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The Public-Private Nature of Harmonization Networks[a]

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I. Explaining Public-Private Collaboration: Harmonization Networks on Health Standards

1. Introduction

In thinking about how I could best contribute to this joint session of the transnational private regulation and the informal international law making HiiL projects, and in line with the "horizontal questions", it became clear to me that the most interesting aspect to concentrate on would be on the public private nature of the international drugs and medical device harmonization networks, that is the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), the Global Harmonization Task Force (GHTF) (as well as International Cooperation on Cosmetics Regulation (ICCR)). All of these networks are what Cafaggi refers to, in his categorization of different public-private relationships, as "collaborative rule making" bodies. That is, they are bodies in which the regulatory authorities and the industry associations draft guidelines jointly. [1]

This paper relies on the case studies I have conducted,[2] and I do not repeat the findings here, except for some main points that are central for our debate today. The ICH is a network of drug regulatory authorities and industry associations from the US, Europe and Japan. The ICH was set up two decades ago, in 1990. The co-sponsors are the European Commission; the European Medicines Agency (EMA) (previously the Committee for Proprietary Medicinal Products (CPMP)); the European Federation of Pharmaceutical Industries' Associations (EFPIA); the Japanese Ministry of Health and Welfare; the Japan Pharmaceutical Manufacturers Association (JPMA); the United States Food and Drug Administration (FDA); the Pharmaceutical Research & Manufacturers Association of America (PhRMA) (formerly the PMA); and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA). IFPMA provides ICH's secretarial services, is

[1] F. Cafaggi, New Foundations of Transnational Private Regulation, EUI Working Papers, p.18.
[2] For a detailed account of the ICH, please see : Ayelet Berman, The Accountability of Transnational Regulatory Networks : The Case of the ICH) (henceforce, the « ICH paper »).Executive Summaries of the VICH and GHTF are also available. All papers are available on the www.informallaw.org site

funded by the three industry partners EFPIA, JPMA and PhRMA,[3] and is located in Geneva. The purpose of the ICH is to harmonize drug registration rules concerning the quality, efficacy and safety of drugs between its member countries, but in practice they have become global standards adopted by a wide range of countries.

The FDA and EMA are involved in additional harmonization networks that are structured and designed almost identically to the ICH. The VICH is a similar network of US, EC and Japanese drug regulatory authorities and industry associations for the harmonization of veterinary drug rules. The Global Harmonization Task Force is a network of medical devices regulatory authorities and industry associations form the US, Europe, Japan, Canada and Australia. Its goal is to harmonize medical devices registration rules.[4]

Part I of this paper seeks to understand why the regulatory authorities decided to collaborate with the industry rather than only among themselves, or "transgovernmentaly". Their goal being the harmonization of "social" regulations for the protection of public health –- regulations which domestically are within the authority of regulatory authorities ---a network of drug regulatory authorities could arguably have sufficed, or have been more appropriate. Why then this public private collaboration?

The existing literature on private regulation mentions several factors that explain the rise of private actors as international political actors, or as participants in international standard setting activities. Cafaggi in "New Foundation of Transnational Private Regulation" lists seven factors that have contributed to the emergence of TPR: the need for international harmonization, weakness of states as global rule makers, weakness of state regulation in monitoring compliance with international standards, weakness of public international law, technology, technical standards and governance of distributional effects.[5] Another factor often mentioned is the dependence of governments on expertise of the private sector in developing standards for highly

[3] http://www.ifpma.org/Issues/index.php?id=420.
[4] For a detailed overview of the VICH and GHTF, see my executive summaries on the informallaw.org site.
[5] Cafaggi, p.3-7.

specialized products. [6] This last factor, as demonstrated below, is indeed a major factor in explaining the public-private nature of the networks. But we will also point out to additional factors, in particular the role of US domestic politics, resource limitations of domestic bureaucracies, and historical institutionalism in bringing this collaboration about. These all will be discussed in detail below.

In trying to explain why the network was set up as a public-private collaboration, we can learn most by examining the ICH. The ICH was a "first". It was the very first time drug regulators and industry ever met beyond the bilateral level on such a large and public platform,[7] and it was the first time that the pharmaceutical industry acted as a global political player.[8] After the ICH had proved to be successful, the public-private network model was copied in the other networks during the 1990's. In understanding the original motivations, we, therefore can learn most from the ICH. The private-public nature of the later networks (VICH, GHTF, ICCR) is best explained by historical institutional theory, or path dependency.[9]

But before answering the question why the ICH was set up as a public-private network, I will shortly touch on two related preliminary questions that will allow us to better understand the public-private context. First: what were the motivations for harmonization? And second: why was network structure preferred over a formal intergovernmental organization (say the WHO)?

Part I of this paper is organized as follows: Section 2 studies the motivations for harmonization, and Section 3 explains why a network form was preferred over a formal intergovernmental organization. In section 4 we set out the factors that explain the public-private collaboration of the parties.

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[6] Buethe and Mattli, International Standards and Standard Setting Bodies, 448,453.

[7] The *Pharmaceutical Business News, 1991; DAVID W. JORDAN, International Regulatory Harmonization: A New Era in Prescription Drug Approval Notes, 25 Vand. J. Transnat'l L. (1992).494*

[8] DAN KIDD, *International Conference on Harmonization of Pharmaceutical Regulations, the European Medicines Evaluation Agency, and the FDA: Who's Zooming Who*, 4 Ind. J. Global Legal Stud (1996-1997).186. See also Kaitin, K. I. (2002) Editorial - Regulatory Reform at a Crossroads, *Drug Information Journal,* vol. 36, pp. 245-246.

[9] Institutional Path dependancy theory XXXX

Part II of this paper addresses accountability problems that rise from the joint industry-regulatory authority structure, in particular the problem of imbalanced representation, regulatory capture and industry's conflict of interest.

Finally, the paper focuses on the EC and the US, as these were the two dominant actors in the networks studied.

2. Why harmonize drug registration rules?

According to the existing literature, starting in the 1980's, with increased trade integration, divergent national standards became one of the most significant non-tariff barriers to trade.[10] In some cases, differing standards were introduced to protect domestic producers, and in others, they were "social", and protected legitimate public policy purposes, such as workplace safety or consumer, health or environment protection. In some cases the divergence simply reflected differences in tastes or accidents of history.[11]

These diverging regulations became to be considered non-tariff barriers to trade,[12] or what has been termed a "3rd generation barrier to trade".[13] According to economic theories these barriers increase the cost of production or entry for foreign producers, [14] and influence the competitiveness of industry.[15] Since "social" regulations such as on health or safety matters are recognized as protecting legitimate public policy purposes,[16] rather than calling for abolishing them, there was increased demand for

[10] Tim Buethe and Walter Mattli, International Standards and Standard Setting Bodies, p.447, in Oxford Handbook on Business and Government.
[11] Tim Buethe and Walter Mattli, International Standards and Standard Setting Bodies, p.447, in Oxford Handbook on Business and Government.
[12] Tim Buethe and Walter Mattli, International Standards and Standard Setting Bodies, p.447, in Oxford Handbook on Business and Government.
[13] Mauro Petriccione, *Reconciling Transatlantic Regulatory Imperatives with Bilateral Trade*, in GEORGE BERMANN, et al., Transatlantic Regulatory Cooperation: Legal Problems and Politcial Prospects (Oxford University Press. 2001).
[14] Regulatory Reform in the United States: Enhancing Market Openness through Regulatory Reform (OECD, 1999), p.18, http://www.oecd.org/dataoecd/23/46/2756360.pdf
[15] H. K. NORDÅS & H. KOX, Quantifying Regulatory Barriers to Services Trade. OECD Article
[16] Regulatory Reform in the United States: Enhancing Market Openness through Regulatory Reform (OECD, 1999), p.7. http://www.oecd.org/dataoecd/23/46/2756360.pdfso

international harmonization of such standards.[17] In the past two decades, harmonization is considered central to any liberal policy approach of market-oriented, trade and investment friendly regulation, and the OECD, for example, considers "the principle to harmonize" as key. [18]

As we shall see next, this production or entry cost argument in favor of harmonization was indeed a factor underlying harmonization in this case study. The desire to reduce R&D costs was the central rationale. That said, there were also additional considerations specific for public health that go beyond the general theory of harmonization. Moreover, the fact that the idea of harmonization actually *materialized* is related to regional and domestic political events that took place at the time: the emergence of the EC as an international actor, and domestic developments in the US, in particular political pressures on the FDA due to the "drug lag", as well the financial crisis of the agency. We discuss all of these factors in the following sections.

A. Costs, Patients, and Ethical Issues

The research-based pharmaceuticals industry (i.e., the industry that develops *new* drugs as opposed to generic drugs) is characterized by very high drug development costs. The average cost to develop a drug is USD 1.3 billion over the course of 10 to 15 years.[19]

INSERT DIAGRAM ABOUT R&D PROCESS AND COSTS (IFPMA site)

In order to be able to market a drug in any jurisdiction and to receive a market authorization, one must demonstrate to the authorities that the drug fulfills the criteria of safety, efficacy and quality. While the principles were and remain similar in the different jurisdictions (in particular in the developed world), over the years, the

[17] W. Mattli, Public and Private Governance in setting International Standards, 200 in Kahler and Lake, Governance in a Global Economy (2003)

[18] Regulatory Reform in the United States: Enhancing Market Openness through Regulatory Reform (OECD, 1999), p.9 http://www.oecd.org/dataoecd/23/46/2756360.pdf

[19] IFPMA site. In contrast, the development of a generic drug costs USD 2-3 million over the course of one year.

practices and specific regulatory guidelines diverged, resulting in duplicative testing of animals and human beings.[20]

In the 1980's, as research, development and manufacture of new drugs spread globally, but in particular among the US, Europe and Japan (which jointly held 95% of the market), the effect of the divergence in regulatory requirements became more important, and the functional interdependence between them grew, [21] requiring the regulatory authorities to depart from their traditional domestic environment and cooperate internationally. [22]

