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The Distributional Effects of Transnational Pharmaceutical Regulation[a]

Ayelet Berman[b]

[a] This paper will be presented at the conference on ***The Distributional Effects of Transnational Regulation,*** Scuola Superiore della Pubblica Amministrazione, Rome, 20-21 May 2012.
[b] PhD candidate, International Law, Graduate Institute of International and Development Studies

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INSTITUT DE HAUTES ÉTUDES INTERNATIONALES ET DU DÉVELOPPEMENT
GRADUATE INSTITUTE OF INTERNATIONAL AND DEVELOPMENT STUDIES
CP 136 – CH-1211 GENÈVE 21
TÉL +41 22 908 57 00
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The Distributional Effects of Transnational Pharmaceutical Regulation

Ayelet Berman[1]

Draft Paper – To be presented at the "The Distributional Effects of Transnational Regulation" Conference, 21-22 May 2012, Rome

Abstract

The International Conference on Harmonization (ICH) brings together the drug regulatory authorities and pharmaceutical industry associations from the U.S., EU and Japan. The ICH harmonizes the rules for the registration of drugs between these countries, and has issued to this end guidelines which have been domestically implemented by its members but which have also become global standards adopted in (non-member) emerging and developing countries. Following a review of the pharmaceutical and economic literature, and based on Cafaggi's and Pistor's analytical framework of the distributional effects (wealth, power, regulatory) of transnational regulation, the paper analyzes the distributional effects of two of the ICH's most important standards: the Good Manufacturing Practice (GMP) and the Good Clinical Practice (GCP). As both standards significantly increase the cost attached to regulation, they have had distributional effects. First, they have been to the detriment of entities, companies and countries that lack sufficient resources, and have advantaged resourceful companies and countries. In practice, this means that they have benefited larger, privately held, export-oriented companies, and have been to the detriment of smaller, locally oriented, or governmentally funded companies/entities (even more so in developing countries) (i.e. wealth effects). Second, in certain contexts, they have promoted the commercial interests of the multinational pharmaceutical industry over the interests of patients in receiving much needed medicines or treatments (i.e. power effects). Third, the standards have generally improved the regulatory and scientific capacity of those companies and countries that have adopted them (i.e. regulatory capacity effects). It concludes that many of these distributional effects can be linked back to the governance structure of the ICH: While the members are the main beneficiaries, non-members have been subject to distributional effects that are to their detriment.

1. Introduction

The drug regulatory authorities and pharmaceutical industry associations of the European Union, United States and Japan came together in 1991 to set up a body

[1] PhD candidate, International Law Unit, Graduate Institute of International and Development Studies (Geneva), ayelet.berman@graduateinstitute.ch
http://graduateinstitute.ch/ctei/home/ctei_people/assistants/berman.html

that would harmonize the technical requirements for the registration of new drugs – the International Conference on Harmonization (ICH). The national regulatory requirements were creating barriers to market access, and with increasing international trade, there was a desire to remove or minimize such barriers. In the past two decades the ICH has been very productive and effective, and has become an important international body in setting pharmaceutical standards. Its harmonized guidelines have all been adopted by its members. Interestingly, with globalization and the shifts taking place in the global pharmaceutical market (such as increased production in emerging countries) many non-ICH countries have been following ICH standards too.

Cafaggi and Pistor set out a typology of distributional effects, and suggest three kinds of distributional effects: wealth, power and regulatory capabilities.

The purpose of this paper is to examine the distributional effects that ICH guidelines have created along these three kinds. To this end, the paper focuses on two of the ICH's most significant guidelines: the Good Manufacturing Practice, and the Good Clinical Practice. It also dedicates a separate section to the question of distributional effects on regulatory capability. What is interesting is that despite being of an unexciting, technical nature, these guidelines have had significant economical and social effects – which we shall address. For investigating such effects, the paper has reviewed the medical, pharmaceutical and economic literature for empirical work.

Particularly, the paper is interested in the distributional effects ICH standards create between *ICH members* (reflecting high income, developed countries and their pharmaceutical industries) and *ICH non-members* (reflecting developing or emerging countries and their pharmaceutical industries). As we shall see, there is a strong link between the membership structure of the ICH and the distributional effects it creates. From a wealth and power perspective, ICH guidelines have benefited ICH members, but have in some aspects been to the detriment of some of ICH's non-members. From a regulatory perspective, they have benefited all.

This result is interesting, as it raises another important question: to what extent do ICH members (or other club networks for that matter) need to be accountable towards those non-members that are negatively affected by their actions?

The paper is organized as follows: First, we provide a background of the ICH (section 2), and second, a short overview of the drug development process (section 3). Section 4 gives a short overview of ICH guidelines in general. We then move on to discuss the ICH GMP in greater detail. Section 5 provides an overview of the ICH GMP, and section 6 concerns its distributional effects. Here, we address two kinds of effects: its effects on local producers (6A), and its effect on access to medicines in developing countries (6B). Section 7 moves on to discuss the ICH GCP and provides an overview of the ICH GCP. Section 8 addresses the ICH GCP's distributional effects. First, in the context of non-commercial trials (8A), and then its effect on the development of drugs for

neglected diseases (8B). Section 9 concerns the effect of ICH guidelines on regulatory capability. Section 10 concludes.

2. Background on the ICH

The ICH was set up in 1991, and is a transnational public-private network composed of drug regulatory authorities and R&D pharmaceutical industry associations (i.e. industry dealing with the development of *new* drugs)[2] from the U.S., EU and Japan. At the time, the pharmaceuticals market had become increasingly international and the discrepancies in the technical requirements related to the registration of new drugs among these major trading partners (reflecting about 90% of the market) was hampering trade and delaying the introduction of new drugs.[3] The ICH's main purpose has, accordingly, been the harmonization of such technical requirements. To this end, it has issued guidelines, which are adopted domestically by its members. The guidelines, despite originating from a 'club', have become de facto global standards adopted by many non-member countries worldwide.[4]

The public parties are the U.S. Food and Drug Administration (FDA), the European Commission DG Health and Consumers, the European Medicines Agency (EMA), the Japanese Ministry of Health, Labor & Welfare (JMHLW) and the Japanese Pharmaceuticals and Medical Devices Agency (JPMDA). The private parties are the Pharmaceutical Research & Manufacturers Association of America (PhRMA), the European Federation of Pharmaceutical Industries' Associations (EFPIA) and the Japanese Pharmaceutical Manufacturers Association (JPMA). The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) runs the Secretariat. [5]

Certain "interested parties" (both public and private) or "observers" may attend too (without voting rights):

The ICH has invited "interested parties" to expert working groups (where it develops the guidelines) if these are of relevance to its work.[6] Interested Parties

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[2] The 'research-based' industry is in the business of researching and developing new pharmaceuticals. In contrast, the generics industry does not develop new drugs but copies drugs whose patents have expired.

[3] For a detailed history of the events leading up to the ICH, see A. Berman, 'The Public-Private Nature of Harmonization Networks,' presented at the Informal International Lawmaking (IN-LAW) workshop, 17-18 March 2011, Netherlands Institute for Advanced Study in the Humanities and Social Sciences (NIAS), Wassenaar, the Netherlands, available at http://graduateinstitute.ch/webdav/site/ctei/shared/CTEI/working_papers/CTEI-2011-06.pdf

[4] For a more detailed overview of the ICH, see A. Berman, "Informal International Law-Making in Medical Products Regulation" in J. Pauwelyn, R. Wessel, J. Wouters (eds.) *Informal International Law-Making: Case Studies* (TOAEP, 2012) (forthcoming); "Public-Private Harmonization Networks: The Case of the International Conference on Harmonization (ICH)" in S. Cassese et al. (eds.) *Global Administrative Law: Cases, Materials, Issues* (Institute for International Law and Justice: NYU School of Law, and Institute di Ricerche sulla Pubblica Amministrazione, 3rd edition, 2012) (forthcoming)

[5] See www.ich.org accessed 11 Oct. 2011. A. Berman, ' Informal International Law-Making in Medical Products Regulation' in J. Pauwelyn, R. Wessel, J. Wouters (eds.) *Informal International Law-Making: Concepts and Cases* (TOAEP, 2012) (forthcoming).

[6] e.g. Expert working group on 'Development and Manufacture of Drug Substances : Q11' (www.ich.org) . See ICH, 'Final Concept Paper Q11: Development and Manufacture of Drug

are those organizations that are expected to implement or to be regulated by the outcome of ICH efforts. These include the World Self-Medication Industry (WSMI) and the International Generic Pharmaceutics Alliance (IGPA). Originally, the purpose was for ICH guidelines to apply to the approval of new pharmaceuticals, but over time, some ICH guidelines (in particular those on quality) have been used to approve generic medicines. Consequently, the generic industry has an interest in the ICH process too. Other interested parties may also be determined by the Steering Committee over time. For example, the Over the Counter industry and pharmacopoeia authorities have also been invited to send representatives to some of the working groups.[7]

Regulators from developed countries such as Swissmedic (the Swiss drug regulator) on behalf of EFTA countries, and Health Canada (the Canadian drug regulator) have been "observers" since the ICH was first set up. The WHO is an observer too. Being a universal organization that encompasses both ICH members and non-ICH countries as its members, the WHO's role is to liaise between the conflicting interests of its members. ICH members are high-income countries, and interested in new pharmaceutical innovation, whereas non-ICH countries are emerging and developing countries, interested in affordable pharmaceuticals, that is, generic medicines.[8] The WHO's main role is, hence, to act as a link between ICH members and non–ICH members. It circulates ICH draft guidelines for comments to non-ICH countries, and disseminates the final guidelines too. The WHO also has a role in facilitating training efforts aimed at strengthening regulator capacity and harmonization activities of non-ICH countries. Despite the WHO's formal involvement, in practice there is no evidence that the interests of developing countries have been taken into account in the ICH process.

NGOs representing 'diffused interests'[9] such as of patients, are not participants at the transnational level (though they may comment on drafts through the domestic or transnational notice and comment procedures.[10])

Substances' (11 April 2008) http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Concep_Paper/Q11_Concept_Paper.pdf accessed 11 October 2011.

[7] "FAQS", available at http://www.ich.org/about/faqs.html, last accessed on 21 November 2011.

[8] While the WHO encourages harmonization, it has, as its priority, the global access to essential medicines of good quality. See Dr. Lembit Rägo, "Mechanism for Outreach beyond ICH Participants", The Sixth ICH, Osaka, Japan, 12-15 November, 2003, available at http://www.ich.org/LOB/media/MEDIA1383.pdf, last accessed on 21 November 2011.

