorisation by the Member States’ competent authority [often the drug regulatory agencies] is only possible “*if there has been a vote in favour by the ethics committee*”.

h- In such cases, the authorities ask companies to perform post-approval efficacy and safety studies (PAES and PASS studies).

i- Directive 2001/20/EC made it obligatory to take out insurance for all human trials.

Cosignatory organisations

AIM. The Association Internationale de la Mutualité (AIM) is a grouping of autonomous health insurance and social protection bodies operating according to the principles of solidarity and non-profit-making orientation. Currently, AIM's membership consists of 41 national federations representing 29 countries. In Europe, they provide social coverage against sickness and other risks to more than 150 million people. AIM strives via its network to make an active contribution to the preservation and improvement of access to health care for everyone. More info: www.aim-mutual.org. Contact: corinna.hartrampf@aim-mutual.org.

Nordic Cochrane Centre. The Nordic Cochrane Centre is part of the Cochrane Collaboration. The Cochrane Collaboration is an international not-for-profit international network of more than 28,000 dedicated people from over 100 countries preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care. More information: www.cochrane.org. Contact: pcg@cochrane.dk

HAI Europe. Health Action International (HAI) Europe is a non-profit, European network of consumers, public interest NGOs, health care providers, academics, media and individuals working to increase access to essential medicines and improve their rational use through research excellence and evidence-based advocacy. More info: www.haieurope.org. Contact: ancel.la@haieurope.org

ISDB. The International Society of Drug Bulletins (ISDB), founded in 1986, is a worldwide Network of bulletins and journals on drugs and therapeutics that are financially and intellectually independent of pharmaceutical industry. Currently ISDB has around 80 members in 41 countries around the world. More info: www.isdbweb.org. Contact: press@isdbweb.org

MiEF. The Medicines in Europe Forum (MiEF) was launched in March 2002 and reaches 12 European Member States. It includes more than 70 member organizations representing the four key players on the health field, i.e. patients groups, family and consumer bodies, social security systems, and health professionals. Such a grouping is unique in the history of the European Union and is testament of the importance of European medicines policy. Contact: pierrechirac@aol.com

TACD. The Transatlantic Consumer Dialogue (TACD) is a forum of US and EU consumer organisations which develops and agrees on joint consumer policy recommendations to the US government and European Union to promote the consumer interest in EU and US policy making. More information: www.tacd.org. Contact: tacd@consint.org or hammerstein.david3@gmail.com

Wemos. Wemos influences international policy in such a way that the right to health is respected, protected and promoted. In doing so, Wemos devotes special attention to vulnerable sections of society. Wemos advocates ethical conduct, coherent policy and equal access to care. Its lobbying work focuses on lasting improvements in Dutch, European and global policy. More information: www.wemos.nl. Contact: annelies.den.boer@wemos.nl