

Clinical Trials and Data Transparency – The Public Interest Case

A Briefing Paper

By Atholl Johnston, Meir Perez Pugatch &
David Taylor

September 2013



This briefing paper was commissioned by the trade associations of the research-based biopharmaceutical industry, PhRMA and EFPIA. The views represented here are those of the authors only.

An electronic version of the report is available at:

http://www.pugatch-consilium.com/reports/PC_Report_Clinical_Trials.pdf

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A Briefing Paper

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List of Abbreviations

CCI	Commercially Confidential Information
CTs	Clinical Trials
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
IP	Intellectual Property
MMR	Measles, Mumps and Rubella combined vaccine
PhRMA	Pharmaceutical Research and Manufacturers of America
R&D	Research and Development
RDP	Regulatory Data Protection



A Brief Summary of the European Medicines Agency Draft Policy on *Publication and access to clinical-trial data*

Objective: The public and scientific community obtain increased access to enhance knowledge about medical advancements and regulatory accountability without compromising personal privacy or long-term incentives for biopharmaceutical R&D.

Scope: Personal data and CCI receive special treatment; all other data submitted to the EMA following the introduction of the draft policy will be proactively published.

- **Protection of CCI:** All data containing CCI will not be published. Generally speaking CTs data is not considered to represent CCI. CCI mainly refers to CTs data which characterise or relate to the drug itself, but may also include data protected by intellectual property rights and/or linked to the legitimate economic interest of the owner.
- **Protection of personal data:** All data relating to an identifiable person will only be accessible on a controlled basis. It must first be adequately 'de-identified', after which it will only be made accessible to parties which agree to appropriate use as determined by the EMA.
- **Open access:** All other data will be available for download from the EMA's website.

Timeframe: Data will be made available at the time of publishing of the EPAR.

Regulation of secondary analyses: All analysis based on released data must be publicly accessible following a temporary period of protection. The EMA will not necessarily review secondary analyses.

First published on 24/6/13; the full draft policy is accessible using the following link: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500144730.pdf



Executive Summary

In this paper we were asked to review the draft policy issued recently by the EMA and entitled *Publication and access to clinical-trial data*.

The view taken by the EMA in this draft policy, and the view taken in this paper, is intended to optimise the benefits to public welfare resulting from the creation and publication of clinical trials data, with a particular focus on strengthening the efficient and safe use of existing health technologies and encouraging the development of new ones.¹

In the draft policy, the EMA takes the view that expanding publication and access to detailed clinical trials data will help to resolve scientific logjams or gaps in knowledge on a given medicine or condition, as well as enhancing cooperation in research areas that have been lacking attention.

The move towards greater transparency and coordination in the design and conduct of CTs is a worthy goal. The EMA's initiative represents part of wider efforts to optimise the increasingly complex and costly ecosystem in which R&D in the biopharmaceutical field is carried out. Enhancing the collection and use of clinical trials data will also benefit other siloes of the R&D process, ultimately to the benefit of the public's welfare.

The aspiration to achieve these goals is both merited and valuable. At the same time, it is important to note that at least two other components of the biopharmaceutical R&D environment – maintaining the privacy and confidentiality of patient data and protecting the intellectual property rights and trade secrets generated in the clinical trial phases – are also part of the puzzle. A balance between all of these pieces must be achieved.

Certain elements of the draft policy may be counterproductive in this respect. Specifically, the following problems can be identified in the EMA's proposed text and overall approach to the publication of and access to clinical trials data:

- **Need for a better understanding of the realities of the pharmaceutical market:** Primary CT data can reasonably be regarded as private property. Policymakers should therefore consider that the release by regulators of such

detailed information might distort competition in the pharmaceutical market and should also consider how this could affect biopharmaceutical innovation. Protection against abuse by third parties, at least to some extent, is possible. Remedies for the potential distortion of competition could include the introduction of checks on the competencies of the institutions/groups to which these data are released, coupled with supportive legal reforms. The latter might seek to ensure that bodies such as universities are financially liable for the costs attributable to the publication of reckless or deliberately misleading research findings by employees. In addition, remedies might also include ensuring that no uncompensated losses in intellectual property protection result from the release by regulators of previously confidential data.

- **Conflicting policies regarding regulatory data protection:** There is some contradiction between the draft policy and the underlying rationale and legal frameworks for the protection of clinical data via regulatory data protection. Greater clarity is required on the scope of protection of CTs data based on existing legal frameworks and actual practice, i.e. such that all sensitive clinical information is protected for the duration of exclusivity.
- **Possibility for gaps in protection of patient privacy:** The draft policy does not adequately ensure that the measures that would be put in place to protect against disclosure of personal data, including so-called de-identification of data, do not actually lead to a greater ability to re-identify patients. This should include proven and effective safeguards against re-identification technologies.
- **Further 'bureaucratisation' of an already bureaucratic system:** Policymakers should bear in mind the complexities and costs involved in establishing and operating a system for the early release of CTs data. They should consider whether it is possible to actually create an effective system

in which patient privacy is protected and where the expected benefits in public welfare outweigh the costs.

- **Inconsistency between the EMA's regulatory objectives and the wider macroeconomic objectives of the EU:** Finally, policymakers should take into account the overall strategic goals of growing the knowledge economy and the importance of high-tech industries such as the biopharmaceutical field to this growth. Measures which reduce incentives for further investment by private innovator companies in Europe, including the additional uncertainty and erosion of existing intellectual property protection and the subsequent distortion of competition, risk not only diminishing Europeans' access to advanced medical treatments but they also risk further weakening the industry's vital contribution to European economic growth and jobs.

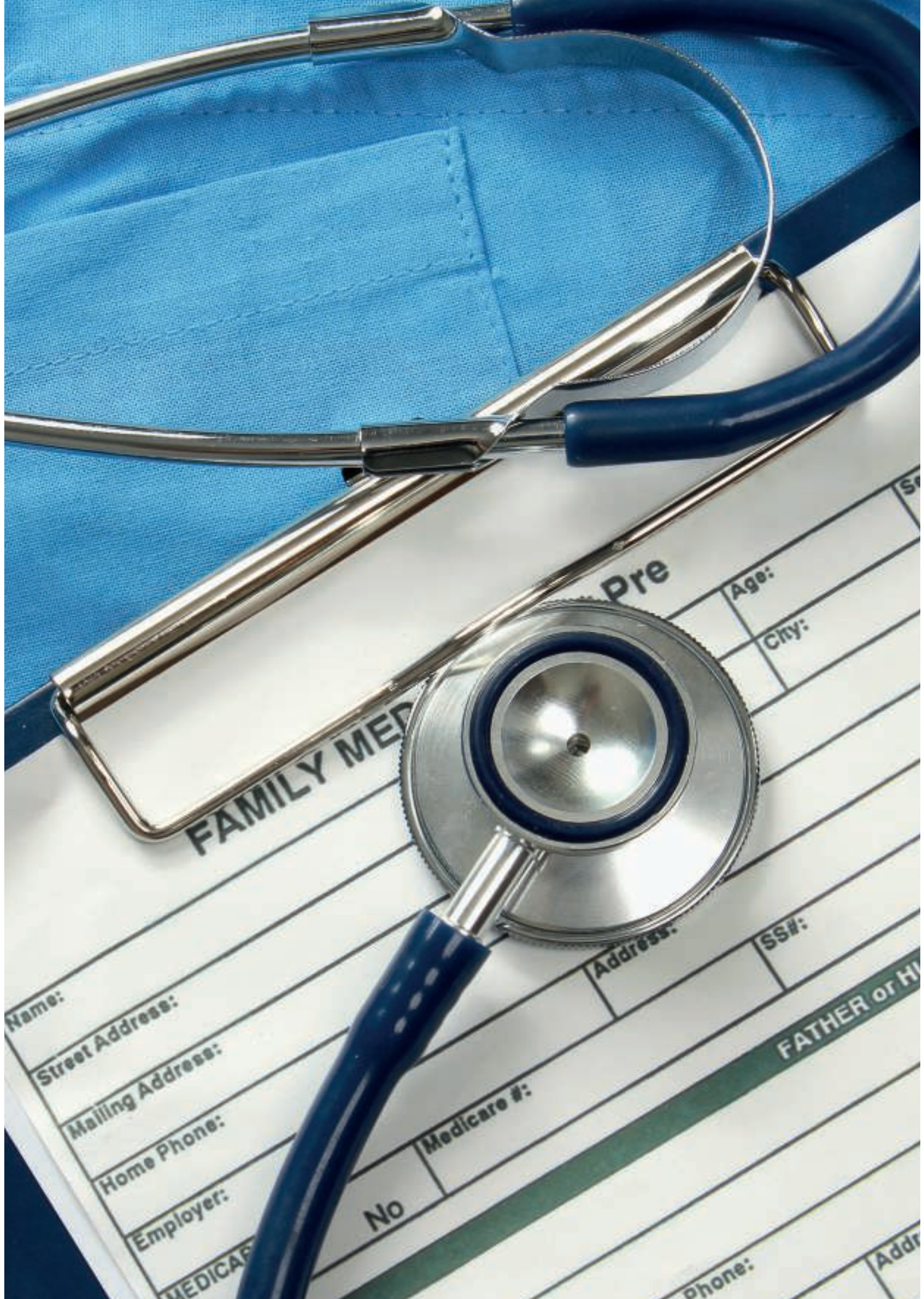
The release of large amounts of detailed clinical data proposed in the EMA's document *Publication and access to clinical-trial data* is not a direct or practical solution to these problems, or to the problems the Agency identifies in the current environment for clinical research in Europe. It may be one piece of the puzzle, but on its own the practical use of such data is limited; it is unlikely that it will provide insights or generate new research that will significantly affect public welfare. The considerable variation in methodology and presentation of data sets are just a few elements that would make them difficult to interpret and apply by the public. Furthermore, gaps in current knowledge are in some cases due to lack of research and not lack of transparency in publishing of clinical trials data; examples of this include the lack of coverage of women and infants/children for many disease areas.