[9] Richard B. Stewart, 'Accountability, Participation, and the Problem of Disregard in Global Regulatory Governance (Draft Paper)' (IILJ International Legal Theory Colloquium: Interpretation and Judgment in International Law, NYU Law School 2008) <http://www.iilj.org/courses/documents/2008Colloquium.Session4.Stewart.pdf>

[10] For an oversight of the participation possibilities in the ICH, especially at the domestic level, see A. Berman, "The Role of Domestic Administrative Law in the Accountability of IN-LAW: The Case of the ICH", in J. Pauwelyn, R. Wessel, J. Wouters (eds.) *Informal International Lawmaking* (Oxford: Oxford University Press, 2012) (forthcoming). A similar version is available as A. Berman, "The Role of Domestic Administrative Law in the Accountability of Transnational Regulatory Networks: The Case of the ICH", IILJ Emerging Scholars Paper 22 (2012), available at http://www.iilj.org/publications/documents/IILJEmergingScholarsPaper_Berman_FINAL.pdf

The ICH's main organs are the Steering Committee (SC) and the Expert Working Groups (EWGs) (where the guidelines are developed). Industry and regulators have an equal number of seats in both, and decisions are reached by way of consensus.[11]

Once adopted, the guidelines are implemented by the domestic regulatory authorities, usually as legally non-binding rules (typically termed guidelines or guidance documents, such as FDA "guidance document" or EMA "guidelines"), and in few cases as binding regulations.[12]

In the past two decades, with globalization, the pharmaceuticals market is in the process of undergoing a major shift. The development and manufacture of drugs has shifted from ICH countries to developing and emerging economies including Asia, Eastern Europe, Central/South America, Gulf countries and South Africa, with China and India becoming major players in this field. These developments have generated a growing interest of non-ICH countries in the ICH, and vice versa. The globalization of the pharmaceutical market has also had an effect on the institutional structure of the ICH, and is to some extent mirrored in the ICH's governance bodies. The ICH has set up two bodies to deal with these changing economic realities: the Global Cooperation Group (GCG) and the Regulators Forum. These bodies allow for greater communication with non-ICH countries, but do not provide them any decision rights. These bodies include Regional Harmonization Initiatives (RHIs) such as the Asia-Pacific Economic Cooperation (APEC), the Association of Southeast Asian Nations Pharmaceutical Product Working Group (ASEAN PPWG), [13] the Gulf Cooperation Countries 'Gulf Central Committee for Drug Registration' (GCC-DR), [14] the Pan American Network on Drug Regulatory Harmonization (PANDRH), [15] the South African Development Community (SADC),[16] and as of most recently the East African Community

[11] "Formal ICH Procedure", at http://www.ich.org/cache/compo/276-254-1.html.

[12] see A. Berman, "The Role of Domestic Administrative Law in the Accountability of IN-LAW: The Case of the ICH", in J. Pauwelyn, R. Wessel, J. Wouters (eds.) Informal International Lawmaking (Oxford: Oxford University Press, 2012) (forthcoming). A similar version is available as A. Berman, "The Role of Domestic Administrative Law in the Accountability of Transnational Regulatory Networks: The Case of the ICH", IILJ Emerging Scholars Paper 22 (2012), available at http://www.iilj.org/publications/documents/IILJEmergingScholarsPaper_Berman_FINAL.pdf

[13] See "Association of Southeast Asian Nations Pharmaceutical Product Working Group", available at http://www.ich.org/about/organisation-of-ich/coopgroup/asean.html. Last accessed on 21 November 2011. See also Dr. Mod. Zin Che Awang, "Regional Harmonization Initiatives –the Association of South-East Asian Nations", in *Proceedings, 10th ICDRA*, Hong Kong, available at http://whqlibdoc.who.int/hq/2003/a79903_(chp7).pdf. Last accessed on 21 November 2011.

[14] See "Gulf Central Committee for Drug Registration", at http://www.ich.org/about/organisation-of-ich/coopgroup/gcc.html, and Dr. Laila A. Rahman, "Centralized drug registration system in the Gulf Region", in *Proceedings 10th ICDRA*, Hong Kong, 2002, available at http://whqlibdoc.who.int/hq/2003/a79903_(chp7).pdf. Last accessed on 21 November 2011.

[15] "PANDRH", available at http://www.ich.org/about/organisation-of-ich/coopgroup/pandrh.html. Last accessed on 21 November 2011.

[16] "SADC", available at http://www.ich.org/about/organisation-of-ich/coopgroup/sadc.html. Last accessed on 21 November 2011.

(EAC).[17], as well as non-ICH Drug Regulatory Authorities (DRAs), which include emerging countries such as Brazil, China, India, and Russia.[18]

Finally, the pharmaceutical industry 's involvement in the ICH has led to criticism that the ICH is a commercially driven process that has difficulty maintaining a public health-oriented approach.[19] That said, the main argument in support of this joint structure has been that it provides regulators with direct access to expertise and the latest technological and scientific thinking.[20] Industry has much more resources, manpower and expertise on technical and trade issues than regulators, which are always short of resources. And so in keeping up with the newest developments and regulating effectively, regulators are dependent on industry.[21]

As we shall see below, the fact that the ICH is composed of regulators and industry from high-income, developed countries is reflected in the content of the guidelines. This, in turn, has had distributional effects that have not benefited with those that have not been at the drawing board but have nevertheless been subjected to ICH standards.

But before moving on to discuss these effects, let us first take a short look at the drug development process, and what role the ICH guidelines have in this process.

3. Drug Development Process

Medicines are not free to be sold but require an approval by the respective drug regulatory authority in order to be sold in any given jurisdiction. In general, under the law, an applicant must prove that the medicine is safe, demonstrates efficacy and is at good quality. The particular requirements that need to be demonstrated are set out in national regulatory instruments (regulation, guidelines etc.). Hence, regulatory requirements have a very significant impact on how drugs are developed.

In fact, any new drug development process must proceed through several stages in order to produce a product that can pass all regulatory requirements on the

[17] "EAC", available at http://www.ich.org/about/organisation-of-ich/coopgroup/apec0.html. Last accessed on 21 November 2011.

[18] For more information about these developments, see"Informal International Law-Making in the Drug and Medical Devices Field" in J. Pauwelyn, R. Wessel, J. Wouters (eds.) *Informal International Law-Making: Concepts and Cases* (TOAEP, 2012) (forthcoming)

[19] WHO, 'Report of a WHO Meeting: The Impact of Implementation of ICH Guidelines in Non-ICH Countries' (Geneva 13-15 September 2001) http://apps.who.int/medicinedocs/pdf/h2993e/h2993e.pdf. Last accessed on 21 November 2011. J. Abraham, and T. Reed, "Trading Risks for Markets: The International Harmonisation of Pharmaceuticals Regulation", in *Health, Risk & Society*, 2001, vol.3, 113-128.

[20] European Medicines Agency, 'Overview of Comments Received on Draft Guideline "Procedure for EU Guidelines and Related Documents within the Pharmaceutical Legislative Framework"' Doc. Ref. EMEA/125817/2004 (24 June 2005) available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004015.pdf , last accessed on 21 November 2011.

[21] Ayelet Berman, ' The Public Private Nature of Harmonization Networks' (Informal International Law Making Workshop, NIAS, the Hague, Netherlands 2011) <http://graduateinstitute.ch/webdav/site/ctei/shared/CTEI/working_papers/CTEI-2011-06.pdf>.

safety, efficacy and quality of the drug. It takes about 10-15 years to develop a new medicine from the time it is discovered to when it is available for treating patients. The average cost to research and develop each successful drug is estimated to be USD 800 million to USD 1 billion.[22]

The process is roughly divided into three main stages: discovery of the drug (which includes 'preclinical' trials), clinical trials, and regulatory review. [23]

The discovery process includes all early research to identify a new drug candidate and testing it in the lab. Once scientists have one or more optimized compound in hand, they turn their attention to testing them extensively to determine if they should move on to testing in humans. Scientists carry out in vitro and in vivo tests. In vitro tests are experiments conducted in the labs, and in vivo are studies in animals. At this stage scientists try to understand how the drug works and what its safety profile looks like. The process takes approximately 3 to 6 years. At the end of the discovery phase, scientists have candidate drugs to be studied in clinical trials. [24]

A candidate drug must go through extensive studies in humans, to prove that it is safe and effective, before a drug regulatory authority will approve it. This process involves a series of clinical trials, each with its own specific goals and requirements. Clinical trials are conducted in three stages. In phase 1, the testing is performed in a small group of healthy volunteers. In Phase 2, in as small group of patients. And finally, at phase 3, in a large group of patients. The clinical trial process is both expensive and time consuming and ends more often in failure than success. From start to end it takes an average of 6 to 7 years. [25]

Finally, once all three phases of the clinical trials are complete, the company files for marketing approval with a drug regulatory authority. The application includes all of the information form the previous years of work, and the regulators review it to determine whether it demonstrates that the medicine is safe and effective enough to be approved. This review process takes between 0.5 to 2 years.[26]

Once approved, the company manufacturers the medicine. The drugs must be manufactured in good/high quality, and in accordance with Good Manufacturing Practices (GMP).

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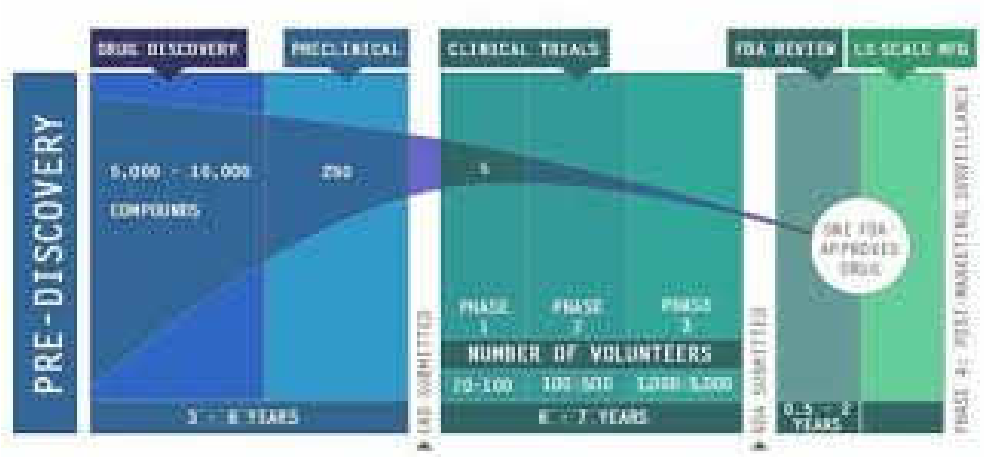
[22] PhRMA, 'Drug Discovery and Development : Understanding the R&D Process » http://www.phrma.org/sites/default/files/159/rd_brochure_022307.pdf (accessed 28 March 2012); (This number included the costs of the thousands of failures. For every 5000- 10000 compounds that enter the R&D pipeline, ultimately only one receives approval.)
[23] PhRMA, 'Drug Discovery and Development : Understanding the R&D Process » http://www.phrma.org/sites/default/files/159/rd_brochure_022307.pdf (accessed 28 March 2012)
[24] PhRMA, 'Drug Discovery and Development : Understanding the R&D Process » http://www.phrma.org/sites/default/files/159/rd_brochure_022307.pdf (accessed 28 March 2012)
[25] PhRMA, 'Drug Discovery and Development : Understanding the R&D Process » http://www.phrma.org/sites/default/files/159/rd_brochure_022307.pdf (accessed 28 March 2012)
[26] PhRMA, 'Drug Discovery and Development : Understanding the R&D Process » http://www.phrma.org/sites/default/files/159/rd_brochure_022307.pdf (accessed 28 March 2012)



Graphic: Drug Discovery and Development Stages (Source: PhRMA)

4. ICH Guidelines

The legislation of all ICH countries is more or less identical in its requirement that a company seeking to sell a new drug needs to prove that the drug is safe, effective and of good quality. The regulators differed however in the actual tests, or technical requirements that they demanded to prove each of these elements. These differences in technical requirements were hampering trade and so the purpose in setting up the ICH was to harmonize these technical requirements. So far about 50 guidelines have been issued. These guidelines have all been domestically implemented in the ICH regions, and many of its standards have become global standards adopted by a wide range of non-ICH countries.