The consequences of diverging regulations were diverse and significant, and it was thought that harmonization would remedy part of these concerns. First, duplicate testing increased R&D costs for exporting companies, and in turn increased drug prices. High drug prices are a concern not only to companies but also to governments whose social security systems provide health coverage (EC),[23] or are generally concerned with the access of the public to medicines (US). Second, duplicate testing slowed down the access to new drugs in different jurisdictions, and the parties considered that the removal of duplicate testing would speed up the drug approval process, and allow for faster access of patients to drugs. [24] Third, duplicate testing also raised ethical concerns of unnecessary tests on animals and clinical trials on humans. Finally, harmonization would also allow for greater regulatory cooperation as harmonization allows regulatory agencies to be better able to benefit from data

[20] Fernand Sauer (Head of Unit « Pharmaceuticals » III/C/3, Commission of the European Communities), *European Harmonisation of Pharmaceutical Rules*. Speech presented at the 6th International Conference of Drug Regulatory Authorities, Ottawa 1991, the European Community and Pharmaceutical Harmonisation (the document is on file with me).
[21] Cafaggi, Transnational Private Regulation
[22] Fernand Sauer, Panel Discussion : The Way Forward, at the First ICH, 7 November 1991, Brussels. (document on file with me).
[23] Governments also fund drug development, usually at the very initial stage, through funding to universities.
[24] The FDA's Task Force on International Harmonization (Task Force Report) stated that the major public health benefits were: 1) to decrease the spread of disease within countries and across borders; 2) to increase consumer or patient access to safe and effective products; 3) to improve the quality, safety, and efficacy of imported drugs; and 4) to increase information transfer between countries on public health issues. See in JOSEPH G. CONTRERA, *The Food and Drug Administration and the International Conference on Harmonization: How Harmonized Will International Pharmaceutical Regulations Become?*, 8 Administrative Law Journal of the American University 927(1995).

evaluations by other agencies -- an important factor when virtually all regulatory agencies are short of resources.[25]

To sum, the rationale for harmonization was reduction of R&D costs, speeding up the access of patients to medicines, ethical concerns and improving the availability of information to regulators that are short in resources. The political and bureaucratic developments that actually allowed harmonization to materialize are discussed next.

B. European Pharmaceutical Harmonization

In Europe, as part of European integration, pharmaceutical harmonization among the 12 members had been in progress since the 1970's. In 1987 the process was nearing its end (planned for 1992), and the EC (the pharmaceutical unit in the Commission), encouraged by its regional success, started seeing the advantages of extending harmonization to its main trading partners Japan and the USA (which with the EC covered 95% of the market). Moreover, more practically, now that European rules were (almost) harmonized, the representation of Europe by the EC alone (rather than all the member governments) became feasible, and enabled the Community to exercise international responsibilities in the pharmaceutical sector.[26] Success of European pharmaceutical harmonization, hence, gave the EC pharmaceutical unit the capacity, [27] and the appetite to become an international player in the international pharmaceutical sector.

Around 1987, accordingly, the EC (pharmaceuticals unit) starts being active at the international level, in venues such as the International Conference of Drug Regulatory Authorities (ICDRA), the WHO and Codex Alimentarius. It also starts conducting bilateral discussions. In the context of and in parallel to GATT negotiations, the EC (pharmaceuticals unit) embarked on bilateral discussions with Japan, seeking to open

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[25] R.B. ARNOLD, *Objectives and Preparation of the Conference and the Role of the Workshops*, *in* Proceedings of the First International Conference on Harmonisation: Brussels 1991 (PF D'Arcy & DWG Harron eds., 1992).8

[26] Fernand Sauer (Head of Unit « Pharmaceuticals » III/C/3, Commission of the European Communities), *European Harmonisation of Pharmaceutical Rules*. Speech presented at the 6th International Conference of Drug Regulatory Authorities, Ottawa 1991, the European Community and Pharmaceutical Harmonisation (the document is on file with me).

[27] VOGEL, *The Globalization of Pharmaceutical Regulation*.11. (Saying that EC regional standards made it possible to seek agreement on global ones.)

its relatively closed market and harmonize rules among them.[28] The FDA, too, started conducting similar harmonization discussions with Japan in parallel.

The EC, now taking on an international role, considered that bringing the three parties together (rather than three sets of bilateral agreements) would produce more efficient results for all of the parties involved, and embarked on a mission to convince the US FDA and the Japanese Ministry of Health to go it together. [29] Discussions with the US and Japan began in 1988, but it was not until 1991 that the first ICH meeting took place in Brussels (and where the major principles of the ICH were endorsed).

To conclude, European pharmaceutical harmonization heading towards completion enabled the EC to take on an international role, which would not have been previously possible.

C. US Domestic Developments

The European initiative coincided with a situation in the US, which was rife for regulatory cooperation. Prior to the mid-1980s cooperation of the FDA with its foreign regulatory counterparts was essentially nonexistent. The FDA being by far the oldest drug regulatory authority enjoyed dominance unmatched by the other regulators and tended to impose its decisions on the rest.[30] It produced its own regulations without much regard, if at all, to what the others were doing, and its regulations came into global use through its dominance. Whilst its standards were more stringent than those of other countries, producers in other countries ended up implementing them, because the US was the biggest market and they wanted to enjoy the economies of scale.[31] Moreover, historically, the FDA was reluctant to surrender parts of the drug approval process, mostly due to the concern that this would lead to the approval of unsafe drugs for which it would be held responsible (In the EU and Japan other factors had been at work as well: the linkage between drug approval and

[28] Interview.
[29] Fernand Sauer (Head of Unit « Pharmaceuticals » III/C/3, Commission of the European Communities), *European Harmonisation of Pharmaceutical Rules*. Speech presented at the 6th International Conference of Drug Regulatory Authorities, Ottawa 1991, the European Community and Pharmaceutical Harmonisation (the document is on file with me).
[30] Interview.
[31] On why companies adopted US stringent standards, see Buethe and Mattli, International Standards and Standards Setting Bodies, 454 (citing David Vogel, Trading Up: Consumer and Environmental Regulation in a Global Economy, 1995 HUP);

government expenditure.[32]) From the 1960's to the 1980's, the FDA and other regulatory agencies were, hence, in what has been termed by political scientists as international "competition" between regulatory authorities, with FDA standards enjoying global dominance.[33]

In the late 80's, however, new global and domestic challenges were approaching the FDA, and the concern over loosing dominance demanded a reassessment of its non-cooperative approach.

At the international level, first, European pharmaceutical harmonization to be completed in 1992 raised competitiveness concerns.[34] If Europe (now such a large market) would become the first jurisdiction of choice for the registration of drugs, this would have adverse effects on US manufacturers that would have to develop and produce according to European standards, diminishing export opportunities.[35] Moreover, the FDA itself would loose its dominance over drug registration, and this could reduce the availability of drugs in the US.[36] Second, the globalization of R&D and manufacturing was also increasingly becoming a limiting factor for the FDA. These concerns and their link with harmonization are nicely reflected in a speech given at the time by then FDA-Commissioner James Benson, saying that: "As we move closer to a consolidated European market in 1992…and as democratic reforms take hold in Eastern Europe and international markets expand, American business will understandable press for a level playing field. We must assure that our regulatory requirements are harmonized with those of other nations to the maximum extent possible, so that American industries are not placed at a competitive disadvantage…"[37]

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[32] DAVID VOGEL, *The Globalization of Pharmaceutical Regulation*, 11 Governance (1998). 17.
[33] On competition between regulatory authorities, see Buethe and Mattli, International standards and SS Bodies, 453-454.
[34] In dealing with this concern, the FDA, accusing the EC of creating a "fortress Europe", went so far as to set up a "Europe 1992" Steering Committee.
[35] R.B. ARNOLD, *Objectives and Preparation of the Conference and the Role of the Workshops*, *in* Proceedings of the first International Conference on Harmonisation: Brussels 1991 (PF D'Arcy & DWG Harron eds., 1992).8
[36] R.B. ARNOLD, *Objectives and Preparation of the Conference and the Role of the Workshops*, *in* Proceedings of the first International Conference on Harmonisation: Brussels 1991 (PF D'Arcy & DWG Harron eds., 1992).8
[37] Speech: James S. Benson - DHHS Advisory Committee, **"STATE OF THE FOOD AND DRUG ADMINISTRATION",** Presented by **James S. Benson,** Acting Commissioner of Food and Drugs of

The FDA, hence, had to reassess its international role due to the threat of losing of its international dominance, and this nicely reflects what has been pointed out by Susan Strange to be as a weakening of the state due to economic integration.[38]
At the domestic level, there were other serious concerns that finally generated change in the FDA's approach. During the 1980's the US FDA had come under much criticism for the "drug lag", that is, the time it took the FDA to approve new drugs (in comparison to Europe). With the AIDS epidemic, [39] and with AIDS activists demanding quicker review of new drugs that were in the development "pipeline", this became a huge political issue which was difficult to deal with, especially at a time where the FDA had very limited resources and was near financial collapse.[40]

Several commissions were set up to review the FDA's problems, and to suggest reforms to the drug lag. Among the most important ones (in our context) were the Advisory Committee on the Food and Drug Administration, also known as the Edwards Commission, which issued its report in 1991.[41] Another body, the Council of Competitiveness, headed by VP Quayle, also issued its recommendations as to how to tackle the drug lag that same year.[42] In November 1991 eleven new reform measures of the drug approval process were introduced, expected to reduce the drug development time from an estimated 9.75 years to 7 years or 5.5 years for drugs

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the DHHS Advisory Committee on the Food and Drug Administration, May 18, 1990, http://www.fda.gov/NewsEvents/Speeches/ucm107156.htm

[38] Susan Strange, The Retreat of the State: The Diffuison of Power in the World Economy (Cambridge : Cambridge University Press, 1996) (to check)

[39] PRESS CONFERENCE WITH:VICE PRESIDENT DAN QUAYLE, SECRETARY OF HEALTH AND HUMAN SERVICES LOUIS SULLIVAN, DAVID KESSLER, COMMISSIONER, FEDERAL DRUG ADMINISTRATION (13 November 1991).

