Brussels, 17 March 2013
Press Release

EU Regulation on clinical trials: close to the finish line

- ***If adopted in early April 2014, the new Regulation on clinical trials should bring greater transparency concerning clinical trial data and results. However, the proposed Trade Secrets directive (published in November 2013) may curb the advances gained in the Clinical Trials regulation.***

In early April 2014, the European Parliament will discuss and **vote in plenary on the proposed Regulation on clinical trials**, which would repeal Directive 2001/20/EC.

If approved, this Regulation will apply by mid-2016 and:

- Allow sponsors to submit **a single application dossier through a centralised, web-based portal** (the EU portal) to all Member States in which the sponsor wishes to conduct a clinical trial; the application will undergo joint "scientific assessment" by the Member States concerned, led by a reporting Member State;
- Attempt to address **differences in the risk to subject safety posed by clinical trials**, by excluding "non-interventional studies" from the scope of the Regulation, and by creating a new category of clinical trials called "low-intervention clinical trials";
- Establish **greater transparency** concerning clinical trial data and results.

This final text is the result of intense efforts by Parliament, Council and civil society

The text available for adoption by Members of the European Parliament (MEPs) is an improved version of the EU Commission's initial proposal from July 2012, particularly with regard to transparency requirements (**a**) (1).

The Environment and Public Health (ENVI) Committee of the European Parliament and the Council have upheld the *protection of trial subjects* by **restoring the role of national Ethics Committees** (a cornerstone of Directive 2001/20/EC) (*Article 4*), and by **making clear that Ethics Committees' opinions are binding** (**b**).

The ENVI Committee and the Council have nonetheless also accepted or adopted **other measures that undermine the protection of trial subjects**:

- they accepted the concept of "**tacit authorisation**" "*in order to ensure that timelines are adhered to*" by Member States (*Recital 8*);
- they **deleted** the Commission's proposal that "*each Member State should establish a **national indemnification mechanism**"* (**c**);
- they agreed that **clinical trials using investigational medicinal products "off-label"** (i.e. not in accordance with the terms of the marketing authorisation) could be **considered "low-intervention trials"** when off-label use is "*supported by published scientific evidence on safety and efficacy"* (*Article 2(3)*) (**d**).

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a- The original proposal included several measures **deregulating clinical research in human subjects**, thereby undermining the protection of trial participants. For more details, read our joint analysis ("New Proposal for a Regulation on Clinical Trials – Joint analysis" 5 February 2013: 12 pages) available at: http://english.prescrire.org/en/79/207/46302/2507/2506/SubReportDetails.aspx

b- "*A concerned Member State shall refuse to approve a clinical trial (...) where an ethics committee has issued a negative opinion*" (*Article 8(3a)).*

c- It was replaced by "*an arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk",* which could lead to the lowest common denominator becoming the standard for damage compensation among Member States (*Chapter XII*).

d- The risk is that manufacturers would be encouraged first to seek marketing authorisation for a narrow therapeutic indication, which would be granted based on evidence from small, short-term standard clinical trials, since the indication would apply to few patients. Then, it would be in manufacturers' interests to encourage off-label use, in order to gather scientific evidence on the safety and efficacy of that medicine when used in these off-label indications. Ultimately, such a provision would entitle the manufacturer to ask for an extension of the marketing authorisation based on the less stringent rules that apply to "low-intervention trials".

Unfortunately, the ENVI and the Council have also **failed**:

- to demand that **investigators (clinicians) — not the trials' sponsors — report all serious adverse reactions to health authorities, both "unexpected" and "expected"**, thus allowing sponsors to continue to withhold safety data;
- to require **comparative clinical trials** so that the new medicine would be compared with the reference ("gold standard") treatment, in order to ascertain its therapeutic advantage (**e**).

On the issue of ***clinical data transparency,*** the Commission had initially proposed that a **summary of the trial's results should be made publicly available within one year** following the trial's completion (alignment with existing US requirements) (*Article 34*).