The guidelines pertain to the different stages of drug development and manufacture described above: Safety topics relate to in vitro and in vivo pre-clinical studies (Carcinogenicity Testing, Genotoxicity Testing, etc.). Efficacy topics relate to clinical studies in human subject (Dose Response Studies, Good Clinical Practices, etc.).[27] Quality topics relate to chemical and pharmaceutical quality assurance (stability testing, impurity testing, Good Manufacturing Practice etc.). The ICH also issues guidelines relating to multidisciplinary topics, that is, topics that do not fit uniquely into one of the above categories (Medical Terminology (MedDRA), Electronic Standards for the Transfer of Regulatory Information (ESTRI), the Common Technical Document (CTD or eCTD), etc.).[28] Whereas the first three topics focus on scientific matters, the last topic concerns regulatory processes. The scientific level of the guidelines is high and reflects state of the art technology.[29]

To prevent any confusion, it should be noted that the ICH guidelines do not create a joint framework for assessing new medicines. This responsibility still

[27] "ICH guidelines", at http://www.ich.org/cache/compo/276-254-1.html.
[28] "Multidisciplinary Guidelines", at http://www.ich.org/cache/compo/276-254-1.html.
[29] WHO, 'Report of a WHO Meeting: The Impact of Implementation of ICH Guidelines in Non-ICH Countries'p.9.

remains in the hands of the regulators, as is evidenced when (even if rarely) they reach different decisions regarding the approval of the same drugs.[30]

This paper focuses on the distributional effects of two of the most significant and most globally adopted guidelines: the ICH Good Clinical Practice (GCP) (which, as its name suggests covers the clinical trials stage), and the ICH Good Manufacturing Practice (GMP) (which, as its name suggests, covers the manufacturing stage). We next provide a closer overview of these guidelines.

5. The ICH Good Manufacturing Practice (GMP): An Overview

The ICH Good Manufacturing Practice (GMP)[31] was issued by the ICH in November 2000 and consequently adopted in 2000/2001 in the ICH member regions as a guidance document/guideline.[32] The WHO GMP (first prepared in the 1990's), which serves as the basis for GMP rules in non-ICH countries, was adapted in line with the ICH GMP.[33] The ICH GMP, hence, applies in ICH countries, but has also become a global standard that is essentially applied in non-ICH countries too. While countries have their own GMP rules, these are normally based on the international WHO/ICH GMP standards.

The ICH GMP covers all aspects of quality assurance in the development, manufacture and control of pharmaceutical products. In practice, this means that it sets out the details regarding the manufacture of pharmaceuticals, such as concerning the temperature of store-rooms, record keeping, personnel, production facilities and equipment, documentation (for example, each step of the production process must be documented and validated), packaging storage and so forth.

The ICH GMP has significantly increased the costs and resources required for producing pharmaceutical products. GMP requirements demand major investments in upgrading manufacturing facilities and processes, as well as maintaining their level.[34] As we shall see below, the costs involved in meeting with GMP standards have had significant distributional effects.

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[30] ,Such as in the case of Avandia, an antidiabetic drug which EMA suspended from use, but is still approved by the FDA.

[31] ICH Harmonised Tripartite Guideline, Good Manufacturing Practice for Active Pharmaceutical Ingredients, Q7, 10 November 2000, (avaialble at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf)

[32] http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html

[33] In fact, from 1969 onward, WHO recommendations for improvements in quality control became progressively inseparable from FDA recommendations on « good manufacturing practice ». The WHO's GMP slowly moved towards an American GMP standards. See Daniel Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* Princeton University Press, Princeton and Oxford 2010) 714-715.

[34] Julie Milstein and Brenda Candries, 'Economics of Vaccine Development and Implementation: Changes Over the Past 20 Years' (The Jordan Report: 20th anniversary, Accelerated Development of Vaccines 2002 73, 74. (Referring to GMP in the context of vaccine development.)

6. The ICH GMP: Distributional Effects

Cafaggi and Pistor do not precisely define the notion of "distributional wealth effects", but it is clear that they are concerned with the question how transnational regulation has affected the distribution of wealth among certain individuals, entities or countries. This section, accordingly, focuses on the question of how the ICH GMP has affected the distribution of wealth among different actors in the pharmaceutical market. Its focus is on the effects it has had in the distributional relations between *developed (i.e. ICH)* countries/entities and *developing/emerging* (i.e. non-ICH) countries/entities. To understand the effects of the ICH GMP it investigates the medical and pharmaceutical literature and the empirical studies conducted there that are relevant to answering this question.

A. Squeeze out of local drug manufacturers

a. The Problem

When we talk about GMP, we are actually talking about the manufacturing stage of drugs, and not the earlier, development stage of drugs. Talking about manufacture of drugs in developing countries, we can roughly distinguish between two kinds of manufacturers: First, manufacturers that are part of the supply chain of innovative (or generic) medicines of western/multinational companies. That is, manufacturers that essentially export their product. With the globalization of production, there has indeed been a major shift in the supply chain from ICH countries to emerging countries. India and China, for example, are currently the biggest producers of active pharmaceutical ingredients (APIs).[35]Second, manufacturers that manufacture drugs for local needs. Developing countries lack the capacities to develop new, innovative drugs, and so when talking about manufacturers producing for local needs, we are actually talking about manufacturers of generic medicines.

Over a decade ago the WHO raised the concern that local manufacturers of generic drugs in developing countries would be squeezed out of the market following the introduction of the ICH GMP. In this context it should first be clarified that the ICH was set up to harmonize the regulatory requirements for the market approval of *new* drugs, yet in practice, quality-related guidelines such as the ICH GMP are being applied universally to all pharmaceutical manufacturers, including for the registration of generic drugs.[36]

[35] Interview with Dr. Lembit Raego, WHO Department of Medicines Policy and Standards, WHO observer to the ICH., 27 May 2010 (Geneva).

[36] Two examples : (1) ICH Q3A (« Impurities in New Drug Substances ») and Q3C (« Impurities : guidelines for the residual solvents ») were developed for new products but their application has been extended by European authorities to cover all products, including generics, registered in the EU; (2) ICH Q7A on GMP for APIs expands requirements for manufacturers of pharmaceutical active starting materials, and so creates increased rigidity in the starting material supply system, with consequent effects on starting material prices and availability. See WHO, 'Report of a WHO Meeting: The Impact of Implementation of ICH Guidelines in Non-ICH Countries' (para. 6.2.). Further, within the EU, GMP certification is a requirement for all manufacturers and demands compliance by all manufacturers. In contrast, safety and efficacy guidelines apply to the innovative industry only.

The problem, so the argument goes, is that the ICH GMP (and other quality guidelines), being a product of ICH countries, reflects standards of 'western', high-income countries that are technology driven. These standards raise manufacturing costs. The guidelines are, hence, too costly for local producers in developing countries to meet. Developing countries do not have the same regulatory capacity and resources to implement the highest technical level of drug regulation and quality control for new drugs. [37] These requirements, consequently, raise the regulatory hurdle for the domestic pharmaceutical industry, create a barrier to market entry and potentially squeeze them out of the market.[38] As local producers in developing country normally manufacture generic drugs, this would mean that domestic generic manufacturers would go (at least partly) out of business.

Tim Reed, has also argued that small, local manufacturers that are manufacturing for local needs can't attain GMP standards. [39] Similarly, in the context of vaccine production, Milstein and others have argued that the ICH/WHO GMP is a standard that is out of reach for vaccine producers in developing countries, with adverse implications for the local development of vaccines.[40]

While no one contends that the good quality of medical products is not important, it is commonly said that the ICH quality standards are unnecessarily high for the approval of generic medicines, and that they are, hence, creating a barrier for the generic medicines industry.

There is empirical evidence in the medical and economic literature that these effects have indeed played out:

Tim Reed conducted fieldwork in Romania and demonstrated that the introduction of ICH GMP (applying to Romania through the EU GMP which in 2004 incorporated the ICH GMP) has forced local Romanian producers to close down. He demonstrates how, in order to comply with GMP requirements, [41] manufacturers were required to reconstruct their facilities, educate their staff, and invest in new devices and equipment.[42] Not having sufficient resources to

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[37] Dr. Lembit Raego, « Panel 2 : ICH and Global Cooperation in THT New Millenium, WHO Perspective », Proceedings, 5th ICH Conference, 2000,p. 303. See also Petra Brhlikova et al., 'Good Manufacturing Practice in the Pharmaceutical Industry' (Tracing Pharmaceuticals in South Asia The Centre for International Public Health Policy, University of Edingurgh 2007) <http://www.sociology.ed.ac.uk/__data/assets/pdf_file/0011/38828/GMPinPharmaIndustry.pdf>p. 30.
[38] Tim Reed, 198.
[39] Tim Reed, p. 214, 215. Comparing between the impact of ICH/EU GMP in Hungary and Czech republic (export oriented pharmaceutical industry) and Romania (locally focused pharmaceutical industry).
[40] Julie Milstein et al., 'Reaching international GMP standards for vaccine production: challenges for developing countries' (2009) 8 Expert Review of Vaccines 559,
[41] In seeking EU membership, full membership of CEE countries was conditional upon the candidate countries' adoption of the 'Acquis Communitaire'. This meant adoption of all EU law, including pharmaceutical law, in its entirety by CEE Accession States. The position of the EC was that the pharmaceutical regulatory policy and practice of CEE Accession States and the EU are to be aligned was a pre-condition for EU enlargement. See Tim Reed, p 159-160
[42] Tim Reed, p.213.

invest in the technology required to meet the requirements, the ICH/EU GMP excluded small, local Central and Eastern European manufacturers from the EU single market in pharmaceuticals.[43] The WHO has also noted the decrease in the number of Romanian domestic pharmaceutical producers.[44]

In India, under pressure from the WHO, public-sector domestic manufacturers of vaccines were closed down due to non-compliance with the WHO GMP[45] (which reflects the ICH GMP as the WHO GMP has been revised and brought into line with the ICH GMP).[46] These Indian companies had been operating for decades. In the pre-globalization era, that is pre-1990, India's pharmaceutical companies remained well below international standards.[47] In 2004 and then in 2007 WHO GMP standards, following the ICH GMP, became more stringent. Consequently, the Indian institutions started to fail complying with them.[48] Much of it had to do with documentation deficiencies. [49] Being government-funded and lacking sufficient funds, they could not meet the GMP standards.[50] It was expected that the Indian private sector WHO certified GMP companies would supply the outstanding vaccines until a new publicly funded plant would be built.[51]

Milstein et al. say that until the mid 1980's vaccine developers were for the most part public sector manufacturers, and GMP was far from an industry wide concept.[52] Now, however, the enforcement of the GMP has caused the disappearance of most public sector manufacturers (in both industrialized and developing countries) of vaccines.[53]

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[43] P.203, 204, 205. Tim Reed, PhD Thesis : The Regulation of Medicines in Central and Eastern Europe, University of Sussex, November 2002 (on hold with me).
[44] See WHO/Regional Office for Europe, Country Profile Romania (2008), available at http://www.euro.who.int/en/what-we-do/health-topics/Health-systems/medicines/country-work2/a-selection-of-country-profiles/romania-2008. According to the APMR, the share of local production has been decreasing, starting in the early 1990s. See also Tim Reed, p.220.
[45] J. Milstein et al., 'Reaching international GMP standards for vaccine production: challenges for developing countries' p.6.
[46] 'WHO Expert Committee on Specifications for Pharmaceutical Preparations' p. 30; http://www.ich.org/fileadmin/Public_Web_Site/Training/GCG_-_Endorsed_Training_Events/APEC_LSIF_JCCT_workshop_Beijing__China_Dec_08/Day_1/Regulatory_perspective_Canada.pdf
[47] Amit S. Ray and Saradindu Bhaduri, 'The Political Economy of Drug Quality: Changing Perceptions and Implications for Indian Pharmaceutical Industry' (2003) 38 Economic and Political Weekly 2303, 2305.
[48] Vaccine worries – R. Ramachandran, 3 April 2008, http://www.pragoti.in/node/710

[49] Vaccine worries – R. Ramachandran, 3 April 2008, http://www.pragoti.in/node/710

[50] Vaccine worries – R. Ramachandran, 3 April 2008, http://www.pragoti.in/node/710

[51] Vaccine worries – R. Ramachandran, 3 April 2008, http://www.pragoti.in/node/710

[52] J. Milstein and B. Candries, 'Economics of Vaccine Development and Implementation: Changes Over the Past 20 Years' 73.
[53] J. Milstein et al., 'Reaching international GMP standards for vaccine production: challenges for developing countries' p.6.