[40] PHILIP J. HILTS, *HEALTH SECRETARY TO REVAMP F.D.A.*, The New York Times June 8, 1991. (Saying that since the beginning of the 1980s the FDA had been in trouble, suffering from budget cuts at a time the Congress was adding to its responsibilities. The result was what officials inside and outside the agency described as a near-collapse as the agency failed to meet even deadlines that were set down in the law.) See also HEARING OF THE SENATE LABOR AND HUMAN RESOURCES COMMITTEE SUBJECT: FINAL REPORT OF THE PRESIDENT'S ADVISORY COMMITTEE OF THE FOOD AND DRUG ADMINISTRATION CHAIRED BY:SENATOR EDWARD KENNEDY, D-MA (MAY 15, 1991). (Saying that "The agency has significant problems and these are especially difficult to deal with in this time of limited resources. …The agency is over-extended, under-funded and whip-sore by multiple layers of bureaucratic review and restraint.")

[41] Institute of Medicine, Food and Drug Administration Advisory Committees (1992), p. 107, http://www.nap.edu/openbook.php?record_id=2073&page

[42] Council on Competitiveness. *Fact Sheet: Improving the Nation's Drug Approval Process* (Washington, D.C., 1991), cited in Institute of Medicine, Food and Drug Administration Advisory Committees (1992), p. 108, http://www.nap.edu/openbook.php?record_id=2073&page.

treating serious diseases. [43] International harmonization was among the reform proposals made, as it was believed that harmonized international regulations would lead to more rapid development of new products, and to a better exchange of data leading to faster approval of new drugs. [44]

As becomes clear by now, the FDA was mainly interested in harmonization for its own bureaucratic, "selfish" concerns. [Insert reference to bureaucratic theory]. It was envisaged as a tool that would help in solving its drug lag problem. Moreover, another major advantage from the FDA's perspective was that it would save costs to the bureaucracy, and that it would permit the FDA to make more efficient use of its resources:[45] It would eliminate the cost to the FDA of developing its own standards, [46] and it would also extend exponentially the technical expertise of the government, and save future FDA resources by enabling cooperation with other countries in the assessment of new products. [47]

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[43]For an overview of the reforms proposed, see *DRUG REVIEW REFORM ANNOUNCED*, PR Newswire November 13, 1991.; Drug Approval Overregulation, Michael R. Ward, http://www.cato.org/pubs/regulation/regv15n4/reg15n4e.html; WARREN E. LEARY, *F.D.A. Announces Plan to Speed Process for Approving New Drugs*, The New York Times November 14, 1991.; PRESS CONFERENCE WITH:VICE PRESIDENT DAN QUAYLE SECRETARY OF HEALTH AND HUMAN SERVICES LOUIS SULLIVAN DAVID KESSLER, COMMISSIONER, FEDERAL DRUG ADMINISTRATION.

[44]Task Force, Cited in TERESA PECHULIS BUONO, *Biotechnology-Derived Pharmaceuticals: Harmonizing Regional Regulations Notes*, 18 Suffolk Transnat'l L. Rev. (1995). Footnote 70; PRESS CONFERENCE WITH: VICE PRESIDENT DAN QUAYLE SECRETARY OF HEALTH AND HUMAN SERVICES LOUIS SULLIVANDAVID KESSLER, COMMISSIONER, FEDERAL DRUG ADMINISTRATION (13 November 1991).(SEC. SULLIVAN saying that: "…That is why I have welcomed the recent recommendations of the advisory committee on the FDA, the Edwards Commission, and the recommendations of the Competitiveness Council, which has generated many of the reforms we are announcing this morning…" And that "The improvements that we are announcing today are an important part of the ongoing series of management and regulatory reforms, many of which have been implemented to make drugs available to those who desperately need them, such as Americans who confront AIDS." And that "In addition, we will harmonize FDA's drug review standards with those of other industrialized nations. Currently, many of the drug studies in animals and humans are duplicated for each country in which a drug is marketed. The development of common procedures would reduce such duplication and speed the approval of drugs worldwide." And that "international harmonization, which will allow for the exchange of precise data with other countries and assure a safe and quicker introduction to markets of certain therapies.")

[45] REPORT OF THE FDA TASK FORCE ON INTERNATIONAL HARMONIZATION, (Dec. 1992), reprinted by FOI Services, Inc., (Cited in TERESA PECHULIS BUONO, *Biotechnology-Derived Pharmaceuticals: Harmonizing Regional Regulations Notes*, 18 Suffolk Transnat'l L. Rev. (1995). Footnote 70); 60 FR 53078 (Policy on Standards)

[46] OMB Circular A-119, sect. 2 (what are the goals of the government in using voluntary consensus standards?)

[47] PRESIDENT BILL CLINTON & VICE PRESIDENT AL GORE, National Performance Review: REINVENTING REGULATION OF DRUGS AND MEDICAL DEVICES (April 1995).Id. at 35 The Policy on Standards at p. 53078 defines the FDA's goals in participating in international harmonization as: To safeguard U.S. public health, to assure that consumer protection standards and requirements are

The ICH was considered the first accomplishment in this international harmonization initiative,[48] and in the years that followed, the FDA whole- heartedly embraced the idea of international harmonization and expanded it from drugs to other areas of FDA regulation. [49] By 1992 a FDA Task Force on International Harmonization had recommended that: "the FDA must begin to consider international standards to a greater degree in the development of FDA standards, and where appropriate, to adopt international standards that provide the required level of consumer protection."[50] It also recommended an overall FDA policy on international harmonization. Soon thereafter, FDA's strategic plan began to recognize standards as the premier focus of the agency's international activities.[51] Harmonization of FDA's regulatory requirements and guidelines with those of other countries was embraced in 1995 as a pillar of Clinton's National Performance Review "Reinventing Drug and Device Regulation (April 1995)". There, international harmonization was identified as a high priority initiative across FDA programs.[52] Finally, the FDA issued in 1995 a "Policy on the Development and Use of Standards with Respect to International Harmonization of Regulatory Requirements and Guidelines".[53] Nowadays the FDA has a "Harmonization and Multilateral Relations Office" within its "Office of International Programs",[54] and it is involved in several harmonization networks, most notably the ICH, VICH, GHTF, ICCR, Codex Alimentarius, and regionally in PANDRH (Pan American Network for Drug Regulatory Harmonization).

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met, to facilitate the availability of safe and effective products, to develop and utilize product standards and other requirements more effectively, and to minimize or eliminate inconsistent standards internationally."

[48] *DRUG REVIEW REFORM ANNOUNCED*. LEARY. PRESS CONFERENCE WITH:
VICE PRESIDENT DAN QUAYLE
SECRETARY OF HEALTH AND HUMAN SERVICES LOUIS SULLIVAN
DAVID KESSLER, COMMISSIONER, FEDERAL DRUG ADMINISTRATION.

[49] Id. at 34.

[50] ERIC M. KATZ, *Europe's Centralized New Drug Procedures: Is the United States Prepared to Keep Pace*, 48 Food & Drug L.J. 577(1993). Footnote 17

[51] "Policy on Standards", at p. 53078.

[52] PRESIDENT BILL CLINTON & VICE PRESIDENT AL GORE, National Performance Review: REINVENTING REGULATION OF DRUGS AND MEDICAL DEVICES (April 1995).

[53] 60 FR 53078 (11 October 1995) "International Harmonization; Policy on Standards". It should be noted that while the policy itself does not define which bodies are considered standard bodies to which the policy applies, it is clear from the background section of the policy [60 FR 53078], that standard activity not only includes formal IOs, but also these networks: Under the heading "Standards Programs and Practices within FDA", under the subheading "Foods and Veterinary Medicine", it refers to VICH. Under the "Biologics and Drugs" subheading, it refers to "ICH". Under the "Medical Devices and Radiation-Emitting Products" subheading, it refers to "GHTF. Thus, it can be concluded that the intent is to apply the policy to these standard setting networks too.

[54] http://www.fda.gov/InternationalPrograms/HarmonizationInitiatives/default.htm

In sum, from the FDA's perspective, international harmonization was a tool to (i) cope with European competition (and competition between bureaucracies), and (ii) to solve domestic political problems, as well as (iii) overcome resource limitations within the bureaucracy. The FDA put it best when it said that "Recognizing the possible synergy between its domestic policy and its international policy priorities, in the 1990's, the FDA sharpened and focused its planning for enhanced alignment of FDA and international standards.[55]

D. Conclusion

The main rational for the international harmonization of drug regulations is reduction of R&D costs, and in turn, lower drug prices. Additional rationales from a health perspective are quicker access to drugs, and ethical concerns of duplicate testing on animals and humans. The idea of harmonization would not have materialized, however, were it not for certain political factors, namely that rise of the EC as an international political actor, and the domestic political concerns and scarcity of resources in the FDA. [56]

But once an understanding had been reached that harmonization would be beneficial, why was a network institutional form preferred over an intergovernmental organization, say the WHO? This is the question we examine in the next section.

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[55] Policy on Standards, 53078

[56] See ICH paper. DEPARTMENT OF HEALTH AND HUMAN SERVICES/FOOD AND DRUG ADMINSITRATION, Policy on Development and Use of Standards with respect to International Harmonization of Regulatory Requirements and Guidelines (60 Federal Register 53078, 11 October 1995).The FDA Policy on Standards explains, at 53078, the goal of harmonisation as follows: "In recent decades, great changes in the world economy, together with expanded working relationships of regulatory agencies around the globe, have resulted in increases interest in international harmonization of regulatory requirements. Increased international commerce, opportunities to enhance public health through cooperative endeavors, and scarcity of government resources for regulation have resulted in efforts by regulatory agencies of different nations to work together on standards and harmonize their regulatory requirements. Such harmonization enhances public health protection and improves government efficiencies by reducing both unwarranted contradictory regulatory requirements and redundant applications of similar requirements by multiple regulatory bodies. Harmonization facilitates cooperation in regulatory activities." The FDA further explains "Harmonization enhances public health protection and improves government efficiencies by reducing both unwarranted contradictory regulatory requirements and redundant applications of similar requirements by multiple regulatory bodies. FDA's harmonization efforts are intended to pool regulators' resources by developing standards for public health protection; reduce industry's compliance costs in the global market; and, minimize impediments to bringing safe food and safe and effective treatments to consumers and patients around the world." See http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofInternationalPrograms/ucm115262.htm

3. Institutional Choice: Why was a network form preferred over a formal intergovernmental organization?

Given this interest in international harmonization, this section deals with the following institutional question: why was a network form preferred over a formal intergovernmental organization, or a committee within the auspice of the WHO?