The introduction of increased transparency also has opportunity costs. These costs are both financial and fiduciary. As indicated above, creating a database of large swathes of clinical data as well as a truly effective gatekeeping system will involve considerable costs (if it is actually possible), with

no guarantee that such an investment will generate the expected returns to public welfare. Moreover, strengthening public scrutiny of the EMA's decision-making to some extent calls into question the Agency's role as a health authority and erodes the public's trust in its ability to act in the interest of public welfare. Shouldn't European citizens be able to depend on the EMA to take into account all relevant clinical trials data in its decision-making, and when necessary demand more detail from companies, or instead should we rely on the public at large to act as judge?

These are all considerations that must be taken into account by both the EMA as well as involved stakeholders. The 'litmus test' for new policies on clinical trials and access to data in the EMA's possession should be the yielding of concrete and direct benefits to public welfare in the form of enhancing the use of existing medicines as well as the creation of new medicines. The draft policy should be assessed and reworked in order to meet these objectives.

The EMA draft policy should aim for a more pragmatic threshold of transparency than is currently suggested by the text. A greater emphasis should be placed on coordination of stakeholders and voluntary disclosure of data. This level of transparency should minimise additional red tape associated with the new policy and seek to better avoid breaches of patient privacy.



1

Introduction

Europe would like to be considered as a critical part of the global knowledge economy, as well as a home for innovation and for cutting-edge research. As stated in the original Lisbon Agenda for Growth² and in the subsequent Europe 2020 priorities,³ Europe's economy and jobs market rely heavily on the growth of its knowledge-based firms.

In October 2012, European Commission Vice President Antonio Tajani, Commissioner for Industry and Entrepreneurship, said:

We cannot continue to let our industry leave Europe. Our figures are crystal clear: European industry can deliver growth and can create employment. Today we tabled the conditions for the sustainable industry of the future in Europe, to develop the investments needed in new technologies and to rebuild a climate of confidence and entrepreneurship. By working together and restoring confidence, we can bring back industry to Europe.⁴

Within the pharmaceutical industry, which ranks as one of Europe's top-performing high-tech sectors, Europe's receptiveness to the conduct of CTs is a key indicator of its attempt to meet these strategic goals.

In an era of austerity measures and on-going criticism of the pharmaceutical industry, the challenges of conducting cutting-edge research in Europe are many and varied. The statistics bear this out. As noted in the European Commission's current proposal for reforming CTs regulations, the number of applications for CTs in the European Union fell by 25% from 2007 to 2011 – and the majority of this decrease is recent, from 2010 to 2011.⁵

According to recent calculations, based on data from the portal clinicaltrials.gov,⁶ Europe (on average) also has a low level of CTs activity compared to other developed countries, including the US and Singapore.

On top of these concerns, a great deal of change is now taking place in Europe in regards to how CTs are being conducted. The European Parliament is preparing to vote on new regulations that would replace the existing European Clinical Trials Directive.

The level of transparency, whether it is voluntary or compulsory, and the extent

to which such regulations might encroach on innovation are now critical topics of discussion and are likely to add to worries about the potential risk and price of doing research in the European Union. Research entities and companies which are directly affected by these obstacles are forced to question how much investment they are prepared to risk in new and future research, which may or may not pay off.

In addition to the economic debates about Europe's ability to innovate, the issue of data transparency also has a strong socio-political element. Following the publication of Ben Goldacre's book *Bad Pharma* and the establishment of the "All Trials" campaign,⁷ there has been considerable discussion as to whether or not the results of CTs funded by competing privately-owned pharmaceutical companies have been made adequately available to the public and to the biopharmaceutical/medical research community. Goldacre argues that they have not, and that as a result "medicine is broken".⁸

Quoting a range of examples including the withdrawal of medicines such as Vioxx and Avandia, he maintains that this alleged scandal needs to be corrected via the (in essence) mandatory registration and open publication of all clinical trial results (though with the caveat of due protection of individual patient confidentiality).⁹

Such external pressures have intersected with a growing interest by the EMA in enhancing the transparency of its services and the public release of information where it can promote the protection and fostering of public health.¹⁰ In this light, it is now consulting on a new policy for a more transparent, open and pro-active system to promote the public release of CTs data.¹¹ The envisioned benefits of this initiative include greater public and sectional stakeholder scrutiny of medicine licensing decisions, in part via the re-analysis by third parties of the primary data belonging to the companies seeking to market innovations.

In some sense, it is difficult to argue a case for confidentiality/secretcy in such a context. To the

extent that the latter slows the gathering of robust, aggregated information about the risks and benefits of alternative therapeutic approaches it is obviously undesirable. However, its costs may in some instances be counter-balanced by positive factors. On occasion, for example, guarantees of forms of secrecy encourage frank disclosures. In the area of air transport safety, confidence in the protection of information from general disclosure on the basis of rules established by the International Civil Aviation Organization has repeatedly led to multilateral sharing of critical information related to aviation safety.¹² In other cases, such as the development of new uses of old medicinal products which in current circumstances cannot effectively gain intellectual property (IP) protection, maintaining secrecy for limited periods of time could be the only way of sustaining investment.¹³

The following briefing paper was commissioned by the trade associations of the research-based biopharmaceutical industry, PhRMA and EFPIA, for the purpose of reviewing the recent draft policy issued by the EMA on transparency of clinical trials data. The views represented here are those of the authors only.

The paper attempts to set out the current state of play on public policy surrounding the transparency of CTs data in Europe, to assess whether or not the public interest case for increased data transparency is sound and, last but not least to raise some key issues that need consideration by policymakers.

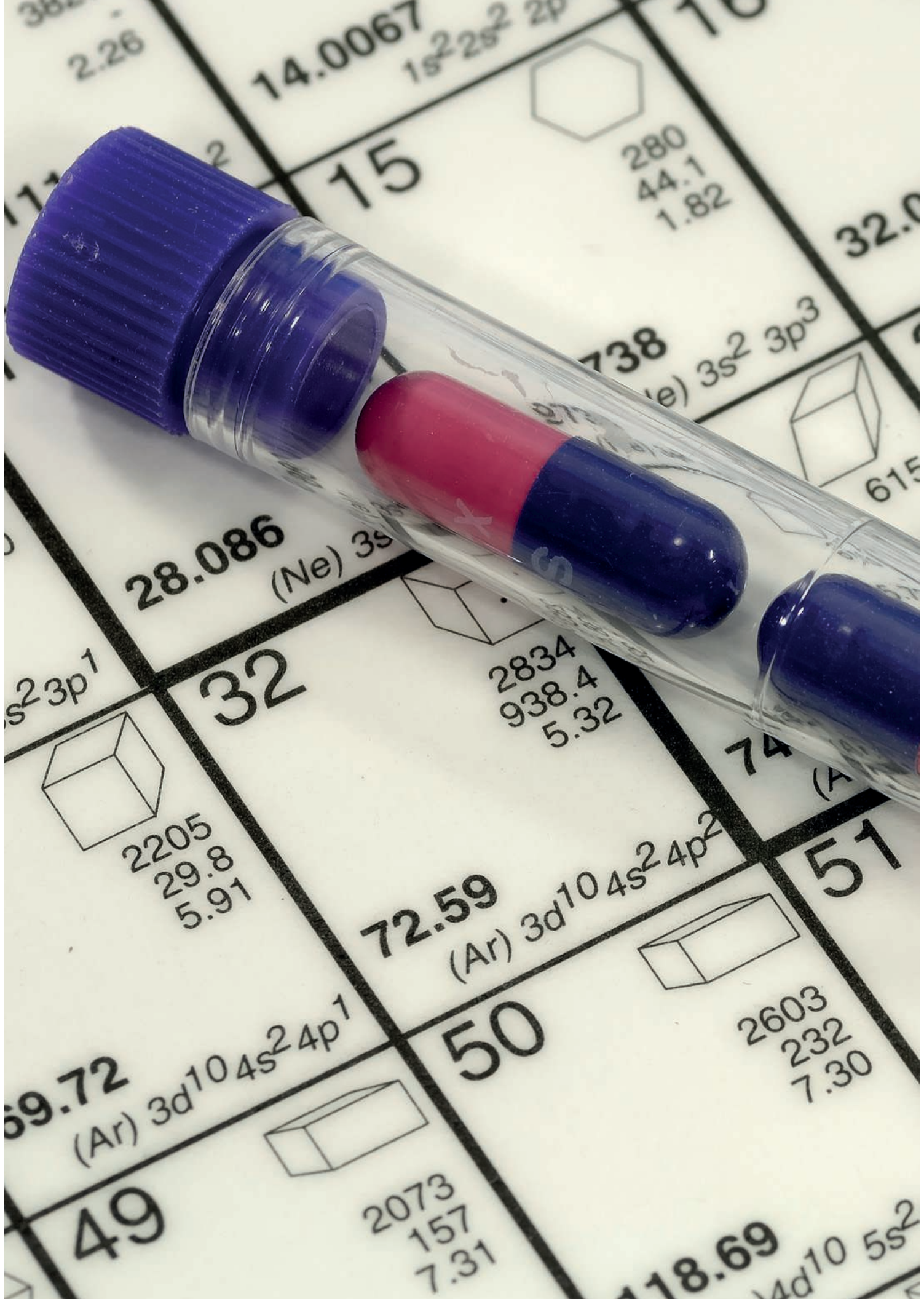
Specifically, the paper will be divided into three main parts.

The first part provides a background discussion on the role of CTs in the process of research and development of new drugs and the purpose and value of maintaining confidentiality of CTs data, as well as a brief overview of the EMA's draft regulation on public access to CTs data.

The second part considers key debates concerning whether increased transparency of CTs data is in the interest of the European public and if it will achieve

the stated objectives of protecting and fostering public health through the efficient and safe use of existing technologies as well as enabling the creation of new technologies, whilst avoiding detriment to patient privacy and biopharmaceutical innovation. The section raises specific points of discussion relating to how the draft policy corresponds with the current biopharmaceutical market and existing EU policies, as well as its potential for introducing more red tape in the R&D process.