In China too, all pharmaceutical manufacturers were required to become GMP certified by late 2004 or face closure. This GMP certification requirement, among others, fueled a trend towards mergers among Chinese companies.[54]

A different but interesting example of the effects of ICH GMP on local producers is in Nepal, which is most likely, a representative example for other developing countries. There, the main preoccupation of local producers is production for the domestic market.[55] Being poor, the national health program is dependent on international aid and the bulk of drug procurement usually bypasses national government and is processed by international agencies (such as the UN), or international sponsors (such as the Global Fund). And these international bodies only procure medical products that are GMP certified, and that have been prequalified by the WHO or approved by an ICH-based regulatory authority (i.e. FDA, Swissmedic etc.).

Here, a word regarding the WHO prequalification program is in place. This program prequalifies medicines used for HIV/AIDS, malaria, and tuberculosis and for reproductive health. It was originally set up to ensure that pharmaceuticals procured by UN agencies meet standards of safety, efficacy and quality. To this end, following investigational procedures, it issues a list of medicines/manufacturers that are qualified.[56] The WHO acts here like a drug regulatory authority. In fact, in addition to products which are listed based on evaluations and inspections carried out by the WHO, it also lists products relying on the assessment and inspection carried out by the US FDA or the EMA (i.e. products that meet ICH standards). [57]

While the list was originally only intended for procurement by UN agencies, in practice it has become a vital list for any organization involved in buying a bulk of medicines, at the international or domestic level. For example, the Global Fund, [58] Medicine for Malaria Venture, or the Office of the U.S. Global AIDS Coordinator, [59] only buy medicines that have been approved by ICH countries or the WHO prequalification program. As only local manufacturers that comply with the GMP standards are approved, the WHO Prequalification program, and ICH standards, indirectly influence the market of pharmaceutical manufacturers in developing countries.

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[54] Y.R. Wang, 'The Chinese Pharmaceutical Market at the Crossraods: Pro-Competition Solutions to Improve Access, Quality and Affordability' (2005) 4 Applied Health Economics and Health Policy 147, 148.
[55] P. Brhlikova et al., 'Good Manufacturing Practice in the Pharmaceutical Industry' 29.
[56] http://apps.who.int/prequal/
[57] http://apps.who.int/prequal/

[58] The GLOBAL FUND QUALITY ASSURANCE POLICY FOR PHARMACEUTICAL PRODUCTS (as amended on 10 November 2009), determines, regarding quality standards, that Global Fund grant funds may only be used to procure HIV, Tuberculosis or Malaria pharmaceuticals that have been prequalified by the WHO Prequalification Programme or authorized for use by a 'stringent regulatory authority' (which is defined as a ICH member country, ICH observer (such as Switzerland) or other drug regulatory authority that has a mutual recognition agreement with thee ICH (such as Australia). (Article 1(1)(i)) Available at http://www.theglobalfund.org/documents/psm/Annex1-%20FullTextRevisedQualityAssurancePolicy_en.pdf
[59] http://www.gpo.gov:80/fdsys/pkg/GAOREPORTS-GAO-04-784/pdf/GAOREPORTS-GAO-04-784.pdf, p.7

In the case of Nepal it has been demonstrated that, following the WHO prequalification program, the GMP inhibits market supply by small, local manufacturers. [60]

These dynamics influence local manufacturers in other developing countries that rely on WHO prequalification. For example in the Indian case mentioned above, following the closure of the domestic manufacturers, the WHO determined that no new products under oversight of the Indian drug regulatory authority would be considered for prequalification, pending strengthening of the Indian drug regulatory authority. [61] Since India yearns to export, this in turn, put pressure on the local drug regulatory authority to close down local manufacturers that do not comply with the GMP.

To conclude, in developing countries that implement the GMP and actually enforce it, the small, local manufacturers are the losers. Who then, are the winners?

First of all, within developing counties, the export-oriented pharmaceutical industry that already operates to international standards, is well placed to switch to ICH GMP compliance, and this will not incur substantial new costs. [62]

Second, big companies that have the resources to comply with the ICH GMP. In fact, such companies do not only benefit thanks to their capability to comply with GMP standards, but in addition also enjoy increased international openness and a facilitated access to the international market. For example, in India a number of large generic drug manufacturers, have become adept at meeting international GMP standards, have consequently been able to export and have been qualified by the WHO prequalification program to sell their products internationally.[63] This alone has led to significant growth in the Indian pharmaceutical industry.[64]

Third, western companies that already comply with ICH standards benefit: When developing countries adopt ICH regulations (often also indirectly, in the sense that lacking regulatory capacity to investigate new applications, they rely on the marketing approval decisions of ICH regulators), or thanks to international procurement decisions that rely on WHO prequalification or ICH standards, producers from developed countries and multinationals have facilitated access to new markets.[65]

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[60] P. Brhlikova et al., 'Good Manufacturing Practice in the Pharmaceutical Industry' p. 29.
[61] J. Milstein et al., 'Reaching international GMP standards for vaccine production: challenges for developing countries' p.6.
[62] Tim Reed, p. 214, 215. Comparing between the impact of ICH/EU GMP in Hungary and Czech republic (export oriented pharmaceutical industry) and Romania (locally focused pharmaceutical industry).
[63] D. Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA*
[64] Scott M. Wheelwright, 'Bioprocessing in Asia' (2005) 3 BioProcess International 20,
[65] See also Suzanne Hill and Kent Johnson, 'Emerging Challenges and Opportunities in Drug Registration and Regulation in
Developing Countries' May 2004)
http://www.hlsp.org/LinkClick.aspx?fileticket=0TXMdaAk5KA%3D&tabid=1643

b. Analysis

In light of the above, and phrased in the terms of the "distributional effects" project, who have been the losers and the winners – in terms of wealth -- of the ICH GMP?

The ICH GMP imposes significant costs, and so in the short term it reduces the wealth of all of the actors. In the long term, the answer in short is that resourceful players are the winners, and the less wealthy players the losers: The ICH GMP increases significantly the costs of production and only pharmaceutical companies with substantial resources can achieve the necessary standards and stay in the game.

As we have seen above, who has the resources varies in the case at hand, but it can generally be concluded that:

Within developing countries (i.e. non-ICH countries):

Small, locally oriented (generic) companies are disadvantaged. It will often also disadvantage governmentally held enterprises (as in the case of Indian vaccine producers), as they do not have the resources to work in accordance with current GMP standards.

Further, in the competition between innovative and generic medicines producers, generic producers are being inhibited as they find themselves subject to the requirement to apply costly standards that are too high for their needs.

Resourceful companies that will be able to meet the GMP standards will stay in the game. Only big companies have the resources to make the major investments required to adapt the systems.[66] Again, who has resources may change from case to case, but typically these are big companies (as in the case of China where GMP has led to mergers). They can spread the fixed costs associated with high quality over large quantities of output, reducing the average cost.[67]

Private companies will also commonly have more resources than governmental companies (as in the Indian case), and so they will be among the beneficiaries.

Companies that are not only big but also export-oriented are potentially even better off: not only do they have resources to stay in the game, they also enjoy the benefits of harmonization, including facilitated access to the international market. [68]

From developed countries (i.e. ICH countries):

[66] Stan van Belkum, 'Electronic submission of regulatory information in support of marketing applications for medicinal products. The eCTD: Work in progress' (2001) 4 Pharmaceuticals Policy and Law 87, 94.
[67] A. S. Ray and S. Bhaduri, 'The Political Economy of Drug Quality: Changing Perceptions and Implications for Indian Pharmaceutical Industry' 2304.
[68] Adrian Kirk, 'ICH seeks harmony on quality' (2008) Pharmaceutical Technology Europe 13, 14.

Companies from developed countries that export to developing countries or multinationals that comply with these standards are most likely to be the beneficiaries of the GMP (such as thanks to the WHO prequalification decisions).[69]

In sum, the ICH GMP benefits resourceful companies and countries, whether this is reflected in big over small companies, private over public companies, developed (ICH) over developing (non-ICH) countries, multinational over domestic companies etc. In addition, resourceful companies that are export-oriented or multinational companies have the potential to benefit most from harmonization.

A little, final caveat to this conclusion is in place though: Many developing countries adopt GMP standards but do not actually implement them and do not enforce them on their local producers. The reason is often industrial policy, that is, the desire to support the local industry. [70] Or indeed, the desire to protect the access of citizens to generic medicines.[71] In other cases, it is simply a lack of regulatory capacities that lead to variable enforcement.[72] In such cases, despite the formal adoption of the GMP, due to its lack of enforcement, the GMP does not squeeze out the local industry. For example, it is known that India has a large industry of small manufacturing companies that produce generic drugs at low cost, on which the GMP is not strongly enforced, and these companies are responsible for about 35% of Asia's substandard and counterfeit drugs.[73]

The above discussed wealth effects do not stop there but (may) create, like a wave, additional after-shocks. These after-shocks reflect 'power effects' and we discuss such effects in the following section.

B. Access of local population in developing countries to medicines

It is often argued that the wealth effects mentioned above, particularly the squeeze out of local producers of generic drugs in developing countries will create adverse effects on the access of the local population to essential medicines. [74]

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[69] Indeed, from th 1970's, when the WHO adopted the FDA's GMP, large, brand-name firms favored the international adoption of GMP as they were better able to meet manufacturing regulations, and at lower cost, than smaller companies and generic drug firms. The imposition of GMP was also a strategy for raising teh fixed and variable costs of rival and generic producers. See D. Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* , 715.

[70] That is the case in Tanzania. See: Chukilizo Nditonda B., 'Availability and Quality of Medicines in Low Income Countries: The Role and Opportunities for European Manufacturers' (23rd Annual DIA EuroMeeting, Geneva, Switzerland 2011)

[71] Such as in the case of China: Vaccine worries – R. Ramachandran, 3 April 2008, http://www.pragoti.in/node/710

[72] D. Carpenter, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* , 721.

[73] Ibid., p.720.