International harmonization of pharmaceutical standards is within the WHO's authority. Article 2(ii) of the WHO's constitution requires the WHO to "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products". More specifically, Resolutions adopted in 1971[57] and in 1987[58] refer to the WHO's role in "the establishment of internationally acceptable basic requirements for drug registration" and "to foster the exchange of information among Member States on drugs including registration and marketing practices". Given this mandate, why did the parties opt for a tripartite network instead?

Existing literature on transgovernmental regulatory networks tends to be descriptive, but it does mention several reasons for the rise of transgovernmental regulatory cooperation. The reasons typically mentioned are functional interdependence,[59] functional equivalency of the bureaucracies,[60] growing technical complexity better handled by regulators than by foreign affairs officers,[61] and technical changes that make communication easier. [62]

The reasons usually mentioned for preferring the network form to an intergovernmental organization, are flexibility,[63] speed, [64] small group size, like-

[57] EB47.R29
[58] WHA37.23
[59] Scahrpf 1993b (125), Finnemore 1996 (325), Keohane and Nye 1974 (41-42), Pollack and Scahffer 2001(27) and Raustiala 2002 (4))
[60] Raustiala 2002 (14-21) Finnemore 1996(325)
[61] Raustiala 2002 (26), Keohane and Nye (1974) 210
[62] Raustiala 2002 (26), Keohane and Nye (1974) 210
[63] Slaughter
[64] Slaughter, Eilstrup (206) ;

mindedness, and homogenous interests.[65] Mette Eilstrup mentions additional factors, including short time horizons.[66]

These explanations are all in the realm of rationale choice theory, focusing on the costs versus the benefits linked to the choice of institution. My research below supports these findings, but adds additional reasons, for instance that the shift from treaty based IOs can be explained by the desire to collaborate with private actors in a manner that would be legally impossible in such organizations. Most notably, the research demonstrates that the international network form is a "copy paste" exercise of European network models, and can, accordingly be explained by historical institutional theory, or path dependency.

A related question, which this section will also address, is whether the network functions as an alternative or rather is complementary to the formal intergovernmental organization (WHO).

A. Small and homogenous group: Most WHO Members were not interested in new drugs

One reason that the network model was preferred over the WHO is that the research based pharmaceutical market was dominated by the US, Europe and Japan –holding about 95% of the market. Most other WHO members (i.e. developing countries) were simply not interested in an initiative to harmonize rules for the registration of *new* drugs. That would have been very low on their priority list, as their main concern was generic drugs.[67] A network where only those with genuine interest have a seat was, thus, set up.[68]

It should be noted that nowadays networks such as the ICH or the Basel Committee, both set up in the late 1980's/beginning of 1990's, are criticized for being "clubs".[69] But the point above demonstrates that at the time of their establishment, they were

[65] Slaughter, Zaring, Raustiala
[66] Mette Eilstrup-Sangiovanni, Varities of Cooperation: Government Networks in International Security, in *Miles Kahler* (ed.), *Networked Politics ;Agency, Power and Governance,* , 206-209
[67] Interviews.
[68] BRAITHWAITE, (212
[69] Zaring

relatively appropriate. With the shift in global powers, their structure increasingly raises problems of non-inclusion (a topic that is beyond the scope of this paper).

B. WHO inadequacy

Lack of WHO leadership: While international harmonization was part of its mandate (see above), the WTO was a bureaucratic organization that proved incapable of leading such an initiative.[70] The WHO had been active in promoting international standards with respect to pharmaceutical products in the late 1960s and early 1970s,[71] but it was unable to provide leadership to international harmonization. WHO leadership failed because at the WHO there has tended always to be a "veto coalition" to block progress on most fronts. [72]

WHO too bureaucratic and slow: Moreover, in contrast to the WHO, the limited number of participants and the network structure enabled a flexible and efficient consensus based body.[73] The WHO was included as an observer to maintain contact with the other WHO members.[74] The network model was, hence, a tool to circumvent the rigidity, inefficiency and slowness of the WHO, and supports the existing literature on transgovernmental regulatory networks mentioned above.[75]

As we can see, the move away of certain actors from the WHO to networks due to the impossibility to reach agreement among a large amount of members is very similar to the phenomenon we witness on the international trade front, and the move from multilateral trade negotiations in the WHO to regional trade agreements. This development is, hence, another element of the breakdown of the multilateral order, and part of a greater shift from multilateralism to regionalism (but this topic is beyond the scope of this paper).

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[70] Interview.

[71] J. IDAENPAEAEN HEIKKILAE, *Role of WHO in Harmonization of Requirements for Pharmaceutical Products*, *in* Proceedings of the first International Conference on Harmonisation: Brussels 1991 (PF D'Arcy & DWG Harron eds., 1992).

[72] BRAITHWAITE, (212

[73] Various interviews

[74] ICH paper; Fernand Sauer, « The European Community Regulatory Perspsective : ICH2 represents the outcome of 4 years of intense and continuous international efforts », ICH2 Panel Discussion, 27 October 1993 (document on file with me)

[75] ANNE-MARIE SLAUGHTER, A New World Order (Princeton University Press. 2004)

C. *Copying the European example*

The ICH was a first in cooperation amongst drug regulatory authorities, and the mode of cooperation was something to be determined in an *ad hoc* manner. The US and Japan did not have any prior experience in transgovernmental regulatory cooperation, and the EC, being the only party with previous experience (from European harmonization), proposed that the parties follow the European pharmaceutical harmonization example. There was simply no other model for regulatory cooperation around, and its advantages struck a bell with them.

The European harmonization model, had been a network of drug regulatory authorities from 12 member states, and collaborated with the European Federation of Pharmaceutical Industries and Associations (EFPIA), an association representing the research-based pharmaceutical industry. European harmonization was described as "a constant and free exchange of views between the 12 regulatory authorities, their experts, and the experts from industry…outside the Community this consultation has been widened to include the EFTA countries, Japan, the USA, and more widely the World Health Organization (WHO) and also other parts of the world, more recently Eastern Europe."[76]

The ICH model was, accordingly, to a large extent a "copy paste" exercise of European institutional models to the international level, and can be best explained by historical institutional theory, or path dependency theory.[77] It also reflects the diffusion of European practices to the international level.[78]

D. *Inclusion of the Pharmaceutical Industry*

The parties sought to join forces with industry associations as co-sponsors (the reasons for which we describe in the next section), and this would have been impossible within the WHO.

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[76] Fernand Sauer, Panel Discussion : The Way Forward, at the First ICH, 7 November 1991, Brussels. (Document on file with me).
[77] Paul David, Why are institutions the Carriers of History? Path Dependence and the Evolution of Conventions, Organizations and Institutions
[78] Reference on diffusion.

E. Temporary Topic and Proved Commitment

Finally, the parties did not set up an alternative treaty based organization because the ICH was intended to be a temporary topic to be concluded within 3 to 4 years. [79] Moreover, a binding treaty would have required the involvement of the political level, but the latter prefer not to interfere except on very important or expensive topics. Since in practice the parties proved to be complying with the gentlemen's agreements, a binding agreement was deemed unnecessary.[80]

F. Conclusion

To conclude, while rational choice theory, which stresses efficiency and costs, [81] has indeed played an important role in the selection of a network form over the WHO, there is also a historical institutional, or path dependency element in copying the European model. The networks set up after the ICH – the VICH, GHTF and ICCR, being set up after the ICH by similar actors, and following the ICH's success, are also best explained by path dependency theory. [82]

Their preference not to set up an alternative treaty based organization amongst themselves (say like NAFTA) may also be attributed to the (initially intended) temporary nature of the project. It would be interesting to examine whether in other case studies the temporary nature of projects also contributed to their informal nature. Finally, experience over the life cycle of a project is also a factor in the formality/ informality decision.[83] When compliance proved not to raise any problems after the "gestation" stage, the parties felt that there wasn't any need (to waste time and money) for a binding agreement.

Finally, it is interesting to point out that harmonization (and more generally, networking) with other regulatory authorities is now embedded in the US Federal Food, Drug and Cosmetic Act. Section 903(3) of the FD&C Act mandates the FDA to engage in harmonization networks, and determines that it is among the FDA's

[79] Interview
[80] Interview
[81] The Rational Choice of International Institutions, Snidal et al.
[82] On the distinction between historical institutionalism (focusing on path dependancy), rational choice institutionalism (focusing on efficiency) and sociological institutionalism (focusing on legitimacy), see Peter Hall and Rosemary Taylor, Political Science and the Three New Institutionalisms, *Political Science* 1996, 936-957
[83] On life cycle theory, see Bernstein, Regulating Business.

mission to "participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements;" [84] Sec. 803(3) of the FD&C Act, which is concerned with the FDA's Office of External Relations, requires the FDA to engage in cooperation with foreign governments in order to reach harmonization, stating that:: "The Secretary shall regularly participate in meetings with representatives of other foreign governments to discuss and reach agreement on methods and approaches to harmonize regulatory requirements." [85] It also states that "The Secretary shall support the Office of the United States Trade Representative, in consultation with the Secretary of Commerce, in meetings with representatives of other countries to discuss methods and approaches to reduce the burden of regulation and harmonize regulatory requirements if the Secretary determines that such harmonization continues consumer protections consistent with the purposes of this Act."[86]

As to the question whether the network is an alternative or complementary to the intergovernmental organization (WHO), in light of the discussion above, we can conclude that on the one hand the network form is an *alternative* to the WHO, in particular for developed countries. Harmonization could have taken place in the WHO or in the network, but the parties preferred the network for the reasons mentioned above. Moreover, being high-income countries, they had the resources to set up an effective alternative forum, a capacity poor countries do not have. On the other hand, harmonization of drug/medical devices etc. rules is a very specific topic, and the WHO covers a much broader range of topics that are of relevance to ICH members (including on diseases, medicines, medical devices, standards and many other issues). In that sense, the ICH is *complementary* to the WHO, as it addresses a very specific and limited topic, beyond the broad range of topics encompassed and coordinated by the WHO. The WHO also brings developing and developed countries together and coordinates between them – a factor that tends to be missing in networks that are usually characterized by like-mindedness, but that is still high in need (say on the spread of communicable diseases). The need for both kind of institutions will,

[84] 21 USC §393.
[85] 21 USC sec. 383.
[86] [Reference]

therefore, remain, and Slaughter's original prediction that networks would supersede IOs and represent the emerging "real new world order",[87] does not seem plausible.