The concluding part of the paper presents final thoughts and key recommendations for future action.



2

Clinical Trials and Data Transparency: The Current State of Play

Before discussing the key elements of the EMA's draft policy on access to clinical trials data, it is important to put them in context by briefly explaining the biopharmaceutical R&D process and the role of clinical trials and data protection in that process.

Testing a drug candidate, medical device, intervention or diagnostic tool in different groups of human volunteers is an integral part of developing new medicines or medical treatments. Naturally regulatory authorities will not approve use of a new medicine or treatment without extensive proof that it is safe and effective in humans.

2.1 The biopharmaceutical R&D process

The entire research and development process surrounding the creation of a new drug is a very involved and a financially risky process. Various sources cite different figures for the length and cost of drug development, ranging from 10 to 15 years and \$1.3 to \$1.8 billion.¹⁴ Significant resources are invested in basic research and drug discovery as well as the approval, manufacture and post-marketing monitoring of new drugs. The initial phases involve basic research on disease processes, the discovery of new compounds with potential for treatment, development of the most promising compounds and analysis of selected compounds in test tubes and animals, which takes roughly between 3 and 6 years.

Very few compounds actually make it past this stage to be tested in humans. At the other end of the pipeline, the process of market authorisation and manufacturing the drug to scale can take between 6 months to as much as 2 years, after which the drug must continue to be monitored and studied as it goes on to be used in earnest by the general public.

The testing of drug candidates in human volunteers via clinical trials,¹⁵ however, represents the largest and most risky investment in the R&D process. The clinical trial process represents an undertaking of 6-7 years per drug candidate.¹⁶ One study estimates that the clinical research phase now represents at least 65% of the total cost of the whole R&D process.¹⁷ The process includes complying with a wide range of regulations governing international best practices related to the quality, safety

Figure 1 – The biopharmaceutical R&D process

Research and discovery: Scientists attempt to isolate new chemical or biological entities using advanced screening and synthesising techniques.

Pre-clinical development: Initial safety tests and assessment studies, such as toxicology, are performed on animals.

Clinical development:

Phase 1: Initial phase tests a drug candidate in 20-100 healthy volunteers to assess how the body processes it and what side effects manifest themselves. A drug must show a minimum level of safety in order to move to the next phase of studies.

Phase 2: Examines a drug candidate's effectiveness in treating a targeted disease relative to other existing drugs or to a placebo. It explores whether the candidate acts against the disease and if it causes any adverse reactions in patients, and how this measures up to existing treatments. Studies involve 100 to 500 volunteers, all of whom experience the targeted disease or condition.

Phase 3: If the candidate is proven safe and effective in the first two phases, the study is shifted to a far larger scale, from 1,000 to 5,000 subjects. Studies test the safety and effectiveness of the drug candidate in different populations and conditions. This phase generates a large amount of data on the candidate in order to understand as clearly as possible the safety risks associated with the drug and to identify the right dosage and mode of use. Due to the scale of operations, Phase 3 studies are the most costly and time-consuming trials.

Registration: Results of pre-clinical and clinical studies and proof of meeting international standards are submitted to drug regulatory authorities for their review.

Phase 4: Biopharmaceutical companies must submit a plan for on-going monitoring and study of the drug as part of its approval for marketing. These studies are intended to safeguard larger scale use of the drug by monitoring any adverse effects that become evident as well as identifying what appears to be the most appropriate and effective manner of use. Post marketing studies typically provide the largest amount of evidence on a drug relative to data gathered in earlier phases.

and efficacy of drugs, for instance, Good Laboratory Practice guidelines on conducting toxicity studies, Good Manufacturing Practice and protecting the rights of patients through Good Clinical Practice.¹⁸ Despite the huge investment in this process, one recent analysis suggests that only 16% of candidate compounds which are tested in humans are likely to be approved by drug authorities.¹⁷

Figure 1 provides a basic overview of the biopharmaceutical R&D process, with a particular focus on the stages of clinical research.²⁰

2.2 Clinical trials and regulatory data protection

Considering the vast financial resources and extensive time needed to acquire and prepare CTs data for registration, these data can be viewed as proprietary 'know-how' belonging to biopharmaceutical companies. Due to their commercial significance, the data are formally protected by a type of intellectual property known as RDP.

RDP allows the data owner to prevent third parties, such as generic manufacturers or biosimilar companies, from accessing or using the data without his consent.

The legal and economic rationale for RDP is based on the concept of trade secrets.²¹ The protection of trade secrets essentially means that third parties are not legally permitted to use them without the consent of owners, but are allowed to produce the data on their own. The caveat for RDP as a form of trade secret is that the data produced by biopharmaceutical companies during the CTs phase of development must be submitted to national health regulatory authorities as part of the process of approving the drug for use. Ideally, the innovator would keep clinical test data within the company, but due to safety regulations, it is mandatory to release them to drug authorities, who have the responsibility of protecting them.

This responsibility has two conceptual and practical layers. The first – non-disclosure – is quite

straightforward. Non-disclosure aims to ensure that rival companies and generics developers do not gain financial advantage by accessing the registration file of the original product. The second layer – non-reliance – aims to prevent the authorities themselves from relying on the registration file of an original drug in order to compare it to the chemical and toxic levels of a potential generic substitute (bioequivalence tests).

The first layer is often provided by government non-disclosure laws at the central or institution level. In the EU, Regulation EC No1049/2001, in reference to all documents in possession by EU institutions, precludes disclosure of commercially sensitive information contained in such documents. Article 4(2) states:

The institutions shall refuse access to a document where disclosure would undermine the protection of:

- commercial interests of a natural or legal person, including intellectual property,
- court proceedings and legal advice,
- the purpose of inspections, investigations and audits,

unless there is an overriding public interest in disclosure.

In other words, under EU law data submitted as part of the marketing authorisation process which is of commercial interest or constitutes any type of intellectual property – including RDP – should not be released in the majority of cases (i.e. unless a strong public interest case for disclosure can be made). This includes disclosure to generic, biosimilar or innovator companies.

In terms of the second layer, the regulatory framework of RDP defines the number of years that will elapse before regulatory authorities may accept the submission of a generic drug product or biosimilar application or review and approve its use on the basis of the data that was submitted to these authorities by the sponsor of the reference drug. The US model currently provides a five-year period

of RDP to drugs with new active ingredients and a twelve-year period for biologics.²²

In the EU, the same level of protection is provided to drugs with new active ingredients and biologics, based on an '8+2+1' model.²³ Under this formula, eight years must pass after approval of a reference product before a generic or biosimilar application can be submitted and two additional years must pass before it may be approved for marketing by the authorities. An additional year of protection is afforded in cases where new indications for an existing product are approved within the first eight years of exclusivity.²⁴

The language on the term of protection for RDP is embedded in the rules for submission and authorisation of generic drugs and biosimilars. Specifically, Article 10 of Directive 2001/83/EC states:

*The applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community. A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product.*²⁵

In essence, under the EU's provision, the only clinical trial data a generic company needs to submit in its application for market authorisation are from the bioequivalence studies. In other words, a generic company is able to rely on the information generated by the innovator instead of producing its own clinical data. However, the 8+2+1 formula for RDP created by the EU does not allow generic companies to apply this pathway until eight years have passed since the initial authorisation of reference product.

Although the same formula may also apply to biosimilars,²⁶ unlike generic drugs the results of some pre-clinical and clinical tests are required for market authorisation. Article 10(4) states:

*Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products...the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided... The results of other tests and trials from the reference medicinal product's dossier shall not be provided.*²⁷

Why does CT data need to be protected? As discussed above, each new medicine has to undergo a complex and lengthy process of selection, testing and development in order to make it safe for human use and effective in terms of treatment. Although the data collected during this process must be submitted to regulatory authorities in order to prove safety and effectiveness, it nevertheless may contain strategic information on a product, including its fundamental structure, components and function, as well as the research protocol, analysis methods, etc. RDP acts as a guarantee against free-riding on the huge investment involved in collecting such data for a temporary period of time. As such, it provides innovator companies with an important incentive (or, to put it another way, removes a crucial disincentive) for investing in the clinical development and testing of new medicines or new uses of existing medicines. RDP will also act as the sole form of intellectual property protection for a molecule in particular cases, where the term of protection of the patent or patents associated with the molecule expire before the product is approved for marketing.

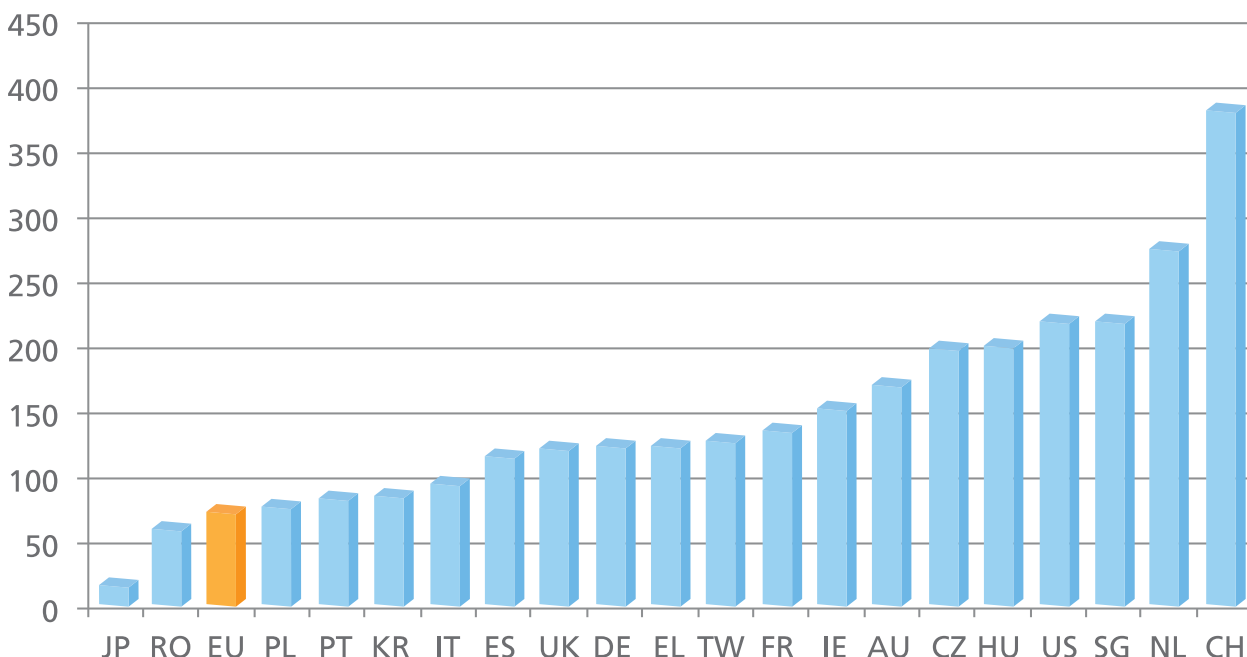
The wider reasoning for RDP speaks to the strategic importance of biopharmaceutical innovation to the economy and public welfare. Encouraging further innovation, including in the biopharmaceutical field, will no doubt yield significant macroeconomic and health dividends. Indeed, recent studies show that biopharmaceutical innovation, measured by the number of new drugs or drug classes launched per year relative to previous years, has led to concrete societal and financial benefits, including an increase in life expectancy and drop in hospital utilisation.²⁸