[74] Most, if not all, production of medicines in developing countries is of generic medicines e.g. ICH Q7A on GMP for APIs expands requirements for manufacturers of pharmaceutical active starting

First, some background: The main health concern of developing countries is the availability of essential drugs to their local population. 'Essential medicines'[75] are overwhelmingly generic medicines. For example, in Tanzania, local manufacturers supply the majority of essential medicines.[76] In many developing countries, essential drugs required for the prevention and treatment of locally endemic conditions (which are often generic drugs) are not supplied by the major multinationals, but by *local* producers. In fact, in many countries the domestic pharmaceutical industry supplies most of the drugs consumed in the country.[77] The *local generics industry* is, hence, particularly important for developing countries. [78]

What the WHO (as well as others) have been concerned with is that ICH standards are unnecessarily high in the sense that they are not necessarily justified by safety concerns in the context of generic drugs. [79] The standards are commercially driven and not based on public health needs.[80] They should not, the WHO says, be applied directly in developing countries.[81] If producers are unable to meet what may be unsubstantiated quality standards, the adverse impact of the withdrawal of these drugs on the health of the population would be

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materials, and so creates increased rigidity in the starting material supply system, with consequent effects on starting material prices and availability. See WHO, 'Report of a WHO Meeting: The Impact of Implementation of ICH Guidelines in Non-ICH Countries' (para. 6.2. "Implication of the use of ICH guidelines by non-ICH drug regulatory authorities: Quality")

[75] Essential medicines are medicines that satisfy the priority health care needs of a population. They are selected with regard to disease prevalence, evidence of efficacy, safety, and comparative cost-effectiveness. The WHO Model List of Essential Medicines is a list of over 350 medicines. The overwhelming majority of medicines in this list is generic. See WHO, 'Medicines: essential medicines', Fact sheet no. 325, June 2010. http://www.who.int/mediacentre/factsheets/fs325/en/index.html

[76] Ministry of Health and social welfare, Tanzania ' In depth Assessment of the Medicines Supply System in Tanzania', 2008, http://www.who.int/medicines/areas/coordination/tanzania_assessment_supply.pdf (accessed 4 April 2012). P. 36

[77] Tim Reed, p.215-216. Refering to Romania where (as of 2001) 80 percent of drugs consumed in Romania were locally produced. In 2002, the Romanian national association of domestic producers (APMR) reported 88 domestic producers out of which 20 were responsible for 90% of the domestic supply. See WHO/Regional Office for Europe, Country Profile Romania (2008), available at http://www.euro.who.int/en/what-we-do/health-topics/Health-systems/medicines/country-work2/a-selection-of-country-profiles/romania-2008

[78] The overwhelming majority of development of new drugs takes place in developed countries. Developing countries do not have the capacity to discover and develop new drugs For example Tanzania: Country Data Profile on the Pharmaceutical Situation in the Southern African Development Community (SADC), United Republic of Tanzania, 2009, available at http://www.afro.who.int/en/clusters-a-programmes/hss/essential-medicines/edm-country-profiles.html (accessed 4 April 2012), p. 10. Says explicitly that Tanzania lacks such a capacity.

[79] In the empirical study conducted by Tim Reed, he demonstrated how many industry and regulators in Romania considered the GMP requirements as unnecessarily high. Tim Reed, p.219.In conversations held with WHO and Swissmedic officials, I have been told similarly that ICH standards are unnecessarily high for generic medicines.

[80] Implication of the use of ICH guidelines by non-ICH drug regulatory authorities: Quality, Para 7.

[81] Dr. Lembit Raego, « Panel 2 : ICH and Global Cooperation in the New Millenium, WHO Perspective », Proceedings, 5th ICH Conference, 2000,p. 301.

far more dramatic than that of any hypothetical risk posed by failing to achieve ICH standards. [82]

The WHO's concern, from a public health perspective, is hence not only that the adoption of ICH standards in developing countries may unnecessarily squeeze out local generic drug producers, but more importantly, that it will have adverse effects on the availability of drugs to the local population.[83]

Tim Reed similarly mentioned in the Romanian context, that since the overwhelming majority of drugs supplied to the local population had its origin in local producers that could not live up to the GMP standards imposed by the authorities, that this would have an adverse effect on the availability of cheap drugs.[84]

Another related argument has been that higher vaccine prices (as a result of higher GMP costs) will lead to lesser public access to vaccines, unless governments will intervene.

The problem is that while there is evidence that the GMP has squeezed out local producers in developing countries that have enforced the GMP, there is much less evidence (at least in the research I've conducted so far), if at all, on its effect on access to medicines in developing countries. It is unclear whether the void created by closure of local companies has indeed led to a shortage in drugs in these countries, or whether the void was filled by other sources.

For example, in the Indian case described above the domestic vaccine manufacturers that were closed down constituted the backbone of the Indian national immunization programme that protects children against vaccine preventable diseases, such as diphtheria and tetanus. It provided them with the bulk of their requirements. Their closure, hence, was expected to impact the national immunization programme badly, with a serious reduction in the availability of certain vaccines.[85] It is unclear, however, whether this indeed created a shortage in vaccines.

To conclude, phrased in the "distributional effects" terminology, the argument is that ICH GMP empowers 'northern' *commercial* interests, at the cost of 'southern' *patient* interests. In this case, the issue is not so much about money but rather the promotion, through ICH standards, of the *interests* of the export-oriented pharmaceutical industry, at the cost of the interests of local patients whose access to drugs is being undermined. It should be stressed, however, that in the

[82] WHO, 'Report of a WHO Meeting: The Impact of Implementation of ICH Guidelines in Non-ICH Countries' 2, 21-24. See also Prescrire, 'ICH: An Exclusive Club of Drug Regulatory Agencies and Drug Companies Imposing its Rules on the Rest of the World' (2010) 19 Prescrire International 183, and WHO, 'Global Harmonization and the ICH' Essential Drugs Monitor (2001) http://apps.who.int/medicinedocs/en/d/Jh2977e/4.html, accessed 9.

[83] WHO, 'Report of a WHO Meeting: The Impact of Implementation of ICH Guidelines in Non-ICH Countries' (para. 6.2. "Implication of the use of ICH guidelines by non-ICH drug regulatory authorities: Quality")

[84] Tim Reed, p. 216.

[85] Vaccine worries – R. Ramachandran, 3 April 2008, http://www.pragoti.in/node/710

research I have undertaken so far, I have not yet come across empirical evidence substantiating these claims. And so this requires further inquiry.

7. The ICH Good Clinical Practice (GCP) Guideline: An overview

A. Background

Over recent years there has been massive proliferation of regulations affecting the conduct of clinical trials. This process began in 1964 with the Declaration of Helsinki made by the World Medical Association (WMA). The Council for International Organizations of Medical Sciences (CIOMS) produced its International Ethical Guidelines for Biomedical Research Involving Human Subjects in 1982. Revised in 2002, these guidelines are intended to guide lower-income countries in applying the ethical principles that were laid out in the Declaration of Helsinki. Another set of international clinical trial guidelines was produced by the World Health Organization in 1995. The WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products were developed to provide a global standard for clinical trials. They were intended to complement existing regulations in those WHO member states that had already enforced clinical trials legislation or to provide a basis for new regulations in countries that had not.

The perceived differences between standards in the US, Europe and Japan drove the harmonization process led by ICH, which developed a comprehensive guideline setting out 'Good Clinical Practice'. The ICH Good Clinical Practice (GCP) was issued in 1996.[86] The ICH GCP was adopted by the ICH members in 1996/1997 as a domestic (legally non-binding) guidance document/guideline, [87] but later made its way into binding regulation.

The ICH GCP is an *ethical* and *scientific* quality standard for designing, conducting, performing, monitoring, auditing, recording, analyzing and reporting clinical trials, that is, trials that involve the participation of human subjects. At the *scientific* level, it provides assurance that the data and reported results are credible and accurate. At the *ethical* level, it ensures that the rights, safety and well being of trial subjects are protected.[88]

B. The ICH GCP started out as a commercial 'club' standard but ended up as a 'global' standard

The objective of the ICH GCP Guideline was to provide a unified standard for the EU, Japan and the U.S. to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. It was developed with consideration

[86] ICH Hramonised Tripartite Guideline, Guideline for Good Clinical Practice (E61), 10 June 1996, available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf.

[87] http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

[88] http://ichgcp.net/

of the good clinical practices of the ICH members.[89] The ICH GCP focuses on commercial clinical trials, that is, clinical trials performed by the pharmaceutical industry for new medicinal products.

The ICH-GCP is now the de facto global standard by which trials are run and has become a requirement for clinical trial conduct in many non-ICH countries,[90] and international research is now regularly conducted under the ICH GCP.[91] It has, hence, been a tool for the *diffusion* of the practices of ICH countries to non-ICH countries, or more generally of 'northern' practices to 'southern' countries. Moreover, as we shall see below, it is now also applied in non-commercial clinical studies.

C. ICH GCP has significantly increased the costs and time of clinical trials

Clinical trials, for the development of drugs and vaccines, have become increasingly time consuming and expensive.[92] While this situation is a result of various factors, the ICH GCP is among the factors that have contributed significantly to the increase in the bureaucracy, and consequently of the costs of clinical trials. [93] The ICH GCP introduces a rigid bureaucracy, with onerous procedural requirements for data management, documentation and reporting of trials. For example, the requirements regarding the monitoring of clinical data and the keeping of records have increased the level of complexity so that they now comprise third to two thirds of total clinical trial cost.[94] Thus, in comparison with the 1990's, it requires 5-20 times the funds to initiate a similar trial.[95]

The ICH GCP has also led to the growth of clinical trial duration.[96] In comparison with the 1990's, it takes 4-5 times longer to conduct a similar trial.[97]

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[89] http://ichgcp.net/introduction

[90] Clinical Research in Resource-Limited Settings: Enhancing Research Capacity and Working Together to Make Trials Less Complicated
Trudie A. Lang,[1,2*] Nicholas J. White,[1,3] Tran Tinh Hien,[4] Jeremy J. Farrar,[1,5] Nicholas P. J. Day,[1,3] Raymond Fitzpatrick,[6] Brian J. Angus,[1] Emmanuelle Denis,[1] Laura Merson,[5] Phaik Yeong Cheah,[3] Roma Chilengi,[2] Robert Kimutai,[2] and Kevin Marsh[1,] PLoS Negl Trop Dis. 2010 June; 4(6): e619.
Thomas Bollyky, Iain M Cockburn and Ernst Berndt, Bridging the Gap : Improving Clinical Development and the regulatory pathways for health products for neglected diseases », Clinical Trials 2010 ; 7 : 719-734, http://ctj.sagepub.com/content/7/6/719.full.pdf+html, p. 721

[91] Department of Health and Human Services, Office of Inspector General, The Globalization of Clincial Trials: A Growing Challenge in Protecting Human Subjects, September 2011, available at http://oig.hhs.gov/oei/ reports/oei-01-00-00190.pdf (accessed April 2012), p. 3

[92] Thomas Bollyky, Iain M Cockburn and Ernst Berndt, Bridging the Gap : Improving Clinical Development and the regulatory pathways for health products for neglected diseases », Clinical Trials 2010 ; 7 : 719-734, http://ctj.sagepub.com/content/7/6/719.full.pdf+html, p. 20 <>>

[93] L. Duley, K. Antman, J. Arena et al, Specific barriers to the conduct of randomized trials, Clinical Trials 2008 ; 5 : 40-4

[94] E. Eisenstein, R. Collins, B. Cracknell et al. Sensible approaches for reducing clinical trials. Clinical Trials 2008 ; 5 : 75-84.

[95] Salim Yusuf, Damage to important clinical trials by over-regulation, Clinical Trials 2010, 7 : 622-625, avaialable at http://ctj.sagepub.com/content/7/6/622.full.pdf+html, p.624

[96] L. Duley, K. Antman, J. Arena et al, Specific barriers to the conduct of randomized trials, Clinical Trials 2008 ; 5 : 40-4 (TO READ !!)