The Environment and Public health (ENVI) Committee of the European Parliament and the Council have improved on this proposal, by adopting a number of **other major provisions**:

- A statement that **Clinical Study Reports (CSRs)**, which are comprehensive documents presenting clinical trial results in a detailed and structured manner, "*should not be considered commercially confidential once a marketing authorisation has been granted, the decision-making process on the application for a marketing authorisation has been completed, or an application for marketing authorisation has been withdrawn*" (*Recital 20a*). Moreover, when the trial has been conducted to support a marketing authorisation, CSRs will have to be made **publicly available within 30 days after the marketing authorisation decision or the application's withdrawal** (*Article 34*); and in the event of "*non-compliance with the provisions laid down in this Regulation"* on the "*information intended to be made publicly available to the EU database" or on "subject safety"*, Member States are required to apply **dissuasive penalties** (*Article 89a*) (**f**);
- A statement that ***"reasons for temporary halt and early termination"*** of a trial, as well as **regulatory documents about a trial's authorisation** should not be considered commercially confidential (*Recital 20a*);
- Clarification of the responsibilities of the **European Medicines Agency (EMA)** in terms of maintaining an **EU database** in which all information regarding clinical trials will be stored, part of which will be publicly accessible (*Article 78(3)*).

New Trade Secrets directive: focus on industrial interests creates cause for concern

Just when it seemed that the new Regulation on clinical trials would finally deliver greater transparency, on 28 November 2013, the European Commission published a new proposed directive on Trade Secrets, which gave significant cause for concern (2).

As a result of pressure from North American negotiators during the Transatlantic Trade and Investment Partnership (TTIP) talks, this proposed directive: includes a very broad definition of trade secrets; encourages litigation, particularly by preserving the confidentiality of trade secrets during and after legal proceedings; and establishes dissuasive sanctions. The trade association of the European pharmaceutical industry promptly celebrated the release of the proposed directive on trade secrets: "*Almost every aspect of the drug development process involves the generation and application of substantial amounts of technical information and know-how, including the (...) clinical trials phase*." (3).

In view of these developments, we call upon Members of the European Parliament to:

- **remain extremely vigilant during the forthcoming discussions on the proposed Trade Secrets directive,**
- **and demand that clinical data on pharmaceutical products and medical devices remain outside the scope of this directive.**

Association Internationale de la Mutualité (AIM)
Health Action International (HAI) Europe
International Society of Drug Bulletins (ISDB)
Medicines in Europe Forum (MiEF)
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e- According to the Declaration of Helsinki, this requirement is an ethical principle for medical research involving human subjects. It would moreover have been an important incentive to transform the current corporate-based research and development model into a new model that meets real public health needs.

f- In fact, according to several studies, CSRs are NEVER commercially confidential (refs 4,5). We therefore repeatedly advocated that they must be released no later than one year after the trial's completion.

References:

1- Council of the European Union "Consolidated text of the draft regulation on Clinical trials on medicinal products for human use as approved by the Permanent Representatives Committee (Part 1) on 20 December 2013" http://register.consilium.europa.eu/doc/srv?l=EN&t=PDF&gc=true&sc=false&f=ST%2017866%202013%20INIT: 152 pages.

2- European Commission (Directorate General Internal Market and Services) "Proposal for a Directive of the European Parliament and of the Council on the protection of undisclosed know-how and business information (trade secrets) against their unlawful acquisition, use and disclosure COM(2013) 813 final - 2013/0402 (COD)" Brussels, 28.11.2013: 26 pages.

3- The European Federation of Pharmaceutical Industries and Associations "EFPIA welcomes the Commission's Proposal on the protection of undisclosed know-how and business information ("Trade Secrets")" press release published on 28 November 2013. www.efpia.eu: 1 page.

4- Doshi P and Jefferson T "Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports" *BMJ Open* 2013; 3: e002496.

5- Wieseler B et al. (Institute for Quality and Efficiency in Health Care, Germany) "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.

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Endorsing organisations

AIM. The Association Internationale de la Mutualité (AIM) is a grouping of autonomous non-profit health insurance and social protection bodies operating on the principle of solidarity. 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.

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, founded in 1986, is a worldwide network of bulletins and journals on drugs and therapeutics that are financially and intellectually independent of the pharmaceutical industry. Currently ISDB has about 80 members representing 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 organisations representing the four key players on the health field, i.e. patient 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 to the importance of European medicines policy. Contact: pierrechirac@aol.com

NCC. The Nordic Cochrane Collaboration is part of the Cochrane Collaboration, 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: Peter Gøtzsche (pcg@cochrane.dk)

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

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