Table 1 – Calculating the number of CTs per million inhabitants

	Number of clinical trials, Aug 2013	Population (2012)	CTs per million population
Czech Republic	2,246	10,514,810	204
France	9,368	65,696,689	142
Germany	10,471	81,889,839	128
Greece	1,424	11,280,167	129
Hungary	2,050	9,943,755	205
Ireland	787	4,588,798	157
Italy	6,077	60,917,978	100
Netherlands	4,779	16,767,705	281
Poland	3,242	38,542,737	83
Portugal	956	10,526,703	87
Romania	1,395	21,326,905	66
Spain	5,534	46,217,961	120
United Kingdom	7,955	63,227,526	126
European Aggregate	40,746	517,785,815	79
United States	70,537	313,914,040	225
Japan	2,816	127,561,489	22
Australia	4,061	22,683,600	177
Singapore	1,124	5,312,400	225
South Korea	4,526	50,004,000	91
Switzerland	3,093	7,997,152	387
Taiwan	3,057	23,333,000	133

Source: clinicaltrials.gov (August 2013), World Bank (2012), Pugatch Consilium calculations; Taiwan's population is drawn from National Statistics Office, Republic of China

Figure 2 - Number of CTs per million inhabitants



Source: Pugatch Consilium calculations based on clinicaltrials.gov (August 2013) and World Bank (2012); Taiwan's population is drawn from National Statistics Office, Republic of China

2.3 Clinical trials in the 21st century

We now live in an age of advanced medicine, a globalised economy and national governments who increasingly focus on cost containment in order to finance the ever-growing demands on their healthcare systems. In such challenging times, the breadth and complexity of requirements for, and costs of, generating clinical data have soared. Regulations governing CTs have steadily become more detailed and demanding.²⁹ In addition, since global demand for medicines is constantly growing, it is imperative to gather data that matches the locations and populations in which a product will be marketed. In many countries, treatments may only be reimbursed by payers for small subsets of patients or based on very specific parameters for effectiveness.³⁰ Highly refined techniques for analysing specific disease and physiological processes, even to the generic and cellular levels, are needed to meet such requirements.³¹ The last decade has seen the total number of procedures

required per trial more than double, staff and infrastructure needs growing by over 60%, and the length of trials rising by a quarter.³²

The complexity of conducting CTs and generating the necessary data for regulators requires an ever-increasing level of investment by biopharmaceutical companies. This is true for biologics and biosimilars as well as for new chemical entities.³³

Across the board, the ability to safeguard proprietary elements of clinical data is all the more valuable and necessary for securing a return on investment. Eroding existing guarantees on secrecy of clinical data, such that competitors get a free-ride, is not likely to help encourage greater investment in biopharmaceutical R&D.

2.4 Current clinical trials activity – Spotlight on Europe

Clinical research arguably represents one of the most significant investments involved in the

biopharmaceutical R&D process. For both developed and developing countries, hosting CTs and making brand new medicines available can deliver major health, economic and social benefits.³⁴ Healthcare systems are able to provide their citizens with access to cutting-edge innovations and influence the development of medicines around the needs of the country's population.³⁵

The attractiveness of a given country as a site for CTs depends on a range of factors including: the characteristics of the population related to the specific product to be tested; the availability and willingness of the population to participate through the duration of the trial; the infrastructure of local hospitals and research centres; the ability of physicians and supporting medical staff to carry out CTs and work with international organisations; the ease of the regulatory system including approval of clinical trials; the stability of the legal system (including protection of intellectual property); and the costs of performing clinical trials.³⁶

In this context, CTs are conducted across the globe, but at this stage continue to be concentrated in the major developed countries. How do European countries measure up in relation to other leading countries in terms of the ability to attract clinical trials?

The most recent data suggests that the EU is losing ground as a competitive biopharmaceutical environment compared to other biopharmaceutical innovation hubs, for instance the US, Singapore and Australia. To illustrate, the average amount of clinical trial activity is subsiding relative to previous years.

Looking at the number of CTs registered on clinicaltrials.gov, a database of registered CTs taking place globally, Table 1 shows that Europe³⁷ on aggregate currently has a total of 40,746 CTs registered; the US 70,537; Australia 4,061; Singapore 1,124; South Korea 4,526; and Taiwan 3,057.³⁸

Broken down by population, Europe has roughly 79 trials per million inhabitants. As Figure 2 suggests,

this level is well behind the US and Singapore, which both have 225 CTs per million taking place; Australia and Taiwan are also considerably ahead of Europe.

Of the individual EU member states sampled here, Figure 2 shows that certain countries perform better than others. Switzerland and the Netherlands are among countries which rank ahead of the US and notably above the European aggregate. However, most European countries are significantly weaker than the US, including the Mediterranean countries Greece, Italy, Spain and Portugal as well as Northern European countries such as Germany and the UK.

A number of elements may be responsible for the declining performance in CTs of many EU member states. Among these, the lack of a centralised procedure for authorising CTs and the use of tough cost containment measures in the wake of the recent financial crisis and economic recession could both be contributing factors.³⁹

2.5 European efforts to enhance the public health benefits from biopharmaceutical R&D – Draft policy on greater transparency on CTs data

In light of its dwindling position as a biopharmaceutical hub, there has been extensive debate in Europe on streamlining the regulatory requirements for conducting CTs in the EU.⁴⁰

One key element of this debate has been whether or not to include stronger language in EU law with regards to disclosure of CTs data, such that clinical trial results would be more publicly accessible.⁴¹

The current draft regulations on CTs being considered by the European Parliament would not view data in clinical study reports as trade secrets once a marketing authorisation is granted to the product under investigation in the study. The draft regulations would also require the publishing of summary results of clinical studies by a deadline of one year following the completion of the study.⁴²

The EMA itself has discussed the concept of

disclosure of CTs data as well as many other types of data in its possession for several years. Since 2006, it has taken steps to identify which types of documents may be made available upon request, and which information, including personal data and what it terms CCI, will be safeguarded.⁴³ Beginning in 2010, the EMA (along with other EU and European bodies such as the Heads of Medicines Agencies) has taken the explicit initiative to open up access to CTs data upon request, once it has finalised the marketing authorisation for the drug concerning which the data has been submitted.⁴⁴ It continues to protect CCI and personal data from disclosure as part of this process.

Most recently, in light of the current efforts and pressure to increase transparency in clinical trials, the EMA's proposed policy on publication and access to CTs data reflect a shift towards an even fuller and more open approach.⁴⁵

The stated objective of the draft policy entitled *Publication and access to clinical-trial data*, issued in June 2013 is to increase access to data and scrutiny of decisions by the EMA without compromising personal privacy or long-term incentives for biopharmaceutical R&D.⁴⁶

In particular, the draft policy would open up much of the CTs data included in a study report to other scientists for review and analysis as part of follow-on research, although it is not clear at what stage this data would be available. It would appear that data will be made available at the time of the publishing of the EPAR, i.e. the market authorisation; but it is not clear whether this means that data will not be available to the public until the end of the clinical development programme.

The intended purpose of disclosing CTs data is to enhance knowledge about and access to medical advancements:

Access to CT data in an analysable format will benefit public health in future. It will make drug development more efficient by establishing a level playing field that allows all drug developers

*to learn from past successes and failures, and it will enable the wider scientific community to make use of detailed and high-quality CT data to develop new knowledge in the interest of public health.*⁴⁷

The EMA draft policy would also allow the public to access the data in order to enhance regulatory accountability and scrutinise decisions (although not at the expense of scientific and patient-centred rationale):

*The Agency also takes the view that a high degree of transparency will take regulatory decision-making one step closer to EU citizens and patients, and promote better-informed use of medicines.*⁴⁸

Notwithstanding these objectives, according to the draft policy any type of disclosure would also need to avoid jeopardising patient privacy or enabling usage of patient data not approved by the study subjects.

The EMA recognises that these are somewhat conflicting objectives, and that ultimately its approach to disclosure of CTs data must strike a balance that secures long-term public health benefits.⁴⁹

In the context of these objectives, the EMA takes a position similar to that of the proposed amendment to the draft EU regulations that overall CTs data should be treated in light of the public health benefits that may be exacted based on it, rather than its value related to commercial interests.