[97] Salim Yusuf, Damage to important clinical trials by over-regulation, Clinical Trials 2010, 7 : 622-625, avaialable at http://ctj.sagepub.com/content/7/6/622.full.pdf+html, p.624

D. ICH GCP: commercial vs. non-commercial trials

In the world of clinical research, there are two kinds of clinical trials: commercial and non-commercial (or academic) clinical trials. The ICH GCP was written for *commercially* driven *new drug* registration studies. But investigational product trials represent only a portion of the many types of clinical research studies. And in practice the ICH GCP has been applied to all types of clinical research, both commercial and *non-commercial, academic* trials. The reasons for this broad application are diverse. One reason is that they have become accepted, familiar practice. Another very important reason is that medical journals will only publish the results of clinical trials that have been registered with a public registry,[98] and a precondition for registration is that the clinical trials follow the ICH guideline on clinical trials.[99] This has created a lot of pressure on academic researchers to conduct trials in accordance with the ICH GCP.

The application without discrimination of the ICH GCP to all clinical studies -- both commercial and non-commercial clinical-- has given rise to research evidencing and criticizing the adverse effects of the ICH on non-commercial clinical trials. Before we go on to discuss these effects, first, a short explanation is in place to clarify the difference between commercial and non-commercial trials. While they have similarities, they also have important differences. [100]

Commercial clinical trials are conducted by the pharmaceutical industry on *new* medicinal products.

Non-commercial clinical trials are clinical studies initiated and driven by academic researchers for non-commercial purposes. The primary aim of non-commercial trials is to *improve patient care*, or *treatment methods*, rather than to develop new pharmacological entities.[101] They seek to improve and refine treatments with existing medicines: they are often conducted to improve therapeutic strategies and establish new state-of-the-art treatments. Their independent approach includes the assessment of the therapeutic effects, safety and socio-economic implications of both established and new treatments within the real conditions of the health systems. These types of trials are done without the involvement of the pharmaceutical sector.[102] Non-commercial clinical research therefore contributes to the evaluation of various treatment strategies and options as a basis for developing therapeutic guidelines and governmental policies.

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[98] C. De Angelis et al., 'Clinical trial registration: a statement from the International Committee of Medical Journal Editors' (2004) New England Journal of Medicine

[99] Trudie Lang, Phaik Yeong Cheah, and Nicholas J. White, 'Clinical research: time for sensible global guidelines' (7 May 2011) 377 The Lancet 1553, 1554

[100] 'Facilitating International Cooperation in Non-Commercial Clinical Trials' 2011) http://www.oecd.org/dataoecd/31/8/49344626.pdf

[101] McMahon, A.D., D.I. Conway, T.M. MacDonald, and G.T. McInnes. 2009. The unintended consequences of clinical trials regulations. *PLoS medicine* 6 (11):e1000131.

[102] Francoise Meunier et al., 'Throwing a wrench in the works?' (2003) 4 The Lancet Oncology 717,

Moreover, the market-driven pharmaceutical industry does not pursue research and development for a number of diseases because of the small number of patients involved (as is the case with orphan diseases such as cystic fibrosis) and the insufficient profitability of the treatments (e.g. pediatric therapies, or treatments for diseases in developing countries, i.e. neglected diseases). Non-commercial clinical research, hence, steps in here.

To sum, while indeed many clinical trials are commercial, non-commercial trials form a substantial and critical element of medical research. The ICH GCP has had an effect on the distribution of commercial and non-commercial research conducted, which we look at next.

8. The ICH GCP: Distributional Effects

In this section, the paper focuses on the distributional effects of the ICH GCP on non-commercial trials in Europe (8A), and its effect on the development of medicines for neglected diseases in developing countries (8B).[103] These effects have been substantiated by empirical evidence in the medical and pharmaceutical literature.

To a large extent, the discussion focuses on distributional *power* effects, that is, how the ICH GCP distributes power among *ICH members* and *ICH non-members*.

A. The Application of the ICH GCP to non-commercial trials in Europe

a. The EU Clinical Trials Directive

Following the ICH's 2001 adoption of the GGP, the EU adopted the ICH GCP in Directive 2001/20/EC, known as the "Clinical Trials Directive".[104] In addition, it issued the 'GCP Directive' in 2005.[105] The Clinical Trials Directive provides the regulatory framework for conducting clinical trials in the EU. The EU has, hence,

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[103] It should be noted that the ICH GCP has had many effects which are worth studying, but are not covered here due to paper length limitations. For example, there is evidence in Japan that small, domestic pharmaceutical companies were squeezed out, as they were incapable of conducting clinical trials in accordance with the ICH GCP. The ICH GCP's effects on the human rights of subjects participating in clinical trials in developing countries is another area that has received a lot of attention. The ICH GCP's "informed consent" requirement has also raised a major discussion regarding the ethical effects of the ICH GCP in developing countries.

[104] DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001on the approximation of the laws, 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. This Directive is currently under review due to criticisms voiced.

[105] COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products; Harmful impact of EU clinical trials directive;
Academic clinical research in cancer seems to have no future in Europe
Akseli Hemminki, Pirkko-Liisa Kellokumpu-Lehtinen, BMJ. 2006 March 4; 332(7540): 501–502.

essentially made the ICH GCP a legal requirement.[106] As mentioned above, while the ICH GCP was created for the regulation of the pharmaceutical industry, the EU Directive has been applied to non-commercial trials too.

b. The problem

The bureaucracy introduced by the EU Directive increases costs. Costs for bureaucracy and resource requirements to handle paperwork have doubled, and delays have increased by 90%.[107] This had made clinical trials too expensive for non-commercial bodies, such as for academic investigators that are supported by grants. Consequently, this has led to a reduction in non-commercial clinical trials.

Some commentators have referred to the Clinical Trials Directive as the "death knell for academic clinical trials".[108] Others have said that some academic organizations will go completely "out of business", whereas others will be able to accommodate the new requirements, but forced to decrease their clinical research activities. This increase in costs has also meant that it has become almost impossible for academic researchers to initiate and conduct pharmaceutical trials without the involvement of a pharmaceutical company, particularly in areas that do not attract much funding or involve a drug that is close to the end of or outwith patent protection.[109]

As to the evidence base, over the past decade there have been several reports that have demonstrated that the fall in academic trials can be attributed directly to the EU Clinical Trials Directive.[110] There is indeed a lot of accumulating evidence that suggests that many research units and individual researchers have withdrawn from noncommercial clinical trials altogether because of the EU Directive, with consequent negative effects on access of patients to medicines. [111]

For example, by the end of 2005, a research group in the UK noted that they had "almost stopped doing drug studies", and it was estimated that the proportion of

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[106] The European Commission currently wants to replace the EU directive on clinical trials – which is currently undergoing revision – with a regulation so as to ensure greater uniformity among member states in implementing the revised provisions. The EU commissioner for health and consumer policy John Dalli announced this at a 7 March 2012 meeting. The reason is that experience shows that co-operation amongst Member States is very difficult and costly if each Member State bases its work on 'similar, but different' transposing national laws. See Vibha Sharma, 'Review of EU clinical trials framework on track; directive to be replaced with regulation', *Scrip Regulatory Affairs,* 30 March 2012.

[107] John Dalli, 'Commissioner Dalli delivers speech on "Clinical Trials Directive- Meeting Patients' Needs"' Brussels 2012)

[108] Alyn H. Morice, 'The Death of Academic Clinical Trials ' (2003) 361 Lancet

[109] Harmful impact of EU clinical trials directive Trial of alerting drug in fibromyalgia has had to be abandoned...Christopher D Hanning, and Patricia Rentowl, BMJ. 2006 March 18; 332(7542): 666; Harmful impact of EU clinical trials directive...and so has trial of melatonin in cancer related weight loss...Max Watson, research fellow, BMJ. 2006 March 18; 332(7542): 666.

[110] Clinical trials in paediatric haematology‐oncology: are future successes threatened by the EU directive on the conduct of clinical trials? Chris Mitchell, Arch Dis Child. 2007 November; 92(11): 1024–1027.

111 McMahon, A.D., D.I. Conway, T.M. MacDonald, and G.T. McInnes. 2009. The unintended consequences of clinical trials regulations. PLoS medicine 6 (11):e1000131

noncommercial trials had reduced from 40% to 14%. Further, the largest independent cancer research network in Europe (EORTC) reported that the number of new trials dropped from 38 in 2001, to 19 in 2004, to seven in 2005; trial costs had increased by 85% and trial initiation was five months slower. Paperwork and documentation increased "a lot." This, consequently, hindered the access of patients to new treatments.[112] Senior oncologists have similarly reported a 75% decrease in academic clinical trials between 2003 to 2005 and concluded that cancer patients in the future ''should be worried''.[113] The EU Directive also led to the abandonment of a trial to address fibromyalgia,[114] and of a trial of melatonin, and it eroded the normally very high rates of recruitment into pediatric cancer trials (an area of very little interest to the pharmaceutical industry).[115] There were around ten to 20 studies in pediatric oncology starting per annum before implementation of the Directive, and this dropped to a handful following the Directive. Mitchell and others say that for children with cancer "the effect of the EU directive has been appalling".[116]

While no one is contending the need for good clinical practice, there has been much criticism that the ICH/EU GCP sets out costly and time-consuming requirements that are not justified in the case of non-commercial, academic trials. For example, McMahon et al. have argued that while the extremely detailed instructions on data management and reporting of trials may be appropriate for drug companies seeking to license a new pharmaceutical entity, these requirements are not justified in non-commercial trials. Others working in the field similarly claim that there is no evidence to support the utility of this bureaucracy for academic studies, as the bureaucratic requirements do not significantly improve the protection of patients or the credibility of the trial data.[117] It is claimed that the appropriate level of supervision would be expected to differ for a drug undergoing first use in humans and a long marketed drug now being tested for a new treatment.[118]

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[112] Harmful impact of EU clinical trials directive: Academic clinical research in cancer seems to have no future in Europe, Akseli Hemminki, Pirkko-Liisa Kellokumpu-Lehtinen, BMJ. 2006 March 4; 332(7540): 501–502.

[113] Harmful impact of EU clinical trials directive
Academic clinical research in cancer seems to have no future in Europe
Akseli Hemminki, Pirkko-Liisa Kellokumpu-Lehtinen, BMJ. 2006 March 4; 332(7540): 501–502.

[114] Harmful impact of EU clinical trials directive: Trial of alerting drug in fibromyalgia has had to be abandoned..., Christopher D Hanning, consultant in sleep medicine and Patricia Rentowl, research assistant, BMJ. 2006 March 18; 332(7542): 666.

[115] Harmful impact of EU clinical trials directive...while paediatric oncology is being scuppered, Christopher D Mitchell, BMJ. 2006 March 18; 332(7542): 666.

[116] Clinical trials in paediatric haematology‐oncology: are future successes threatened by the EU directive on the conduct of clinical trials?
Chris Mitchell, Arch Dis Child. 2007 November; 92(11): 1024–1027.

[117] McMahon, A.D., D.I. Conway, T.M. MacDonald, and G.T. McInnes. 2009. The unintended consequences of clinical trials regulations. PLoS medicine 6 (11):e1000131; D.J. Flavell, S.U. Flavell, and R. Sullivan, 'European Clinical Trials Directive: responses made to MHRA consultation letter MLX 287' (2003) 362 THE LANCET 1415, , F. Meunier et al., 'Throwing a wrench in the works?'