4. Explaining collaboration with private actors: Why were the harmonization networks set up as collaborative, public-private networks?

After a (long) introduction explaining why the parties sought to harmonize their drug registration rules, and why a network form was preferred over cooperation in the auspices of the WHO, the purpose of this section is to explain why the ICH was set up as a collaborative, public-private rule making network.

Given the apparent cost advantages of international harmonization one would easily be mistaken to presume that the pharmaceutical industry was the driving force behind the ICH process. In reality, however, that was not the case.[88] As mentioned above, the EC took leadership and successfully succeeded in convincing the industry (in particular the internationally-oriented segment of this industry) that it would benefit from this endeavor.

The benefits the industry could gain from harmonization would be the reduction of duplicative testing, gaining regulatory certainty, and consequently the reduction of costs. The pharmaceutical industry, being a heavily regulated industry, seeks as much certainty, clarity and consistency as possible in terms of what regulators expect from both them and their competitors. [89] Harmonized guidelines would provide such clarity and remove duplicative testing, which in turn would reduce R&D costs. Moreover, in order to recover the high R&D costs, companies must market their products internationally,[90] and harmonization would simplify that.

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[87] SLAUGHTER, *The Real New World Order* p. 184
[88] See IFPMA (1997) *The ICH Harmonisation Process,* Available at: http://www.ifpma.org/ich4 (27 April 2002). [not available] [From Tim Reed's PhD]; Interview.
[89] ERICA SMITH SEIGUER, JOHN J., *Perception and Process at the Food and Drug Administration: Obligations and Trade-Offs in Rules and Guidances*, 60 Food & Drug L.J. (2005).23-24, 29-30
[90] USHIDA, *Presentation by Mr Ushida, Minister and Charge[apostrophe] d'affaires of the Japanese Mission to the European Community*, *in* Proceedings of the first International Conference on Harmonisation: Brussels 1991 (PF D'Arcy & DWG Harron eds., 1992).7

That said, for many pharmaceutical companies development costs were not a burning issue at the time (nowadays they are as the R&D pipeline is drying up),[91] and some pharmaceutical companies lacked interest in the long- term savings in R&D costs, as their leadership was primarily interested in immediate cash flow. [92] Moreover, European companies operating in Japan also feared to loose the competitive advantage (over other foreign competitors), which they had slowly established in the local climate. [93] But overall, in the three regions, the industry gave its full support, from the very beginning, to the initiative.[94]

But why then did the regulators, in particular the EC, want to have the industry on board? As mentioned above, the subject matter is social regulations, a topic that is within the authority of regulatory authorities and which could (and should?) have remained within a transgovernmental ambit. Why then were industry associations brought into the process? In what comes next, we set out the main factors underlying this development.

A. Path Dependence: Copying the European example

First, and probably foremost, as mentioned above, the ICH was designed in light of the European pharmaceutical harmonization model. As noted above, in the EC, the framework for harmonization, headed by the Committee on Proprietary Medicinal Products (CPMP), was based on open and extensive consultation both during the preparation and prior to adoption of the technical requirements, and extensive interaction between scientific experts and transparent discussion between regulatory authorities and industrial partners. [95] Since most of pharmaceutical R&D is performed

[91] interview
[92] Fernand Sauer, Panel Discussion : The Way Forward, at the First ICH, 7 November 1991, Brussels. (document on file with me).
[93] At the time it was very difficult for foreigners to integrate in the closed Japanese system, so companies that had achieved this were weary about giving it up.
[94] Fernand Sauer, « The European Community Regulatory Perspsective : ICH2 represents the outcome of 4 years of intense and continuous international efforts », ICH2 Panel Discussion, 27 October 1993 (document on file with me) , *CONFIDENTIALITY URGED IN DRUG REGS*, Pharma Marketletter October 5, 1992. (US Pharmaceutical Manufacturers Association vice president and general council, Bruce Brenner, saying that the association "strongly supports the FDA initiatives in fostering cooperation efforts with foreign governments to facilitate international harmonization of the drug regulatory system.")
[95] MARTIN BANGEMANN, *Welcome Address by Mr. Martin Bangemann, Vice President of the Commission of the European Communities*, *in* Proceedings of the first International Conference on Harmonisation: Brussels 1991 (PF D'Arcy & DWG Harron eds., 1992).

by industry, the EC created fora for exchanges between industry experts (through EFPIA) and experts from CPMP, [96] and EFPIA became an active supporter of the harmonization process. [97] In fact, already in its very first bilateral efforts in Japan in 1987, EFPIA joined the mission to consult them on the obstacles to trade.[98]

It should be noted that this opening up of doors by the EC to business interests was not a phenomenon limited to the pharmaceutical unit, but an approach generally taken at the time by the EC (as well as EP) with the emergence of a distinct EU public policy. This openness was recognition by EU institutions that they no longer had the resources to deal with the expansion of policy without the active participation of technical experts.[99]

In the EC collaboration was based on a network of national regulators in the CPMP, with industry participating as a discussant.[100] In the ICH (and later on in the other networks), the industry's position became more institutionalized with permanent members in the expert working groups and Steering Committee. [101] Nevertheless, the inclusion of industry has its origin in European harmonization, and therefore, is well explained by path dependency theory.

B. The Dependence of Regulatory Authorities on the Industry for Information

The existing literature on the rise of business as a political actor and standard setter– whether at the domestic level or at the transnational level – has related this phenomenon to the dependency of government on business for information. The recognition by government agencies of their lack of expertise to develop standards for

[96] The CPMP had working parties on quality, safety, efficacy, pharmacovigiliance and biotechnology..
[97] Fernand Sauer, « The European Community Regulatory Perspective : ICH2 represents the outcome of 4 years of intense and continuous international efforts », ICH2 Panel Discussion, 27 October 1993 (document held by me) Fernand Sauer (Head of Unit « Pharmaceuticals » III/C/3, Commission of the European Communities), *European Harmonisation of Pharmaceutical Rules*. Speech presented at the 6th International Conference of Drug Regulatory Authorities, Ottawa 1991, the European Community and Pharmaceutical Harmonisation (the document is on file with me).
[98] interview
[99] David Coen, European Business-Government Relations, p.290 in David Coen, Wyn Grant, Graham Wilson (eds.), The Oxford Handbook of Business and Government
[100] Interview
[101] See ICH paper, GHTF and VICH executive summaries.

highly specialized products and the practical experience to assess how feasible and efficient a particular technical solution may be, has led governments throughout the advanced industrialized countries to draw increasingly on the expertise of the public sector.[102]For example, the dependency of EU institutions on business due to their demand for increased specialized technical expertise to formulate policy has been described.[103] In studies on business lobbying in the United States, business is said to provide information and technical guidance that other interests may not be able to provide.[104] . The shift from intergovernmental standardization to transnational (non-governmental) standardization has also been explained by the lack of technical expertise and financial resources to deal with ever more complex and demanding standard issues.[105] In sum, this dependency on information has generated change in the involvement of business in domestic and transnational standard setting, Indeed, Susan Strange was among the first to point out that changes in information were among the factors that alter "the basic relationship in any political economy –that between authority and market."[106]

This theoretical work is very much supported by the results of this case study. With the speed in which pharmaceutical science develops, in wanting to stay on the cutting edge of research, the regulatory authorities are dependent on industry as an "informant" for their expertise. 95% of the drug development takes place within the industry, and the industry is ahead of the regulators when it comes to new scientific developments. [107] Moreover, industry draws the best scientists, has much more resources, manpower and expertise on technical issues than regulators, which are always short of money, cutting jobs etc. Since this information is often kept secret, [108] in keeping up with the state of the art, regulators are dependent on the information

[102] Buethe and Mattli, International Standards and Standard Setting Bodies, 453.
[103] David Coen, European Business-Government Relations, p.302.
[104] Bauser, Pool, and Dexter 1963 ; Heinz et al. 1993 (cited in Timothy Werner and Graham Wilson, Business Representation in Washington, DC (Oxford Handbook on Business and Government), p.264
[105] Buethe and Mattli, International Standards and Standard Setting Bodies, p.448
[106] Susan Strange, « Territory, State, Authority, and Economy : A New Realist Ontology of Global Political Economy », in Robert W. Cox (ed.), The New Realisms : Perspectives on Multilateralism and World Order (Tokyo : United Nations University Press, 1997), p.9. (to check)
[107] This point was raised in all interviews. In most countries, except for the FDA, regulators first hear about a new drug when a request for approval is submitted. Therefore, the industry is ahead of regulators in all scientific matters. Dr. Petra Doerr, Interview.
[108] JOE COLLIER & IKE IHEANACHO, *The pharmaceutical industry as an informant*, The Lancet (November 2, 2002).7.

provided by the industry. Industry expertise is also critical in maintaining a competitive edge.[109]

But regulatory authorities are not only dependent on industry for scientific or technical expertise. The multinational industry, with its global production and organizational structures, is also best informed about the regulatory differences between the countries, and what the obstacles to trade are.[110]

Finally, the pharmaceutical industry, being well organized, has the capacity to contribute, making their increasingly important political role in standard setting plausible.[111]