With regards to the protection of CCI, the draft policy states that:

*The Agency respects and will not divulge commercially confidential data or information. In general, however, CT data cannot be considered CCI; the interests of public health outweigh considerations of CCI.*⁵⁰

Yet at the same time, the proposed framework would seek to ensure future investment in biopharmaceutical research and development:

*A sustained and high level of bio-pharmaceutical research activity is a precondition for future improvements in public health. The policy has no intentions to negatively impact on the incentives to invest in future bio-pharmaceutical R&D; it is designed to guard against unintended consequences, e.g. breaches of intellectual property rights that might disincentivise future investment in R&D.*⁵¹

In this context, the draft policy aims to continue to safeguard protected know-how inasmuch as it is important for incentivising investment in biopharmaceutical R&D. Specifically, the document states that disclosure will not be allowed “where [it] may undermine the legitimate economic interest of the owner of the information”, including with regards to trade secrets and commercial confidences.⁵²

According to the draft policy, CCI would comprise very specific elements of the studies, mainly details about the product itself, i.e. bioanalytical characterisations, in vitro tests and other studies that do not involve patients.⁵³

Apart from data designated as commercially confidential, as long as a document does not contain personal patient information (i.e. it only covers aggregate data) it is acceptable to be ‘open access’. Individual data sets or related ‘raw’ data⁵⁴ will not be made available unless personal details are removed (or patients are “de-identified”) and only to registered parties who agree to specific terms related to appropriate use.

It is also worth mentioning that secondary or follow-on analyses would not necessarily be reviewed by the EMA:

The Agency cannot guarantee that all secondary data analyses that are enabled by the policy will be conducted and reported to the highest possible scientific standard; this is not possible with a truly open approach. However, the Agency will put in place measures to ensure the best-possible protection of public health (and

*regulatory decisions) against claims resulting from inappropriate analyses.*⁵⁵

Interestingly, the proposed framework would provide a kind of RDP to secondary analyses:

*[T]hose who conduct secondary analysis should also be allowed a reasonable period of time during which their analyses and deliberations are protected against external interventions.*⁵⁶

The EMA draft policy is currently open to public consultation, with the policy due to be finalised later in 2013.⁵⁷

The draft policy has raised several debates, on top of those already taking place around the “All Trials” campaign, including: how exactly to achieve transparency of CTs data without eroding the protection of trade secrets; the effect greater transparency could have on incentives for investment in biopharmaceutical R&D and in turn on public health outcomes; whether it is possible to de-identify patients from clinical data; and, if so, how to do it in a cost-effective manner and one which does not weaken public trust in the medicines regulatory system.



3

Public Interest and the EMA Draft Policy

When it comes specifically to the public interest case for increased data transparency, three questions should be considered in relation to the social and political environment in which the current debate has been conducted. These are:

1. Is there good reason to believe that greater transparency of CTs data is likely to generate major new health gains in Europe or elsewhere?
2. In pursuing the goal of greater transparency, what types of possible harm to the public's health might be anticipated and, as far as is possible, avoided?
3. Could stakeholders other than research-based and generic pharmaceutical companies have sectional interests in this field which could conflict with broadly defined European or global public interests?

These questions raise several important concerns about the EMA's suggested approach to increasing transparency of CTs data and the true impact the draft policy could have on public welfare. Such concerns include detrimental effects on the availability of existing medicines, patient privacy and incentives for investing in new and improved treatments due to premature competition. These elements will be discussed in detail one by one.

3.1 Contextualising key considerations about the public interest case

Before addressing these questions and the issues they raise it is worth emphasising that the main protagonists in this debate are not as far apart as is sometimes suggested. As, for instance, the recent *British Medical Journal* 'head to head' between John Castellani of the US trade association PhRMA and Ben Goldacre⁵⁸ highlighted, both accept the importance of industrial investment in CTs and ensuring that all information generated that is relevant to public health protection is rapidly disseminated. Likewise a recent joint statement by PhRMA and EFPIA (the European pharmaceutical industry trade association) has underlined the value of comprehensive positive and negative result sharing with good independent researchers and communicating findings to patients and the public.⁵⁹ Indeed, some major pharmaceutical companies, such as GSK, have already declared full support

for the open release of all CT trial data submitted to agencies such as the EMA.⁶⁰

As far as they exist, disputes are mainly related to the detail of how common welfare-linked goals are to be achieved, and the extent to which there is trust and good will between drug authorities and individuals involved in the relevant processes. However, there are genuine concerns that need to be understood for the present debate to be fully resolved.

One area which needs more clarity is that of distinguishing between the perceived 'absolute' safety of medicines (in reality all drugs are toxic if used inappropriately) and their relative safety. This last is a dynamic function of the costs and benefits of each therapy in very closely defined circumstances. Simplistic approaches tend to assume rigid 'on/off' divides between 'safe' and 'unsafe' and 'effective' and 'ineffective' treatments. That is, safety and efficacy are implicitly regarded as inherent physical properties of molecules, as distinct from being contextually defined characteristics of medicines. Errors of this type can lead to misleading analyses, which pool data in ways which either understate the potential value of treatments used in an optimal manner and/or can overstate it when they in reality are used sub-optimally.

3.2 Is there substantive evidence that greater CT transparency is likely to generate major health gains?

In the aftermath of the Thalidomide tragedy at the start of the 1960s and (in England) more recent events such as the murders committed by Dr Harold Shipman and the reported occurrence, due in large part to professional failings, of avoidable deaths in the Mid Staffordshire and other NHS Trusts, there has been increased emphasis on regulating the safety of both medicines and medical and other health care practices. There should be no question that whenever an active danger to health has been (or could be) identified relevant information should be rapidly evaluated and disseminated. It is

also possible that further emphasis on publishing CTs findings will help further improve regulatory decision making and generate fruitful new research hypotheses.

Nevertheless, the view taken in this paper is that compared with the health gains that could be generated by, for example, improving the treatment of childhood illness in poor communities and/or treating hypertension more effectively globally, the value of any such benefits gained from increasing public access to CTs data will at best be modest. Seen in this light, claims that existing regulatory processes for biopharmaceuticals (including review of pharmaceutical test data by regulatory health agencies as well as safeguarding of that data) which allow wide scale health gains to be achieved are inherently defective risk being exaggerations, albeit that any system can always be further improved.

Some observers may find this conclusion questionable. But against this the practical public health gains likely to be derived from, say, the now agreed publication of additional trial data appertaining to the anti-influenza drug Tamiflu (oseltamivir phosphate, which was purchased in bulk by various health administrations as a precautionary measure in case of the need to slow the spread of pandemic influenza with a high mortality rate) are hard to calculate. Openness may of course be taken to be inherently desirable. But any suggestion that neuraminidase inhibitors are inherently ineffective as anti-influenza virus agents would be difficult to reconcile with the evidence already available. Further, no clinical trial is likely to be able usefully to simulate a real lethal pandemic situation and the emergency actions that may be needed to prevent or delay disease transmission and create windows of opportunity for, for instance, effective vaccine manufacture.

Dismissing well-intended measures involving the stockpiling of effective antiviral drug supplies as no better than the equivalent of planning to give an individual 'a stiff whisky' in case of infection could be seen as ignorant. Likewise, many of the other examples raised in documents such as *Bad Pharma* appear to be of limited relevance to the question

posed above, and do not really address the type of public health benefits or the extent to which patients could be expected to benefit from greater transparency of CTs data in relation to the those derived from the actual use of drugs under existing data preservation practices.

For instance, in the case of past steroid over- and under-use in contexts such as emergency and antenatal care the core problem was arguably a general lack of methodological expertise across the medical and wider research communities, not a failure to publish trial results *per se*. With regard to medicines such as Vioxx (rofecoxib) and Avandia (rosiglitazone) there are also fundamental doubts as to whether or not it was in the public's interest for either of these potentially safe and effective treatments to have been withdrawn, as opposed to their usage indications being better defined. In the case of rosiglitazone the FDA has now reconsidered its position. But it is too late to recover either the patient welfare or the financial losses associated with the withdrawal of that anti-diabetic medicine.

3.3 Might pursuing greater CT transparency be harmful to the public's health?

Following on from the above, there is always a danger in areas like pharmaceutical and public health policy formation that attention-seeking or other unbalanced interventions in high profile areas will counter-productively draw attention away from more important issues. Any suggestion that 'medicine is broken' because of a bias in CTs data publication rather than, for instance, failures of the world-wide medical profession and other agencies to pay adequate attention to prevention and/or the optimally effective population level use of established low cost medicines is arguably one-sided.

The case put forward by the EMA for fuller transparency in CT-derived data publication demands respect, and as noted above has gained the support of some research-based as well as generic pharmaceutical companies. Yet rational

reasons exist for caution with regard to accepting without modification the Agency's proposed way forward.

Potential for abuse of data to the detriment of patients and companies

Abuse of data refers to the risk that deliberately selective or otherwise flawed data re-analyses will mislead media commentators, medicine users and/or political decision makers in ways that will cause not only commercial harm but also reductions in patient welfare.

Re-analyses by third parties have the potential to be publicly distributed without legal or regulatory checks on their integrity, especially in relation to what they may or may not say about initial studies. One such example is the media scare about the now-retracted claim of a link between the MMR vaccine and autism, which took place despite being published in a high impact, peer-reviewed medical journal.⁶¹ It is crucial to have an objective and robust review of evidence on a given pharmaceutical product. Such a measured approach tends to promote the safe use of medicines over the long term (relative to other, more reactive approaches) and also curbs undue backlash against products for which the benefits of use outweigh the risks. As such, the possibility that as a result of increased transparency clinical data will enter unqualified hands or be used/applied in a manner that is not empirically sound should be minimised.

The EMA recognises this potential but does not provide clear details as to how it plans to address the issue.⁶² What will these measures consist of, what is the budget to enforce them, and what are the penalties for violating them? Who will compensate the patients and/or commercial companies for the consequences of an inappropriate adverse secondary analysis? These currently remain open questions with no answers in the EMA documentation, and they leave industry in a position of uncertainty, which harms the potential for investment in R&D.

Potential for gaps in patient and individual privacy

There is a genuine risk that publication of detailed trial data could lead to the identification of patients and other individuals, compromising patient confidentiality and privacy.