[118] K. Woods, 'Implementing the European clinical trials directive: Discussions continue in the European Commission and the United Kingdom
' (2004) 328 BMJ 240,

Indeed, it is now commonly accepted that the EU Clinical Trials Directive is not entirely fitting for academic research. Recently, John Dalli, the European Commissioner for Health and Consumer Policy, stated that "There is broad agreement that the rules for clinical trials should, in principle, also apply to sponsors other than industry. However, we have to be aware of the limitations for these 'academic sponsors' in terms of resources, including financial resources."[119]

c. Analysis

To sum, the EU Clinical Trials Directive, which implemented the ICH GCP, was driven by commercial interests, but has had adverse effects on non-commercial entities, and in turn has had adverse effects on patients.

In light of the above, and phrased in the terms of the "distributional effects" project, who have been the losers and the winners – in terms of wealth -- of the ICH GCP in Europe?

As in the case of the ICH GMP, the answer in general is that resourceful players are the winners, and the poor players the losers: The ICH GCP increases significantly the costs of conducting clinical trials and only players with financial (and other) resources can meet the standards and stay in the game. In this case, big, privately held, commercial entities benefit, whereas academic, government funded entities are undermined.

In addition, we can talk about distributional power effects. The squeezing out of academic trials has led to lesser treatments being developed and, hence, been to the detriment of patients. Accordingly, the situation can be portrayed as one where the ICH GCP promotes commercial interests (i.e. ICH members), whereas the interests of non-commercial bodies and 'diffused interests' are undermined (i.e. ICH-non-members).

B. **The Application of ICH GCP in Developing Countries**

In the past decade or so, the problem of access to medicines in developing countries is often mentioned in relation to drug pricing and Intellectual Property rights. An area that is normally overlooked, is the role transnational regulation has in inhibiting such access. In this section, the paper takes a look at the role of the ICH GCP in undermining the access of patients in developing countries to medicines for neglected diseases.

a. The Problem of Neglected Diseases in Developing Countries

One of the central health problems in developing countries is that for many diseases, medicines are non-existent. These diseases, commonly referred to as

[119] J. Dalli, 'Commissioner Dalli delivers speech on "Clinical Trials Directive- Meeting Patients' Needs"'

"Neglected diseases" have generally been defined as communicable, tropical diseases such as malaria, sleeping sickness, chaga sieases and leishmaniasis, for which there is essentially no pharmaceutical research and development. [120] Indeed, only a small fraction of the total worldwide expenditure on health research and development is devoted to the development of medicines for such diseases. Neglected diseases are endemic primarily in Africa, Asia and tropical regions of the Americas.[121] An estimated 1.4 billion people,[122] including 400 million children, suffer from one or more neglected diseases. Many of these diseases exact a large and lethal toll, with tuberculosis and malaria alone killing an estimated 2.6 million people annually. Other neglected diseases are less deadly but disable or deform.

These diseases are "neglected" as despite an ever-increasing need for medicines for the treatment of these diseases, drug development is virtually non-existent. With the emergence of a free market-based world order, commercial prospects rather than global health needs guide the direction of new drug development. Between 1975 and 1999 only 16 of 1393 newly marketed drugs were for tropical diseases.[123] The pharmaceutical industry argues that research and development is too costly and risky to invest in low-return neglected diseases, and prefer focusing on "blockbuster" drugs for the developed world. The adverse public health consequences of this evolution for the developing (mostly tropical) world have been grave.[124] Given the high disease burden, developing countries urgently need research to help relieve them from such diseases.[125]

In the past decade there have been initiatives underway that seek to overcome this market limitation through incentive packages and public-private partnerships. The buzzword is "product development partnerships", whereby drug companies work with non-profit organizations (such as the Drugs for Neglected Diseases Initiative, the Medicines for Malaria Venture, the Meningitis Vaccine Project) and academia in drug discovery projects.[126] Philanthropic and public funds absorb the costs and risks of drug development, and industry picks up the projects and markets and distributes them.[127] Thanks to such initiatives, in the past decade there has tremendous progress in the development of drugs and vaccines for neglected diseases, and there are now dozens of candidate products in the pipeline.

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[120] S. Hill and K. Johnson, 'Emerging Challenges and Opportunities in Drug Registration and Regulation in
Developing Countries'
[121] Bollyky, p.722-723.
[122] Janice Hopkins Tanne, 'How the search for new drugs for neglected diseases is paying off' (2012) 344 BMJ 18, 18.
[123] Ibid.18.
[124] Patrice Trouiller et al., 'Drugs for neglected diseases: a failure of the market and a public health failure?' (2001) 6 Tropical Medicine and International Health , p. 945.
[125] Kenneth Calman, 'Conducting Research Ethically in Developing Countries' (2002) 7 Drug Discovery Today
[126] J. Hopkins Tanne, 'How the search for new drugs for neglected diseases is paying off' 18.
[127] Ibid.

Certain global initiatives to systematically this problem are underway too. For example, most recently, the Consultative Expert Working Group on Research and Development: Financing and Coordination convened by the WHO, issued a report on "Research and Development to Meet the Needs in Developing Countries: Strengthening Global Financing and Cooperation". The report proposes innovative financing and cooperation options to tackle this problem, including a recommendation to reach a binding International Convention on Global R&D.[128]

Despite these initiatives, the situation is still grave, and we next look at the impact the ICH GCP has had on the development of drugs for neglected diseases.

b. The ICH GCP and Neglected Diseases

The ICH GCP was originally developed for the needs of ICH member countries (i.e. developed countries), and it reflects commercial practice, as it was written for commercially driven drug registration studies. In practice, however, the ICH GCP has been 'exported' and become a global standard. So it is now being applied in situations that were not envisaged during its development: in low-income countries and in non-commercial trials, including in cost sensitive clinical trials in neglected disease endemic countries.[129]

The problem is that the ICH GCP is excessive and overwhelming in terms of administration, oversight and documentation in such poor settings. The content is, hence, unaffordable and unreachable in developing countries, particularly in clinical trials for neglected disease, which are highly cost sensitive endeavors. The human and financial resource capacity available to ensure a high standard of design, management, and operation of clinical trials in developing countries lags far behind that available in wealthier nations.[130]In fact, the clinical research and regulatory capacity in many neglected disease–endemic countries is rudimentary.[131]

Moreover, many trials for neglected diseases, such as in Africa, even if sponsored by developed countries, are *non-commercial trials* that are publicly sponsored,

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[128] http://www.who.int/phi/CEWG_Report_5_April_2012.pdf

[129] M. Moran, AL Ropars, J. Guzman, J. Diaz, The New Landscape of Neglected Disease Drug Development, Welcome Trust, London, 2005, p. 25-26 ; Bollyky et al., p.722. Approximately a third of clinical trials for neglected diseases were performed in Africa during 2003-2009.

[130] Clinical Research in Resource-Limited Settings: Enhancing Research Capacity and Working Together to Make Trials Less Complicated
Trudie A. Lang,[1,2*] Nicholas J. White,[1,3] Tran Tinh Hien,[4] Jeremy J. Farrar,[1,5] Nicholas P. J. Day,[1,3] Raymond Fitzpatrick,[6] Brian J. Angus,[1] Emmanuelle Denis,[1] Laura Merson,[5] Phaik Yeong Cheah,[3] Roma Chilengi,[2] Robert Kimutai,[2] and Kevin Marsh[1,] PLoS Negl Trop Dis. 2010 June; 4(6): e619.

[131] Center for Global Development's Working Group on Clinical Trials and Regulatory Pathways on "Safer, Faster, Cheaper: Improving Clinical Trials and Regulatory Pathways to Fight Neglected Diseases", 2011, available at http://www.cgdev.org/files/1425588_file_Bollyky_Clinical_Trials_FINAL.pdf (accessed April 2012) p.29

and are, hence, severely limited in resources.[132] For non-commercial bodies the costs associated with the guidelines are too unaffordable. [133]

Various studies have been conducted demonstrating that the ICH GCP has been an impediment to clinical research in developing countries, with potential adverse effects on the development of drugs for local needs.[134]For example, Bollyky has identified the ICH GCP as being among the main factors that undermine the capacity to conduct clinical trials for candidate neglected disease therapies to patients in developing countries.[135]Lang et al. have also argued that the ICH GCP is an impediment to clinical research in developing countries, and is inhibiting the development of drugs for local needs, or neglected diseases.[136] Yusuf et al. have similarly warned that due to the increased cost and time associated with the ICH GCP fewer trials for neglected diseases are being conducted.[137] He warns that if sensible guidelines for clinical trials will not be developed to reverse the harm caused by the ICH GCP, the battle against disease will be severely slowed down and much of the scarce funds for clinical trials will be wasted. [138]Trouiller et al. have also noted that the ICH recommendations are being regarded as absolute requirements rather than guidelines (which they are) and that the insistence on compliance[139] with such demanding regulations further increases the development costs and creates a major disincentive to small companies from developing countries or emerging markets trying to enter the market. In fact, they point out that only the large and wealthy companies can comply with such increasingly demanding regulations. But these are the companies least interested in neglected diseases.[140]

A Report issued by the Center for Global Development's Working Group on

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[132] Clinical Research in Resource-Limited Settings: Enhancing Research Capacity and Working Together to Make Trials Less Complicated
Trudie A. Lang,[1,2*] Nicholas J. White,[1,3] Tran Tinh Hien,[4] Jeremy J. Farrar,[1,5] Nicholas P. J. Day,[1,3] Raymond Fitzpatrick,[6] Brian J. Angus,[1] Emmanuelle Denis,[1] Laura Merson,[5] Phaik Yeong Cheah,[3] Roma Chilengi,[2] Robert Kimutai,[2] and Kevin Marsh[1,] PLoS Negl Trop Dis. 2010 June; 4(6): e619.
[133] Salim Yusuf, Damage to important clinical trials by over-regulation, Clinical Trials 2010, 7 : 622-625, avaialable at http://ctj.sagepub.com/content/7/6/622.full.pdf+html, p.622
[134] T. Lang, P. Y. Cheah, and N. J. White, 'Clinical research: time for sensible global guidelines' 1554.
[135] Thomas Bollyky, Iain M Cockburn and Ernst Berndt, Bridging the Gap : Improving Clinical Development and the regulatory pathways for health products for neglected diseases », Clinical Trials 2010 ; 7 : 719-734, p. 726.
[136] T. Lang, P. Y. Cheah, and N. J. White, 'Clinical research: time for sensible global guidelines' 1554. Nicholas J. White, Editorial: Clinical Trials in Tropical Diseases: a politically incorrect view, Tropical Medicine and International Health, Volume 11 Issue 10, 21 Sep. 2006, 1483-1484; P. Trouiller et al., 'Drugs for neglected diseases: a failure of the market and a public health failure?' p. 2192.

[137] Salim Yusuf, Damage to important clinical trials by over-regulation, Clinical Trials 2010, 7 : 622-625, avaialable at http://ctj.sagepub.com/content/7/6/622.full.pdf+html, p.624
[138] Salim Yusuf, Damage to important clinical trials by over-regulation, Clinical Trials 2010, 7 : 622-625, avaialable at http://ctj.sagepub.com/content/7/6/622.full.pdf+html, p.624
[139] But any simpler interpretation of GCP is often regarded as inferior or second-class. T. Lang, P. Y. Cheah, and N. J. White, 'Clinical research: time for sensible global guidelines' 1554. Nicholas J. White, Editorial: Clinical Trials in Tropical Diseases: a politically incorrect view, Tropical Medicine and International Health, Volume 11 Issue 10, 21 Sep. 2006, 1483-1484
[140] P. Trouiller et al., 'Drugs for neglected diseases: a failure of the market and a public health failure?' 947

Clinical Trials and Regulatory Pathways on "Improving Clinical Trials and Regulatory Pathways to Fight Neglected Diseases"[141] sets out the factors that significantly increase the risk, delays and cost of clinical trials for candidate drugs and vaccines in the neglected disease pipeline. The changes in clinical trial regulation, which have contributed to the growth of clinical trial duration and costs, are identified as one of the factors.[142] The problem is further enhanced, the report says, due to the lack of regulatory capacity that hinders trials in countries with neglected diseases. [143]

While no one is contending that there isn't a need for good clinical practice, the criticism is that many of the bureaucratic requirements (e.g. mountains of papers, emails, conference calls, and other procedural aspects) add little to the quality of the process in the developing country context.[144] Scientists in the field also say that it is also unnecessary for randomized controlled clinical trials.[145] The ICH GCP does not address country specific issues,[146] and the fact that the ICH GCP does not take the special circumstances of developing countries into concern inhibits research in those countries.