To conclude, from the regulator's perspective, the inclusion of industry in a collaborative rule making process is a tool to overcome the information imbalance that prevails between regulators and the pharmaceutical industry, on two main kind of topics: science and trade barriers.[112] This dependency on information can also be portrayed as a transferal of costs from regulators to private actors,[113] as the information is a "subsidy" that interest groups provide.[114] In Europe, where the social security systems cover medicine expense of the public, this "cost transfer" was justified by the fact that given the chronic crisis of their social security organizations,

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[109] House of Representatives, Committee Reports, 104th Congress (1995-1996), House Report 104-390, NATIONAL TECHNOLOGY TRANSFER AND ADVANCEMENT ACT OF 1995; Committee on Science, Committee Views: SECTION 12. STANDARDS CONFORMITY, http://thomas.loc.gov/cgi-bin/cpquery/?&dbname=cp104&sid=cp104jN8jw&refer=&r_n=hr390.104&item=&&&sel=TOC_79005&

[110] Interview;
[111] US Congress, p.90
[112] ELAINE C ESBER, *The Way Forward: The US. Position*, PROCEEDINGS OF THE FIRST INTERNATIONAL CONFERENCE ON HARMONISATION 549(1991). 551 (Saying, "Major actors in the private sector may be well situated to identify the practical differences in regulatory requirements among regions and to assess the economic and trade consequences that those differences entail. They also may be able to support the scientific research, data collection and data analysis that will provide the raw material for eventually arriving at joint solutions.") See also EUROPEAN MEDICINES AGENCY, Overview of Comments Received on Draft Guideline "Procedure for EU Guidelines and Related Documents within the Pharmaceutical Legislative Framework" (24 June 2005).p.12
[113] Cafaggi also mentions the issue of cost transfer from states to private actors, p.7.
[114] Said in the context of business lobbying in Washington DC, but applicable here too. Hall and Deardorff 2006 (cited in Business in Washington, p.264)

also industry had the *responsibility* to take a more active role in cost containment and optimization of the use of pharmaceutical research funds. [115]

C. US Domestic Developments

The "drug lag" political problem

While the EC proposed a harmonization model based on the inclusion of industry, the FDA was reluctant about talking with industry. The domestic drug lag crisis discussed above also sheds light on why the US departed from its traditional path in this context. Here too, the FDA considered that the development of standards in collaboration with industry would facilitate the development and approval of new drugs. [116]

It should be noted that the reform committees mentioned above also examined whether the existing "style of interaction" between the FDA and the pharmaceutical industry was appropriate to ensure efficiency and quality in the drug review process, and went on to propose new procedures for improving the liaison between regulators and industry in the drug review process,[117] such as lightening up the conflict of interest rules. [118]

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[115] Fernand Sauer, Panel Discussion : The Way Forward, at the First ICH, 7 November 1991, Brussels. (document held by me).

[116] Addendum to 11th report on OMB implementation, p.43

[117] HHS Press release on "Advisory Committee on FDA Final Report", 15 May 1991, at http://www.hhs.gov/news/press/pre1995pres/910515.txt; , *DRUG REVIEW REFORM ANNOUNCED*, PR Newswire November 13, 1991. WARREN E. LEARY, *F.D.A. Announces Plan to Speed Process for Approving New Drugs*, The New York Times November 14, 1991. PRESS CONFERENCE WITH: VICE PRESIDENT DAN QUAYLESECRETARY OF HEALTH AND HUMAN SERVICES LOUIS SULLIVANDAVID KESSLER, COMMISSIONER, FEDERAL DRUG ADMINISTRATION (13 November 1991).

[118] Institute of Medicine, Food and Drug Administration Advisory Committees (1992), p. 107, http://www.nap.edu/openbook.php?record_id=2073&page (The Edwards Commission (1991) found that the conflict of interest policy was causing delays and difficulties in appointing many highly qualified and respected advisors to advisory committees, thereby adversely affecting the FDA's access to scientific expertise.); Council on Competitiveness. *Fact Sheet: Improving the Nation's Drug Approval Process* (Washington, D.C., 1991), cited in Institute of Medicine, Food and Drug Administration Advisory Committees (1992), p. 108, http://www.nap.edu/openbook.php?record_id=2073&page (Quayle's Council of Competitiveness recommended contracting with experts outside of the federal government for reviewing drug approval applications.)

Accordingly, the willingness to cooperate with industry from the FDA's perspective can also be linked to the "drug lag" crisis. From the FDA's perspective, such collaboration enabled (at least partly) outsourcing part of its FDA's duties to outside experts, hence gaining more expertise knowledge, but at lower costs. Given the crisis, efficiency and effectiveness were preferred over "Weberian" bureaucratic accountability.

US favors private standard setting

Another plausible argument is that collaboration with industry associations in international standard setting was in line with the attitude to standard setting that had already prevailed at the time in the US, and reflected just another expression of this attitude. [I still need to conduct some more research/interviews to verify this argument]

The point is that the US has always favored standard setting by private actors. [119] OMB Circular A-119 on "Federal Participation in the Development and Use of Voluntary Consensus Standards" [120], in force since 1976 and codified as the National Technology Transfer and Advancement Act (NTTAA) in 1995, required all federal agencies to rely, whenever possible, on domestic or international private sector-based, voluntary consensus standards in lieu of government-unique standards. They encourage the federal agencies to participate in the standard setting bodies to ensure that the standards created are usable by federal agencies and consistent with their needs. [121] The purpose is, clearly, to reduce to a minimum the reliance by agencies on government-unique standards and to encourage collaboration with private standard setters. [122]

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[119] OMB Circular A-119, sect. 2 (what are the goals of the government in using voluntary consensus standards?); Global Standards: Building Blocks for the Future (March 1992). P.15.
[120] Sec. 6, OMB Circular No. A-119, 58 Fed. Reg. 57,643 (Oct. 26, 1993). The OMB Circular A-119 had been issued several times. The first time in the 1970s, and the NTTAA codified this longstanding policy. See SMG 9100.1, under "background". Sec 12, NTTAA.
[121] Regulatory Reform in the United States: Enhancing Market Openness through Regulatory Reform (OECD, 1999), p.19, http://www.oecd.org/dataoecd/23/46/2756360.pdf; http://standards.gov/standards_gov/index.cfm; JOANNE R. OVERMAN, *The National Technology Transfer and Advancement Act. 10 Years of Public-Private Partnership*, 58 Standards Engineering (January/February 2006).
[122] House of Representatives, Committee Reports, 104th Congress (1995-1996), House Report 104-390, NATIONAL TECHNOLOGY TRANSFER AND ADVANCEMENT ACT OF 1995; Committee on Science, Committee Views: SECTION 12. STANDARDS CONFORMITY,

These rules equally applied to the FDA and may have been a consideration when the FDA decided to include industry associations in the standard setting activity of the ICH. In fact, the FDA had historically embraced the idea of relying on private standard setting, and had already been collaborating in a range of domestic, international, public and private standard setting activities outside the Agency– (e.g. WHO, OECD, ISO, IEC, ANSI and many more).[123] The FDA had implemented the Circular and NTTAA in a FDA "Regulation on Participation in outside standard-setting activities" (1979),[124] and in 1995 the FDA adopted a "Policy regarding the development and use of standards with respect to international harmonization of regulatory requirements and guidelines", and later on a Staff Manuel Guide.[125] These rules direct the FDA to adopt standards developed through non-government organizations (NGOs) and intergovernmental international standards organizations, in lieu of internally developed government-unique standards and guidance.[126]

This collaborative private-public approach to standard setting was also supported by the Administrative Conference of the United States, an independent federal agency dedicated to improving the administrative process, which issued in 1979 a recommendation on "Federal agency interaction with private standard-setting organizations in health and safety regulation."[127] In view of the "wealth of technical

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http://thomas.loc.gov/cgi-bin/cpquery/?&dbname=cp104&sid=cp104jN8jw&refer=&r_n=hr390.104&item=&&&sel=TOC_79005& (Saying that the rules focus the attention of the agencies on the need to work with these voluntary consensus standards bodies, whenever and wherever appropriate, rather than issue government specific standards.)

[123] 21 CFR 10.9(a); SMG 9100.1, under "background".
[124] 21 CFR 10.95 [Initial regulation and consequent amendments: 44 FR 22323, Apr. 13, 1979, as amended at 46 FR 8455, Jan. 27, 1981; 52 FR 35064, Sept. 17, 1987; 54 FR 9035, Mar. 3, 1989; 70 FR 40880, July 15, 2005; 70 FR 67651, Nov. 8, 2005] This regulation encourages FDA participation in outside standard-setting activities that are in the public interest and specifies the circumstances under which FDA employees can participate in various types of standards bodies.
Read more: http://cfr.vlex.com/vid/95-participation-outside-standard-setting-19704312#ixzz1DHYgK9D0
[125] In 1995 the FDA "Policy regarding the development and use of standards with respect to international harmonization of regulatory requirements and guidelines" was adopted. More recently, SMG 9100.1, the "FDA staff manual guide on "common standards--development and use of standards" (2007) has been adopted and provides insights into the history of FDA standard setting.
[126] SMA 9100.1, under "background"
[127] CODE OF FEDERAL REGULATIONS, TITLE 1--GENERAL PROVISIONS, CHAPTER III--ADMINISTRATIVE CONFERENCE OF THE UNITED STATES, PART 305--RECOMMENDATIONS OF THE ADMINISTRATIVE CONFERENCE OF THE UNITED STATES, 1 C.F.R. s 305.78-4, s 305.78-4 Federal agency interaction with private standard-setting organizations in health and safety regulation (recommendation No. 78-4), available at http://www.law.fsu.edu/library/admin/acus/305784.html

knowledge and expertise" which members of private voluntary consensus standard bodies posses (and which agency staff do not), agency participation "may result in the development of standards that adequately address considerations of health or safety more efficiently and effectively than if the agency seeks independently to formulate standards." Hence, it recommended that agency's authorized to issue health or safety regulations" should draw on the knowledge and information available in active technical committees that develop relevant voluntary consensus standards, and should interact in accordance with this recommendation with technical committees…" and that "Agencies with authority to issue health or safety regulations should consider the use of existing relevant voluntary consensus standards in developing mandatory standards."[128]

What all of the above demonstrates is that collaboration with industry in standard setting was in line with the attitude that prevailed (and still does) in the US. (Though some further research is needed to verify this link).[129]

The rationales from a domestic US perspective to collaborate with (domestic or international) private standards were to increase bureaucratic efficiency and effectiveness by relying on the expertise of the private sector, while at the same time reducing (time and human) costs.[130] Collaboration would also better safeguard the

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[128] ADMINISTRATIVE CONFERENCE OF THE UNITED STATES, recommendation No. 78-4, Federal agency interaction with private standard-setting organizations in health and safety regulation [44 FR 1357, Jan. 5, 1979

[129] See also Cafaggi, that mentions technical standard-setting by private actors at the international level as influencing the emergence of private regulatory regimes.