It is paramount that the elements of CTs data which are released under controlled conditions do not include personal patient information. This is especially the case in areas such as the treatment of orphan diseases where there can be aggressive competition between clinicians and others with regard to patient recruitment in trials and/or treatment programmes. All 'sides' are clearly agreed that this should not be permitted to happen. But with the open publication of all trial data the exercise of adequate control could prove in practice harder to achieve than some commentators assume.

A fundamental obstacle to the disclosure of patient level data is that companies are contractually bound to safeguard patient-level data as part of informed consent provisions (see Box 1) agreed by all patients involved in clinical trials. The release of such data by the EMA may breach agreements between patients and companies.

There is also the question of practicality and cost of removing details which may identify individual patients. The EMA itself will have to conduct the appropriate de-identification of data. This task will involve distinguishing and separating individual data sets from the patients they involve. It is not clear how exactly this would take place, i.e. what mechanism or system would be used, or whether it is indeed feasible.

Potential for violation of RDP

The EMA draft policy makes several contradictory statements with regards to the protection of commercially confidential information that suggests the possibility of significant erosion of RDP in the EU.

Explicit contradictions in relation to EU law and in practical terms

As outlined earlier in the paper, the EMA's draft policy states that generally CT data cannot be categorised as such.

Comparing this approach with existing EU law, however, it appears to contradict the level of regulatory data protection provided under Article 10 of Directive 2001/83/EC. As explained above, all data from pre-clinical and CTs must not be used by EMA in the approval of generic or biosimilar medicines for 8-11 years following initial authorisation (depending on the type of use). In other words, the spirit of the law is that such data can be considered 'commercially confidential information'.

Viewing CTs data in this light also supports the idea that it is a form of trade secret (and hence an intellectual property right), such that its release would also appear to constitute a violation of the legal framework on disclosure of information (see Regulation EC No1049/2001 and the relevant discussion above).

It would seem that regarding elements of CTs reports as not commercially confidential – when they are in their totality protected under EU legislation for a period of ten years from not only disclosure to third parties but also reliance on for the purposes of generic approval – is in violation of existing EU law.

Putting this wider point aside for the moment, the EMA draft policy also seems to inaccurately define what data constitute 'commercially confidential information'. In attempting to parse which types of data should be protected, the draft policy does not encompass all commercially sensitive material.

Specifically, the draft policy would limit the protection of CTs data to 'product-specific' data, such as bioanalytical studies, under the assumption that only these data would reveal commercially sensitive information.

However, even if only so-called non-product related details of CTs are released to the public, other

elements inherent in this disclosure would by default unveil details relating to the product. For example, the very fact of disclosing that a trial is underway or personal data of investigators may constitute disclosing confidential information to a competitor. In addition it should be noted that publication of any trial results – whether good or bad – can have profound results on a company's share price or valuation.

The treatment of raw data is another example of details included in CTs data which are not directly linked to a given product but are in fact commercially sensitive and protected by intellectual property. In the EMA draft policy, raw data is included as data that would be made available (provided personal patient information is able to be removed) on a controlled basis, even though the definition of raw data includes elements which may in fact be protected assets, such as Statistical Analysis Software.⁶³

Potential for premature competition and further innovation decline

The EMA's draft policy does in fact recognise the commercial applicability of CTs data, contradicting the statement that it cannot be considered CCI.

Speaking of levelling the 'playing field' in the European pharmaceutical market⁶⁴ is a tacit acceptance of the fact that publishing the data will aid other drug developers, and hence competitors, who will benefit from the knowledge gained. If that is the case, then the information is – by its very nature – commercially sensitive and hence confidential information.

That the draft policy would provide for the protection of secondary analyses – in effect, granting competitors exclusivity – would also suggest that actually it views such analyses as constituting CCI.

Yet, the draft policy is paradoxical – innovators' exclusivity may be violated in order for third parties to access their data, but the secondary data generated is then provided with exclusivity.

Potential for premature competition and further innovation decline

Market competition will be unfairly distorted by the full publication of the structures and findings of CTs undertaken for regulatory purposes, and this is likely to have a negative impact on the development of new medicines in Europe.

The EMA's stated intention in the draft policy is to avoid hindering biopharmaceutical R&D.⁶⁵ Nevertheless, it is difficult to see how it will encourage biopharmaceutical companies to further invest in CTs in Europe.

The draft policy's treatment of innovators' CTs data as not commercially sensitive implies a very simplistic perception of the realities of how drugs are developed, commercialised and tested. It also ignores the fact that by overriding protection of commercially sensitive data, over the long-run public health and welfare is actually damaged due to reduced investment in new medicines and treatments.

Under the draft policy, companies' ability to conduct CTs could be exposed both to competition from other companies as well as to various legal obstacles (including lawsuits) that may stop them from moving forward in the clinical phases.

Imagine, for example, a start-up company wishing to sell a product, which is in Phase 2, to a multinational company. Based on the draft policy, the multinational company would have to check which confidential data has been disclosed or published and to what extent this may limit its ability to compete in the market against other companies dealing with the same drug.

Evidence thus far suggests that these concerns are not unfounded. There is an implicit assumption by the EMA and other groups that the interest in these data is academic. However, according to a recent study by Doshi and Jefferson, the large majority of requests for information to the EMA since it introduced greater access to its data in 2010 have come from pharmaceutical companies,

the media and legal parties (with industry requests representing almost double the amount from the media).⁶⁶ Of course, this might change if data were opened up more widely and public awareness grew but this appears to suggest that there is currently very little academic or public demand for such data.

No reasonable observer is likely to disagree with the view that public interests in safety and fundamental scientific progress should be put ahead of the financial concerns of individual companies. At the same time, however, the public has important economic and social interests in maintaining equitable and functional markets capable of facilitating on-going biomedical innovation. If EMA or other regulatory agencies' publication of investigations that have been privately funded by innovative companies serves to advantage 'me too' or 'similar' medicine manufacturers who do not invest in high-risk research this could, at least in the medium to long term, have a negative net impact on the health and wellbeing of the European public.

Potential for further bureaucratisation

Finally, it is important to consider the additional administrative demands that the draft policy would place on the EMA and stakeholders. Among other things, a process for reviewing requests to access CTs data would have to be established. Data would only be accessible after the EMA has set up a whole new mechanism to review requests with reference to various conditions and sub-conditions. Given the sensitivity and complexity of the data, such a review process would need to be quite nuanced and thorough, and therefore challenging to carry out.

At a time when public money is especially tight, it is worth noting that the resource implications for the EMA as well as for manufacturers, including investing in de-identification technologies, could be quite substantial and will add to the already significant bureaucracy and costs required for dealing with drug development.

3.4 Might stakeholders other than research-based or generic pharmaceutical companies have sectional interests in this area that can conflict with national or international public interests?

It is important not to lose sight of the general agreement that clinical trial findings should be exploited to optimum community effect. It could be the case that positive progress in sharing CTs data is being supported for sectional purposes. In theory, for example, proponents of 'clinical freedom' might want uncontrolled CT data publication as part of a strategic approach to defending doctors' 'rights' to be self-regulating, and able to challenge externally decided rules in areas such as prescribing or other aspects of healthcare provision.

It is also possible that regulatory agencies themselves could have developed sectional as opposed to public interest focused objectives. For example, bodies such as the EMA have on occasions been criticised for failing adequately to communicate with the public about the reasons for and implications of their decisions.⁶⁷

Mass 'data dumping' on the internet by regulatory agencies will never remove the need for high quality communication about issues relating to accessing and using innovative medicines. Yet it might be seen by some as likely to curb political pressures for enhanced regulatory agency performance in this field.

Box 1 – Informed consent and the importance of maintaining patient privacy

Informed consent is one of the most fundamental aspects in any clinical trial. It is aimed at ensuring that any patient who takes part in a clinical trial does so out of his or her own free will and with a full understanding of the process and objectives of that trial.

In the EU the process and concepts of informed consent are provided by Directive 2001/20/EC (Regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use).

Article 2a defines the informed consent as a:

[D]ecision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.

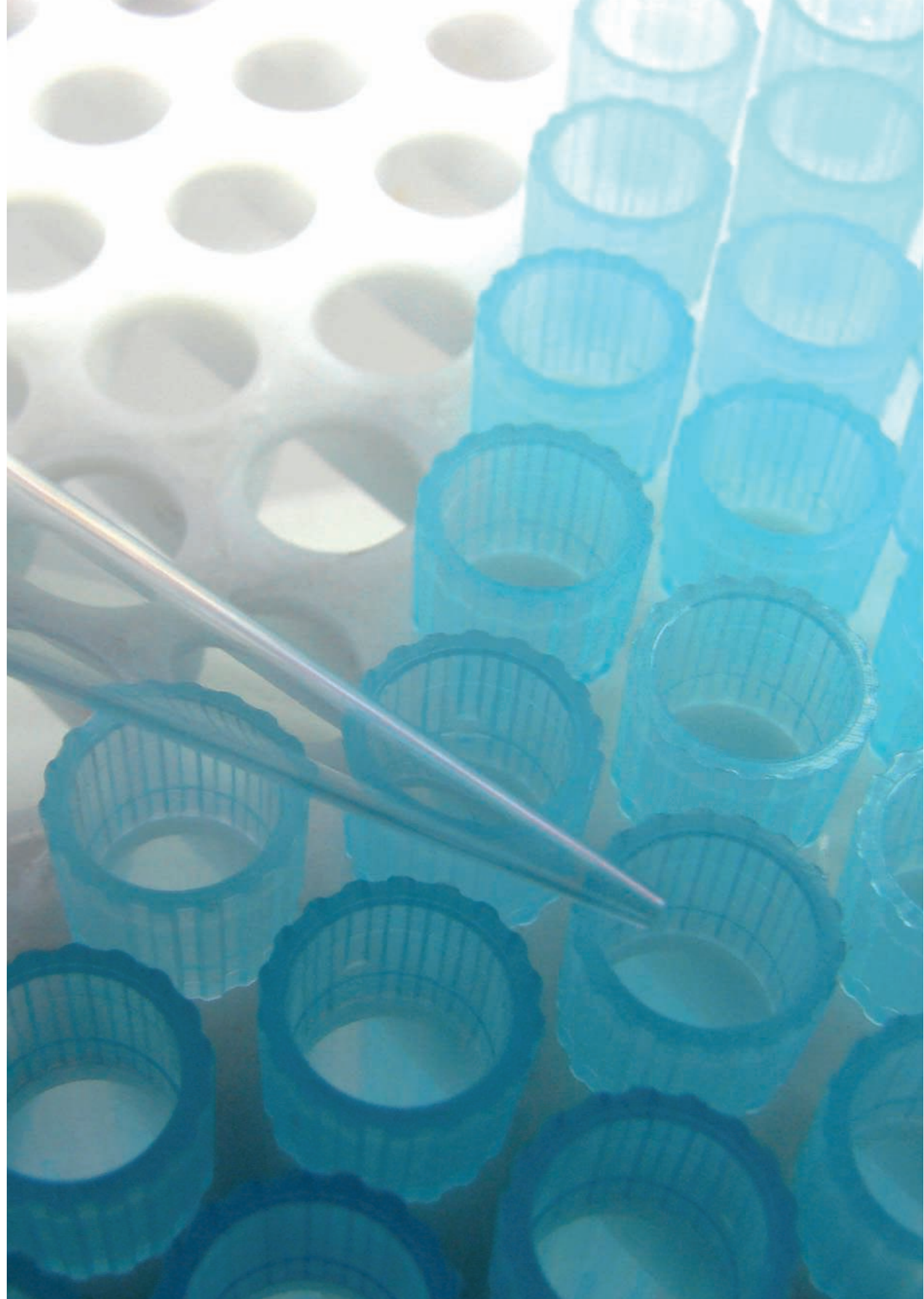
Article 2c also states that clinical trials may only be carried out on the condition that:

[T]he rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him in accordance with Directive 95/46/EC are safeguarded.

The WHO database of informed consent template forms also addresses this issue specifically by stating that it is vital to explain to the individual patient that by taking part in a clinical trial he or she can "be more easily identified by members of the community and is therefore more likely to be stigmatised".*

The WHO also recommends that researchers should emphasise the fact that they are taking all measures to protect patient's privacy and that all data collected from the clinical trial "will be kept confidential and that no-one but the researchers will be able to see it".*

* WHO, Research Ethics Review Committee Informed Consent Templates, Informed Consent Form Template for Clinical Studies, Accessed on 1 September 2013, http://www.who.int/rpc/research_ethics/informed_consent/en



4 Conclusion

4.1 Points of consideration regarding the EMA's draft policy

There is a need for a more in-depth debate in the EU about CTs and data transparency, in which the public interest case is considered in the round, including the potential upsides and downsides to various stakeholders of the EMA making additional CTs data publicly available.

The current initiative's aspiration is valuable. At the same time, while the principle of greater transparency garners widespread support, concerns remain about the impact of the public release of further CTs data on the safe use of existing medicines and on incentives for the development of new medicines.

A balance between all of the pieces of the puzzle – transparency, follow-on analysis, public safety, personal privacy and protection of intellectual property rights and trade secrets – must be achieved.

Certain elements of the draft policy may be counterproductive in this respect. Specifically, the following problems can be identified in the EMA's proposed text and overall approach to the publication and access to clinical trials data:

- **Need for a better understanding of the realities of the pharmaceutical market:** Primary CT data can reasonably be regarded as private property. Policymakers should therefore consider that the release by regulators of such detailed information might distort competition in the pharmaceutical market and should also consider how this could affect biopharmaceutical innovation. Protection against abuse by third parties, at least to some extent, is possible. Remedies for the potential distortion of competition could include the introduction of checks on the competencies of the institutions/groups to which these data are released, coupled with supportive legal reforms. The latter might seek to ensure that bodies such as universities are financially liable for the costs attributable to the publication of reckless or deliberately misleading research findings by employees. In addition, remedies might also include ensuring that no uncompensated losses in intellectual property protection result from the release by regulators of previously confidential data.

- **Conflicting policies regarding regulatory data protection:** There is some contradiction between the draft policy and the underlying rationale and legal frameworks for the protection of clinical data via regulatory data protection. Greater clarity is required on the scope of protection of CTs data based on existing legal frameworks and actual practice, i.e. such that all sensitive clinical information is protected for the duration of exclusivity.
- **Possibility for gaps in protection of patient privacy:** The draft policy does not adequately ensure that the measures that would be put in place to protect against disclosure of personal data, including so-called de-identification of data, do not actually lead to a greater ability to re-identify patients. This should include proven and effective safeguards against re-identification technologies.
- **Further ‘bureaucratisation’ of an already bureaucratic system:** Policymakers should bear in mind the complexities and costs involved in establishing and operating a system for the early release of CTs data. They should consider whether it is possible to actually create an effective system in which patient privacy is protected and where the expected benefits in public welfare outweigh the costs.
- **Inconsistency between the EMA’s regulatory objectives and the wider macroeconomic objectives of the EU:** Finally, policymakers should take into account the overall strategic goals of growing the knowledge economy and the importance of high-tech industries such as the biopharmaceutical field to this growth. Measures which reduce incentives for further investment by private innovator companies in Europe, including the additional uncertainty and erosion of existing intellectual property protection and the subsequent distortion of competition, risk not only diminishing Europeans’ access to advanced medical treatments but they also risk further weakening the industry’s vital contribution

to European economic growth and jobs.

The release of large amounts of detailed clinical data proposed in the EMA’s *Publication and access to clinical-trial data* is not a direct or practical solution to these problems, or to the problems it identifies in regards to the current environment for clinical research in Europe. It may be one piece of the puzzle, but on its own the practical use of such data is limited; it is unlikely that it will provide insights or generate new research that will significantly affect public welfare. The considerable variation in methodology and presentation of data sets are just a few elements that would make them difficult to interpret and apply by the public. Furthermore, gaps in current knowledge are in some cases due to lack of research and not lack of transparency in publishing of clinical trials data; examples of this include coverage of women and infants/children for many disease areas.

The introduction of increased transparency also has opportunity costs. These costs are both financial and fiduciary. As indicated above, creating a database of large swathes of clinical data as well as a truly effective gatekeeping system will involve considerable costs (if it is actually possible), with no guarantee that such an investment will generate the expected returns to public welfare. Moreover, strengthening public scrutiny of the EMA’s decision-making to some extent calls into question the Agency’s role as a health authority and erodes the public’s trust in its ability to act in the interest of public welfare. Shouldn’t European citizens be able to depend on the EMA to take into account all relevant clinical trials data in its decision-making, and when necessary demand more detail from drug companies, or instead should we rely on the public at large to act as judge?

These are all considerations that must be taken into account by both the EMA as well as involved stakeholders. The ‘litmus test’ for new policies on clinical trials and access to data in the EMA’s possession should be the yielding of concrete and direct benefits to public welfare in the form of

enhancing the use of existing medicines as well as the creation of new medicines. The draft policy should be assessed and reworked in order to meet these objectives.

4.2 The big picture – Focusing biopharmaceutical policy reforms where they are most needed

Without significant changes in the climate for innovative research in Europe including a revised approach to the release of CTs data, we can expect to see a continued decline in CTs being conducted here. This will be to the detriment of Europe's innovative economy and ultimately of its patients too.

Achieving the early and (as far as is consistent with rigorously defined public interests) full publication of the details and findings of all CTs submitted in evidence to bodies such as the EMA is, in principle, a desirable end. However, it should not be uncritically accepted that current arrangements are as seriously dysfunctional as is sometimes suggested, or that well intended efforts to further improve them cannot have significant and unwanted unintended consequences. A degree of caution in moving forward is therefore desirable.

In the final analysis, the continued development and rebalancing of the global pharmaceutical market will almost certainly require reforms in areas ranging from (differential and tiered) innovation pricing and the assurance of access to essential treatments in poor communities to the further raising of global IP standards and the on-going introduction of concepts such as conditional and adaptive licensing. To be fully appreciated, the present debate about CTs data transparency needs to be placed in this wider framework. In the shorter term the action needed to remove disputes and institute better practices should centre on establishing a comprehensive as opposed to siloed understanding of all relevant public interests (scientific and socio-economic) in CT data dissemination.

It will also in part depend on a mature acceptance that the research-based pharmaceutical industry and the structures that now exist in regions like Europe to help guide and support 'good pharma' are already amongst humanity's major assets. Like medicine and the other health professions, they will need carefully considered – if also intelligently critical – fostering if the health of the public is to continue to improve as the twenty-first century unfolds.