To sum, the implantation of the ICH GCP in developing country settings has been a detriment to development of drugs for neglected diseases in developing countries, [147]

c. Analysis

Phrasing the above in the "distributional effects" terminology, what we see is that from a wealth perspective, entities (whether commercial or non-commercial) in developing countries lack the sufficient resources to develop drugs, and so the ICH GCP acts as a barrier to market entry. The specific problem with neglected diseases is that big, western companies also do not step in to fill this void.

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[141] Center for Global Development's Working Group on Clinical Trials and Regulatory Pathways on "Safer, Faster, Cheaper: Improving Clinical Trials and Regulatory Pathways to Fight Neglected Diseases", 2011, available at http://www.cgdev.org/files/1425588_file_Bollyky_Clinical_Trials_FINAL.pdf (accessed April 2012)

[142] p. 9

[143] The regions with the highest neglected-disease burden are also those with the most poorly resourced and inexperienced regulators and ethics committees. Many neglected disease–endemic countries, particularly in Africa, have weak or no drug regulatory authorities and little ethical review capacity. Where drug regulatory authorities do exist, they often lack sufficient legal authority to approve clinical trial protocols, authorize importation of study products, inspect sites, or terminate trials. A 2009 WHO report assessing 22 developing country drug regulatory authorities in Africa, Asia, and Latin America concluded that two-thirds of these countries had weak or no mechanisms for regulating clinical trials or exerting proper oversight on clinical investigation.See p.11

[144] T. Lang, P. Y. Cheah, and N. J. White, 'Clinical research: time for sensible global guidelines' 1554. Nicholas J. White, Editorial: Clinical Trials in Tropical Diseases: a politically incorrect view, Tropical Medicine and International Health, Volume 11 Issue 10, 21 Sep. 2006, 1483-1484

[145] Salim Yusuf, Damage to important clinical trials by over-regulation, Clinical Trials 2010, 7 : 622-625, avaialable at http://ctj.sagepub.com/content/7/6/622.full.pdf+html, p.622

[146] WHO, 'Report of a WHO Meeting: The Impact of Implementation of ICH Guidelines in Non-ICH Countries' para. 6.1.

[147] Dr. Lembit Raego, « Panel 2 : ICH and Global Coopertaion in the New Millenium, WHO Perspective », Proceedings, 5th ICH Conference, 2000,p. 301.

At the power level, what we see in the context of neglected diseases is a distribution of power between economic and public health interests. The ICH guideline promotes the interests of commercial interests and undermines non-commercial bodies (i.e. academia). Moreover, it promotes the interests of 'northern' commercial interests (i.e. ICH members) over 'southern' patient interests (non-ICH entities).

Were the GCP also developed with the interests of developing countries in mind, the effects would have been different. Indeed, there have been calls for the development of GCP guidelines that are sensible to the needs of developing countries.[148]

9. Regulatory Capability

Caffagi and Pistor define "Institutional capability" as "the capacity and ability of institutions, organizations, and communities to regulate affairs of relevance to them and choose the appropriate regulatory means. Put differently, a community or entity possesses regulatory capabilities if it has both the option and capacity to make self-determinative regulatory choices."[149]

While in the first part of the paper we have focused on some of the negative impacts of ICH guidelines, in terms of regulatory capability, the effects are overwhelmingly positive. There is no question that the ICH guidelines have had a positive impact on the scientific and regulatory capability of both ICH-countries, as well as in non-ICH countries. We look at these two aspects next.

A. Scientific capability

Non-ICH Countries (i.e. emerging or developing countries) often lack the resources or the knowledge to develop scientific guidelines. The ICH guidelines, which are free and easily accessible online (as well as ongoing training events), have diffused technical, scientific and regulatory knowledge to the pharmaceutical industry and regulatory agencies in such countries. In this sense, they have clearly made a positive impact on the regulatory capability of many countries. To a large extent this can be regarded as a diffusion of Western scientific knowledge to the East, or from the 'North' to the 'South.

The ICH GCP, for example, has clearly contributed to ethical and scientifically sound clinical research. Such improvement has been evidenced in countries such as South Korea (where there is evidence that the quality of clinical trials improved) as well as in Latin America, or Asia.[150]

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[148] T. Lang, P. Y. Cheah, and N. J. White, 'Clinical research: time for sensible global guidelines' ; Yusuf

[149] Cafaggi and Pistor.

[150] E.g. **Implementation of good clinical practice guidelines in vaccine trials in developing countries** Original Research Article
Vaccine, *Volume 25, Issue 15*, *12 April 2007*, *Pages 2852-2857*

B. **Regulatory capability**

ICH guidelines have significantly improved the regulatory review process:

First, a majority of ICH guidelines deal with topics for which no regulatory guidelines previously existed.[151] The ICH guidelines have, accordingly, improved the quality of the regulatory review process by introducing a standardized and structured review process. Previously, in many areas, due to a lack of guidelines, practice had been inadequate and costly. They, hence, are a great contribution to ICH countries or non-ICH countries that follow them. Tim Reed, for example, demonstrates how their introduction has improved the review process by Czech and Romanian regulators. [152]

Second, one of the ICH's greatest accomplishments in improving regulatory review has been the development of the Common Technical Document (CTD). [153]The CTD is a technical document that provides a harmonized structure and format for new drug applications.[154] This structure has benefited both the pharmaceutical industry and the regulators:

The "greatness" of the CTD for the pharmaceutical industry is that it has immensely speeded up and simplified the application for drug approvals in different regions. While the scientific data is developed in the same way for all three regions, the actual applications varied. A large amount of documentation and data are required in submission, and each jurisdiction organized the information differently. A company would have to assemble the submission information for one drug regulatory authority, and then needed to reassemble it for another. The CTD assembles the building blocks of information intended for inclusion in a submission into a consistent harmonized format.

For regulators, the huge advantage is that it significantly eases the communication between regulators in different countries.[155] With similar reports and applications, regulators can easily compare and exchange

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Camilo J. Acosta, Claudia M. Galindo, R. Leon Ochiai, M. Carolina Danovaro-Holliday, Anne Laure-Page, Vu Dinh Thiem, Yang Jin, Mohammad Imran Khan, Shah Muhammad Sahito, Hasan Bin Hamza, Jin Kyoung Park, Hyejon Lee, Hans Bock, Remon Abu Elyazeed, M. John Albert, Carlos Ascaso, Tonette Q. Robles, Mohammad Ali, Philip Ngai, Mahesh K. Puri, *et al.* (regarding clinical trials conducted in Asia)

[151] WHO, 'Report of a WHO Meeting: The Impact of Implementation of ICH Guidelines in Non-ICH Countries' (para. 6.1. "Efficacy and Safety")

[152] Tim Reed, p.195, 197.

[153] http://www.ich.org/products/ctd.html

[154] "CTD", available at http://www.ich.org/cache/compo/276-254-1.html.

[155] ICH, 'The Value and Benefits of ICH to Drug Regulatory Authorities: Advancing Harmonization for Better Health' 2010) http://www.ich.org/fileadmin/Public_Web_Site/News_room/C_Publications/ICH_20_anniversary_Value_Benefits_of_ICH_for_Regulators.pdf.

information. It is, therefore, not surprising that the CTD has been the most widely adopted guideline, also beyond ICH regions.[156]

Third, the collaboration in the ICH allowed the regulatory authorities to develop guidelines would have taken much longer had they needed to do it alone. For example, it would have taken each of the parties much more time to develop a GMP rule without the work of the ICH. [157]

Forth, by sharing similar standards, regulatory authorities can to a larger extent rely on mutual utilization of data, and mutual acceptance of registration data. For example, Japanese regulators sought to accept more foreign data and thereby facilitate the registration of new drugs in Japan.[158]Similarly, by sharing similar standards, regulatory authorities can also to a larger extent rely on mutual recognition agreements (MRA) on the inspection of pharmaceutical plants. For example, the introduction of EU legislation on GMP was considered to help remove a barrier to the implementation of the MRA between the EU and US on the inspection of pharmaceutical plants. [159] In fact, the long-term objective behind the ICH's work on harmonizing GMP standards is to provide a basis for a global system of MRAs.[160]

10. Conclusion

In this paper we have focused on the distributional effects of the ICH GCP and ICH GMP, and also discussed the regulatory effects of ICH guidelines in general. As we have seen, despite their technical nature, they have had significant economic and social effects. There are several conclusions that can be drawn from our discussion:

First, ICH guidelines raise the costs of drug development and production. While this cost reduces in the short term the wealth of all actors involved, in the longer term, it creates pressure on companies that lack sufficient resources, and may lead to their squeeze out (or prevents market entry to begin with). Resourceful entities are at a lesser risk and have the potential to thrive. Not only do they have better chances of staying in the market, they also have the potential to increase their market thanks to internationally harmonized standards. In reality, this means that small, local companies, and governmentally funded entities (and even more so in developing countries) are the losers. The big, export oriented, multinational, privately held companies (and even more so in developed countries) are the winners. This situation is well reflected in our discussion above on the effect of ICH GMP in developing countries, and of the effect of ICH GCP on non-commercial trials.

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[156] Dr. Dawn Ronan, Interview, 9 July 2010 (Geneva).
[157] Sean Milmo, 'European Union Moves Forward with GMP Harmonization' (2001) CMR Focus (talking about the EU)
[158] Churyo Morii, 'Opening Plenary Session: Opening Remarks by the Minister of Health and Welfare, Japan' in P. F. D'arcy and D. W. G. Harron (eds.), *Proceedings of the Third International Conference on Harmonisation, Yokohama 1995* (The Queen's University of Belfast, 1995) p. 16.
[159] S. Milmo, 'European Union Moves Forward with GMP Harmonization'
[160] Ibid.

Second, ICH guidelines create power effects in the sense that in certain settings, and as a consequence of the wealth effects just described, they promote the commercial interests of the pharmaceutical companies at the cost of 'public health' interests, that is the interest of patients to access drugs and treatments. This situation is well reflected in our discussion above of the effect of ICH GCP on non-commercial trials in Europe, and its effect on the development of drugs for neglected diseases.

Third, the ICH guidelines have increased the overall regulatory capacity of all regulatory authorities that have access to them.

Finally, as we have seen, many of these distributional effects can be linked back to the governance structure of the ICH. Being composed of drug regulatory authorities and the R&D pharmaceutical industry, the guidelines reflect commercial interests of high-income countries. These entities have indeed been the main beneficiaries of the ICH guidelines. On the other hand, the fact that academic researchers, developing countries and patients could not influence the content of these guidelines, and that consequently their interests are not reflected in the guidelines, have presumably led to the distributional effects that are to their detriment.

A separate question is to what extent, and through what mechanisms, does the ICH need to be responsive towards those that are adversely affected by its guidelines.

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