[130] On the rationales for relying on private standards see SMG 9100.1 under "background" (saying, inter alia, that "Effective and meaningful participation in the organizations that develop standards for the products FDA regulates is critical. Encouraging these organizations to develop the standards FDA needs advances the interests of both the Agency and the industry. Information exchange to encourage coordination of technical discussions and information dissemination can enable more effective engagement with our stakeholders and develop efficiencies in the standards setting processes. In addition, FDA can take advantage of the management resources of standards-developing organizations (SDOs) to create standards, thereby better using limited FDA resources. FDA can exercise leadership in these SDOs to encourage development of the best possible standards and improve technical requirements."); DEPARTMENT OF HEALTH AND HUMAN SERVICES/FOOD AND DRUG ADMINSITRATION, Policy on Development and Use of Standards with respect to International Harmonization of Regulatory Requirements and Guidelines (60 Federal Register 53078, 11 October 1995) 53081. ("Another benefit of participating in the development of standards at both domestic and international levels is that in sharing technical information with technical groups and professionals outside FDA, staff members have opportunities to learn of other viewpoints on an issue, to establish

public interest (we discuss this aspect in Part II in the section on "Public Interest Safeguards")

Philosophical approach of deregulation and markets

Finally, let's not forget that discussions concerning the ICH were taking place the in the late 1980's, beginning of 1990s, and the openness towards collaboration with industry can also be linked back to the political philosophical approach that prevailed at the times. The Weberian hierarchical model of bureaucracy was being criticized for being inadequate to deal with the complexities and uncertainties created by increasing diversity and rapid technological innovation in an increasingly dynamic regulatory environment.[131] In the US these are the Reagan (1981-1989) and Bush (1989-1993) years, and the dominant political philosophy or attitude of the time is one of markets and deregulation. There was a growing policy of reliance on the private sector to supply government needs for goods and services. [132]

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scientific leadership, and to remain informed of state of-the-art science and technology."[130] And further that "the interaction between CDRH and the manufacturing and health communities that frequently occurs during the standards development process and provides knowledge and insight into the use of products, problems and the effectiveness of solutions.") Mrs. MORELLA, 142 Cong. Rec. H1262 (daily ed. February 27, 1996) [Hearing concerning the NTTAA] (saying that the effect of adopting private sector-developed, voluntary consensus standards would be a reduction in agency operating costs); Mr. BROWN, 142 Cong. Rec. H1266 (daily ed. February 27, 1996) [Hearing concerning the NTTAA] (saying that it would be much cheaper and efficient for government agencies to rely on private-sector voluntary consensus standards, which are considered high in expertise and developed in an open manner, than reinventing the wheel. Moreover, these groups are better equipped with their expertise and involvement than the Government to understand all points of view and to keep up with the state of the art in technical standards.); FDA Addendum to 11th report on OMB implementation, p.43 (saying that by being involved in outside standard setting activities, "economies of time and human resources are often realized in solving problems when consensus-building activities are undertaken and conducted in open, public arenas. The working together of FDA staff with other professionals outside the agency in standards bodies effectively multiplies the technical resources available to FDA." PRESIDENT BILL CLINTON & VICE PRESIDENT AL GORE, National Performance Review: REINVENTING REGULATION OF DRUGS AND MEDICAL DEVICES (April 1995). (Under the Clinton presidency, the FDA was required to review its regulatory processes to determine which requirements could be reduced or eliminated so as to reduce costs, without lowering health and safety standards. In the Report, the FDA proposes several reforms. One of the recommendations is "Harmonizing FDA's drug and device testing requirement with those of other countries, thus expediting worldwide marketing of new products by reducing duplicative testing." It says that work has already begun on drug development and should be expanded to other areas of FDA regulation. In addition, *where appropriate, FDA will adopt international standards developed by multilateral or private sector standard development bodies*. In the long run, this will bring *cost savings* to industry and enhanced opportunities for export of US goods, and may lessen the time needed to bring new products to market." [italics added])

[131] LES METCALFE, *The weakest links: building organisatiunal networks for multi-level regulation*, OECD Regulatory Cooperation for an Interdependent World (1994).

[132] OMB Circular A-119, sect. 2 (what are the goals of the government in using voluntary consensus standards?) .34. He cites Moe, saying that "While American society might want the Federal Government to "do something" about a particular problem area, there is also an aversion on the part of

In fact, many of the reforms introduced at the FDA by the Council on Competitiveness and Edwards Commission mentioned above were a culmination of the process initiated by the "Task Force on Regulatory Relief" (also known as the Deregulatory Task Force) headed by then VP George Bush. [133] The Task Force identified those areas deemed most in need of a relaxation or outright freedom from Government controls.[134]

D. Conclusion

To conclude, the desire of regulatory authorities to collaborate with industry in the standard setting process can be attributed to several main factors: First, it was copying the European collaborative model, and is hence best understood as institutional path dependency. A second factor is the existence of information imbalances between regulatory authorities and industry, and consequently dependence of the former on the latter. Third, the domestic problems (FDA with limited resources standing before burgeoning duties), but also attitudes within the US generated support.

Overall, this process can be understood as one in which domestic regulators, required to get more expert work done, yet with limited resources, outsource the work to private actors which provide them with high expertise at relative lower costs. The costs incurred to the private actors are, obviously, set off by the benefits of having clear, coherent and (almost) identical rules in more markets. This development is similar to the developments we have already seen at the domestic level, and in that sense, are not new. That said, transnational collaboration would not have been possible without the pharmaceutical industry's capacity and resources to perform international roles.

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a substantial portion of the public towards creating a new department or agency since this is seen as just more 'bureaucracy'.

[133] PRESS CONFERENCE WITH:VICE PRESIDENT DAN QUAYLE SECRETARY OF HEALTH AND HUMAN SERVICES LOUIS SULLIVAN DAVID KESSLER, COMMISSIONER, FEDERAL DRUG ADMINISTRATION.

[134] RICHARD L. BERKE, *Deregulation Has Gone Too Far, Many Tell the New Administration*, The New York Times 11 December 1988.

Finally, it is interesting to note that nowadays collaboration or regulatory authorities with private actors at the international level is expressly authorized in certain domestic legal systems. For example, Sec. 903 of the Federal Food, Drug, and Cosmetic Act (FD&C Act),[135] which sets out the FDA's mission, was amended in 1997[136] and since then determines that "the [FDA] shall (3) participate through appropriate processes *with representatives of other countries* to reduce the burden of regulation, *harmonize* regulatory requirements, and achieve appropriate reciprocal arrangements" and that it will "(4) …carry out [*its mission]* … in consultation with experts in science, medicine, and public health, and *in cooperation* with *consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products*. " (italics added)

[135] 21 USC § 393
[136] Food and Drug Modernization Act of 1997

II. The Public-Private Nature of Harmonization Networks and Accountability Concerns: Regulatory Capture and Industry's Conflict of Interest

1. Introduction

As depicted in the first part of this paper, from a regulator's perspective, a joint public-private collaboration on standard development is an arrangement that is justified by the dependency of regulators on expertise, and their resource restrictions. Overall, hence, networks of regulators and industry are geared towards improving the efficiency of the regulatory process, improving its expertise, and thereby legitimizing its output.[137] We can presume, accordingly, that collaborative structures should improve the epistemic legitimacy of the network, that is, the normative authority derived from recognized "expert" knowledge.

That said, looking at the networks' from a political legitimacy perspective, a perspective that focuses on its "democratic accountability" or how accountable it is towards its stakeholders, the joint industry-regulatory authority structure raises several concerns.

The concern is, first, that of regulatory capture by particular interests. The more the pharmaceutical industry influences the perspective of the regulatory agency--so it comes to adopt their interests over and above those of patients--the more the agency could be said to be captured. [138] The problem of capture by the industry at the cost of patients and a public health perspective is aggravated by the fact that the beneficiaries of the regulations (patients and consumers) are not equal participants. [139] The problem is like what has been recognized by Lindblom and Dahl as stakeholder bias in terms

[137] Scharpf/input vs. Output legitimacy
[138] See John Abraham, 1
On capture theory, see M.H. Bernstein, Regulatory Business by Independent Commission (New York, 1955)
[139] See JOHN ABRAHAM, *The Pharmaceutical Industry as a Political Player*, The Lancet (2002). P.6.
BLURRING THE BOUNDARIES, NEW TRENDS IN DRUG PROMOTION, by Barbara Mintzes, ©HAI-Europe 1998, http://www.haiweb.org/pubs/blurring/blurring.intro.html

of institutional power and access,[140] at the cost of consumers and patients that do not have an equal voice. Second, we have a situation where the industry drafts the guidelines, but is at the same time affected by them. This raises the suspicion that their interests may affect their impartiality, and raises the problem of conflict of interests. [141] There are different definitions for the term "conflict of interest", but it generally reflects a situation where a financial (or other) interest could impair an individual's objectivity [142] The substantive underlying concern to all of these notions is that the public interest (i.e., in this case, the safety, efficacy or quality of the drugs, medical devices etc.) will be undermined due to industry interests in cost reduction.[143]

Jut to recall,[144] EFPIA, PhRMA and JPMA, the pharmaceutical industry associations and the drug regulatory authorities essentially enjoy equal rights in the guideline drafting process. They may both suggest a topic for harmonization (i.e., set the agenda), both hold an equal amount of seats in the experts working groups, and in the Steering Committee, and all decisions are reached by consensus. The only, albeit, important, exception, is that the final guideline is signed off by the regulatory authorities alone. However, if one of the industry parties has strong objections to the adoption of the guideline, the regulatory parties may agree to submit the document for

[140] C. Lindblom, R. Dahl, Politics and Markets (1977) (cited in Pamela Camerra-Rowe and Michelle Egan, International Regulators and Network Governance, p. 412 in Oxford Handbook on Business and Government.)