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- ⁶ Pugatch Consilium calculations based on data from clinicaltrials.gov; see Section 2 for a more in-depth discussion of the figures.
- ⁷ See: <http://www.alltrials.net/>
- ⁸ Goldacre, B. (2012), *Bad Pharma: How drug companies mislead doctors and harm patients*, London: Fourth Estate, p.ix
- ⁹ Ibid., pp.91-92, 126-127
- ¹⁰ See: EMA (2013), *Publication and access to clinical-trial data*, p.1. Also, see Section 2 for a more in-depth discussion on the EMA's efforts to increase transparency over the past decade.
- ¹¹ Ibid.
- ¹² International Civil Aviation Organization, "States and industry Agree to Share Critical Safety Information", September 2010, <http://www.icao.int/Newsroom/Pages/states-and-industry-agree-to-share-critical-safety-information.aspx>
- ¹³ In relation to this example it may be worth stressing that the fundamental principle on which all IP law is based is that secrecy is normally undesirable. Provisions such as patents, for example, serve public interests in that they demand publication of discoveries in return for periods of exclusive exploitation of their practical applications. They also serve to encourage future investment in the generation of further innovations.
- ¹⁴ Mestre-Ferrandiz, J., Sussex, J. & Towse, A. (2012), *The R&D Cost of a New Medicine*, Office of Health Economics, p.1
- ¹⁵ The World Health Organization defines clinical trials as: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes". See: WHO, "Health topics: Clinical trials", http://www.who.int/topics/clinical_trials/en/
- ¹⁶ Mestre-Ferrandiz et al (2012), p.24
- ¹⁷ DiMasi, J. and Grabowski, H. (2007), "The cost of biopharmaceutical R&D: Is biotech different?", *Managerial and Decision Economics* 28:472
- ¹⁸ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 'History and Future', <http://www.ich.org/cache/compo/276-254-1.html>
- ¹⁹ DiMasi, J., Feldman, L., Seckler, A. & Wilson, A. (2010), "Trends in risks associated with new drug development: Success rates for investigational drugs", *Clinical Pharmacology and Therapeutics*, Vol.87, No.3, pp.272-277
- ²⁰ US Food and Drug Administration (FDA), "The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective", <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm>
- ²¹ For a review of regulatory data protection, see: Pugatch, M. P. (2006), "Intellectual property and pharmaceutical data exclusivity in the context of innovation and market access", in: Vivas-Eugui, D., Tansey, G., & Roffe, P. (eds.), *Negotiating Health* (Earthscan & International Centre for Trade and Sustainable Development: Geneva); Pugatch, M.P. (2004), "Data Exclusivity in the Context of EU Enlargement", *IPR Bulletin*, No. 12, pp. 10–15.
- ²² 21 USC 355(c)(3)(E)(ii & iii); Section 7002(a), Patient Protection and Affordable Care Act, Public Law 111-148 (2010)
- ²³ The strengthening and harmonisation of the RDP regime in the EU to the 8+2+1 regime was surrounded by strong interest on the part of the European Commission in protecting RDP. As such, the Commission has viewed and continues to view RDP as part of efforts to strengthen the overall pharmaceutical R&D eco-system and attract investment in biopharmaceutical R&D in Europe, and in fact regarding RDP as complimentary with other measures aimed at improving information to patients. (See: European Commission (2003), *A Stronger European-based Pharmaceutical Industry for the Benefit of the Patient – A Call for Action*, Communication from the Commission to the Council, the European Parliament, the Economic and Social Committee and the Committee of the Regions) Moreover, in its dialogue with priority countries on the issue of intellectual property protection including in the pharmaceutical sector, DG Trade emphasises the need for adopting RDP provisions, referred to as "the protection of confidential test data". See, for example, meetings of the EU-China IP Working Group: DG Trade, "Intellectual property: Report of the First Meeting of the EU-China IP Working Group", European Commission, 2005, http://trade.ec.europa.eu/doclib/docs/2010/february/tradoc_145768.pdf
- ²⁴ Paragraph 8 of Directive 2004/27/EC
- ²⁵ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0034:0057:EN:PDF>
- ²⁶ The ten year timeframe/8+2 formula outlined in Article 10, Paragraph 1 of Directive 2001/83/EC appears to apply to biosimilar medicinal products identified in Paragraph 4, although the test requirements are higher for similar biological products than for generic medicinal products.
- ²⁷ See Annex I to Directive 2001/83/EC for further details on the type and quantity of supplementary data required.
- ²⁸ For instance: Lichtenberg, F. & Pettersson, B. (2013), "The impact of pharmaceutical innovation on longevity and medical expenditure in Sweden, 1997-2010: evidence from longitudinal disease-level data", *Economic of Innovation and New Technology*, forthcoming
- ²⁹ Paul, et al (2010) How to improve R&D productivity: The pharmaceutical industry's grand challenge. *Nature Reviews Drug Discovery*. 9(3), 203-214; Torstensson, D. & Pugatch, M. (2010), *Keeping Medicines Safe: A Study of the Regulations Guiding the Approval of Medicines in Emerging Markets*, Stockholm Network
- ³⁰ Sorenson, C. (2010), "Use of Comparative Effectiveness Research in Drug Coverage and Pricing Decisions: A Six-Country Comparison", *The Commonwealth Fund*, Issues in International Health, Pub.1420, Vol.91

³¹ See, for example, the EMA's draft policy on clinical requirements for biosimilars: EMA, *Concept paper on the revision of the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues*, 22 September 2011

³² Getz, K. Campo, R. & Kaitin, K. (2011), "Variability in Protocol Design Complexity by Phase and Therapeutic Area", *Drug Information Journal*, 45(4): 413–420

³³ Mestre-Ferrandiz, et al (2012); Paul, et al (2010); DiMasi, J. and Grabowski, H. (2007b), "The cost of biopharmaceutical R&D: Is biotech different?", *Managerial and Decision Economics*, Vol.28(4-5), 285-291

³⁴ Pugatch, M. & Chu, R. (2011), "The strength of pharmaceutical IPRs vis-à-vis foreign direct investment in clinical research: Preliminary findings", *Journal of Commercial Biotechnology*, Vol.17, pp.308-318

³⁵ Healy, P. (2011), *Which price is right? Regulating the cost of pharmaceuticals in Europe and North America*, Stockholm Network

³⁶ Bramley-Harker, E., Lewis, D., Farahnik, J. and Rozek, R. (2007), *Key Factors in Attracting Internationally Mobile Investments by the Research-Based Pharmaceutical Industry*, London: NERA Economic Consulting; Berndt, E., Cockburn, I. and Thiers, F. (2007), "The Globalization of Clinical Trials for New Medicines into Emerging Economies: Where are they Going and Why?" Paper presented at the UNU-MERIT Conference, Maastricht

³⁷ Europe here refers to the EU28 and associate/candidate countries: Albania, Bosnia and Herzegovina, Iceland, Macedonia, Montenegro, Norway and Switzerland.

³⁸ It is worth noting that the total number of CTs in Europe is not the sum of the number of trials taking place in each country, since in some cases the same trial is hosted by multiple countries.

³⁹ Carone, G., Schwierz, C. & Xavier, A. (2012), "Cost-containment policies in public pharmaceutical spending in the EU", *European Commission Economic Papers* 461, September 2012

⁴⁰ See *Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC* (2012), European Commission, 17/7/2012

⁴¹ Holmes, D. (2013), "Transparency battle resurfaces as EU trial revamp wraps up", *Nature Medicine*, 19, 797, http://www.nature.com/nm/journal/v19/n7/full/nm0713-797.html?WT.ec_id=NM-201307

⁴² See: Amendment 168, "Report on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC", European Parliament report, 10/6/2013, <http://www.europarl.europa.eu/sides/getDoc.do?type=REPORT&mode=XML&reference=A7-2013-208&language=EN>

⁴³ See, for example, EMA (2006), *Rules for the implementation of Regulation (EC) No 1049/2001 on access to EMEA documents*, EMEA/MB/203359/2006, Adopted 2006

⁴⁴ EMA (2010), *European Medicines Agency policy on access to documents (related to medicinal products for human and veterinary use)*, EMA/110196/2006, November 2010

⁴⁵ The draft policy, if introduced, would only apply to clinical data submitted to the EMA after the draft policy enters into effect (expected in 2014).

⁴⁶ EMA (2013), *Publication and access to clinical-trial data*, pp.1-2

⁴⁷ Ibid., p.1

⁴⁸ Ibid.

⁴⁹ Ibid., p.2

⁵⁰ Ibid. There has been some discussion and debate in the EU about what constitutes CCI. For example, in 2007 guidelines issued by the EMA, *Principles to be applied for the deletion of commercially confidential information for the disclosure of EMEA documents* (EMA/45422/2006). It is unclear exactly how these guidelines would apply within the new proposed framework on transparency of CTs data. See also: EMA/Heads of Medicines Agencies (HMA) (2010), *HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing authorisation application – Release of information after the granting of a marketing authorisation*, http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124536.pdf

⁵¹ EMA (2013), *Publication and access to clinical-trial data*, p.2

⁵² Ibid., p.3

⁵³ Ibid., pp.4, 10-11

⁵⁴ "Raw data" refers to data sets and case reports on individual patients, as well as supporting material such as Statistical Analysis Software programmes and records. (Ibid., p.4)

⁵⁵ Ibid. p.2

⁵⁶ Ibid.

⁵⁷ EMA website, "Publication and access to clinical-trial data: an inclusive development process", http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000556.jsp

⁵⁸ Castellani, J. (2013), "Are clinical trial data shared sufficiently today? Yes", *British Medical Journal*, Vol.347, f1881; Goldacre, B. (2013) "Are clinical trial data shared sufficiently today? No", *British Medical Journal*, Vol.347, f1880

⁵⁹ PhRMA, EFPIA (2013), *Principles for Responsible Clinical Trial Data Sharing*, <http://phrma.org/sites/default/files/pdf/PhRMAPrinciplesForResponsibleClinicalTrialDataSharing.pdf>

⁶⁰ GSK (2013), *Global Public Policy Issues: Public Disclosure of Clinical Research*, May 2013, <http://www.gsk.com/content/dam/gsk/globals/documents/pdf/GSK-on-disclosure-of-clinical-trial-information.pdf>

⁶¹ Deer, B. (2011), "How the case against the MMR vaccine was fixed", *British Medical Journal*, Vol.342, c1127

⁶² EMA (2013), *Publication and access to clinical-trial data*, p.2

⁶³ European Patent Office, "Patents for software?", <http://www.epo.org/news-issues/issues/computers/software.html>

⁶⁴ EMA (2013), *Publication and access to clinical-trial data*, p.1

⁶⁵ Ibid., p.2

⁶⁶ Doshi, P. & Jefferson, T. (2013), "The First 2 Years of the European Medicines Agency's Policy on Access to Documents: Secrets No Longer", *British Medical Journal*, Vol.173, No.5, pp.380-382

⁶⁷ Health Action International Europe, International Society of Drug Bulletins & Medicines for Europe Forum, "EU Parliament says no and no again to EMA: Independent groups echo decision", Press Release, 15/5/2012, <http://www.isdbweb.org/documents/uploads/press/EMA.pdf>



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