[141] The National Academies Policy on Committee Composition and Balance and Conflicts of Interest say that for any committee that will be used in the development of reports for use in the government regulatory process « the focus of the conflict of interest inquiry is on the identification and assessment of any interests that may be directly affected by the use of such reports in the regulatory process ». The concern is that if an individual has specifc interests (primarily financial) that could be directly affected by the regulatory process, the individual's objectivity could be impaired.

[142] Examples of definitions: The WHO says that a "Conflict of interest means that the expert or his/her partner *…or the administrative unit with which the expert has an employment relationship*, has a *financial or other interest that could unduly influence the expert's position with respect to the subject-matter being considered*. An *apparent conflict of interest* exists when an interest would not necessarily influence the expert but could result in the expert's objectivity being questioned by others. A potential conflict of interest exists with an interest, which any reasonable person could be uncertain whether or not should be reported.[142]

The US National Academies, an institution which under US federal develops expert reports to the federal government (on science, medicine, engineering and other), defines a conflict of interest as "any financial or other interest which conflicts with the service of the individual because it (1) could significantly impair the individual's objectivity or (2) could create an unfair competitive advantage for any person or organization." See The National Academies (National Academy of Sciences National Academy of Engineering Institute of Medicine National Research Council) POLICY ON COMMITTEE COMPOSITION AND BALANCE AND CONFLICTS OF INTEREST FOR COMMITTEES USED IN THE DEVELOPMENT OF REPORTS May 12, 2003, available at http://www.nationalacademies.org/coi/bi-coi_form-0.pdf

[143] On public interest theory of regulation, see Baldwin and Cave, Understanding Regulation

[144] For a detailed overview, see the ICH paper.

further consultation. Further, patient organizations – that could balance out the industry's view and represent the patients' point of view -- do not have any seat in the ICH, though they may comment during the consultation stage. Beyond the historical reasons for not including patient organizations (they simply were not as prominent two decades ago), the explanation often made for not including them has been that they lack the necessary scientific expertise. [145] Finally, substantial resources are made available by research-based industry, for example it is the IFPMA, which coordinates the process and provides the secretariat. The structure of the other networks, VICH and GHTF, is very similar.

To put these notions within our (INLAW) accountability terminology,[146] situations of imbalanced representation and capture may lead the decision-maker (regulator) to adopt the particular interests of one stakeholder over the diffused interests of other stakeholders (the public). Or in using Cafaggi's regulatory structure: the preference by the regulator of the interests of the regulated firm, at the cost of the beneficiary of the regulation.[147]

Indeed, these concerns are not new, and claims have been raised previously, saying that the ICH is an industry–driven process, while the regulatory authorities have difficulty maintaining a public health-oriented approach.[148] This joins a broader political science literature that has also addressed the problem of capture by business interests in international standard setting.[149]

Part II f this paper is organized as follows. Section 2 covers public interest safeguards that have been put in place to deal with these concerns. Section 3 explains why the pharmaceutical sector is in particular vulnerable to conflicts of interest and capture. Section 4 discusses the impact capture and conflicts of interests are said to have had on the level of standards issued by the ICH. Section 5 provides an overview of

[145] Interviews
[146] INLAW framing paper
[147] Cafaggi, New Foundations, p.9
[148] WHO, Report of a WHO Meeting: The Impact of Implementation of ICH Guidelines in Non-ICH Countries.p 16.
[149] Buethe and Mattli, International Standards and Standard Setting Bodies, 453. Mattli, Public and Private Governance in Setting International Standards, p. 209, 225, in Kahler and Lake (eds), Governance in a Global Economy

international and domestic rules on committee composition and conflicts of interest. Section 6 concludes this part. Part III is a conclusion of Part I and Part II of this paper.

2. Public Interest Safeguards

Concerns about capture and the lack of consideration of non-industry interests in standard setting bodies is not a new problem or one that is limited to this case study In fact, it's a problem that has long been acknowledged to potentially exist in other (domestic and transnational) private standard setting bodies.[150] In view of tackling this problem, governments have imposed on such bodies organizational or procedural requirements in order to encourage compliance with public interest safeguards.[151] In other cases, governments have sought to protect the public interest by working in collaboration with private standard setting bodies. [152]

In the US, OMB Circular A-119 "Federal Participation in the Development and Use of Voluntary Consensus Standards and in Conformity Assessment Activities", issued by the Office of Management and Budget, and codified in 1995 by the "National Technology Transfer and Advancement Act" encourages the participation of federal agencies in private sector-based, voluntary consensus standard-setting bodies. These rules encourage the participation of federal representatives in these bodies "to increase the likelihood that the standards they develop will meet both public and private sector needs."[153]

Moreover, since federal agencies may only participate in such standard setting bodies that develop so called "voluntary consensus standards",[154] US rules actually have "extraterritorial" force not in the inter-state sense so well known in areas such as antitrust, but rather in the transnational sense, as they indirectly set out the procedural conditions that these transnational bodies must abide to. A voluntary consensus

[150] Mattli, Public and Private Governance in Setting International Standards, p. 200, in Kahler and Lake (eds), Governance in a Global Economy
[151] Mattli, Public and Private Governance in Setting International Standards, p. 200, in Kahler and Lake (eds), Governance in a Global Economy
[152] Mattli, Public and Private Governance in Setting International Standards, p. 200, in Kahler and Lake (eds), Governance in a Global Economy
[153] 4.a.(1) of the Circular
[154] Section 6 of the Circular, section 12 of the NTTAA

standards body is defined by the following attributes: openness, balance of interest, due process, an appeals process, and consensus,[155] and federal agencies (in theory, as we shall see below) will only collaborate in bodies that have these attributes.

The FDA implemented OMB Circular A-119 in its binding regulation entitled "Participation in outside standard setting activities" [156] In line with the Circular, the regulation encourages FDA participation in standard setting activities that are outside the FDA (domestic and international), and sets out certain factors with which the standards development activity and the expected standard must conform with. With respect to participation of FDA employees in private standard setting activities, [157] it determines certain minimum standards.[158] The main points are that (i) the activity must be based on sound scientific and technological information, (ii) will not be designed for the economic benefit of any company, group, or organization, will not be used for such antitrust violations as fixing prices or hindering competition, and (iii) that the group or organization responsible for the standard-setting activity must have a procedure by which an interested person will have an opportunity to provide information and views on the activity and standards involved, without the payment of fees, and the information and views will be considered.

Building upon the regulation, the agency published in 1995 a "policy on the development and use of standards with respect to international harmonization of regulatory requirements and guidelines."[159] The policy sets out certain factors with which the standards development activity and the expected standard must conform. These requirements are partly a repetition of the regulation but include additional

[155] 4.a. (1) of the Circular
[156] 21 CFR sec 10.95:
[157] The regulation distinguishes between the rules that apply to standard setting activities "by …United Nations organizations and other international organizations and foreign governments pursuant to treaty,"(21 CFR 10.95(c)) and standard setting activities by "private groups and organizations". (21 CFR 10.95(d).)
[158] 21 CFR 10.95(d) (6) (5). Or (d)(5) (verify)
[159] 60 FR 53078 (11 October 1995) "International Harmonization; Policy on Standards". It should be noted that while the policy itself does not define which bodies are considered standard bodies to which the policy applies, it is clear from the background section of the policy [60 FR 53078], that standard activity not only includes formal IOs, but also these networks: Under the heading "Standards Programs and Practices within FDA", under the subheading "Foods and Veterinary Medicine", it refers to VICH. Under the "Biologics and Drugs" subheading, it refers to "ICH". Under the "Medical Devices and Radiation-Emitting Products" subheading, it refers to "GHTF. Thus, it can be concluded that the intent is to apply the policy to these standard setting networks too.

requirements. The important requirements in our context are that (i) the standard is based on sound scientific and technical information and permits revision on the basis of new information; (ii) The development process for the standard is transparent (i.e., open to public scrutiny), complies with applicable statutes, regulations, and policies, specifically including §10.95 and OMB Circular A-119, and is consistent with the codes of ethics that must be followed by FDA employees ….

Further, the document sets out the "General Principles" that should guide the FDA in its "international harmonization efforts".[160] These include that (i) the harmonization activity should be consistent with U.S. Government policies and procedures and should promote U.S. interests with foreign countries, (ii) the harmonization activity should further FDA's mission to protect the public health, and that (iii) FDA's input into international standard setting activities should be open to public scrutiny and should provide the opportunity for the consideration of views of all parties concerned (…) (italics added)

Moreover, the FDA's standards on ethical conduct apply to the participation of FDA employees in domestic or international standard setting activities that involve representatives of the private sector. [161] There is a whole set of laws and regulations that set out principles and standards and on ethical conduct by government employees.[162] These include limitations and restrictions on acceptance of gifts, meals, travel expenses, and the like.[163] These rules are intended to help ensure that decisions FDA employees make, and actions they take, are not, nor appear to be, tainted by any question of conflict of interest. [164]

Coming back to the case of the ICH, the FDA insisted on inclusion of safeguards in line with these rules. [165] The idea underlying this demand is that transparency, participation, and due process, ethics standards etc. would shield the process from

[160] 60 FR 53078.
[161] SMG 9100
[162] http://www.fda.gov/AboutFDA/WorkingatFDA/Ethics/ucm071702.htm
[163] See Executive Order 12731 of October 17, 1990
"PRINCIPLES OF ETHICAL CONDUCT FOR GOVERNMENT OFFICERS AND EMPLOYEES"
http://www.usoge.gov/laws_regs/exec_orders/eo12731.aspx
[164] http://www.fda.gov/AboutFDA/WorkingatFDA/Ethics/default.htm
[165] Interview

inappropriate industry influence, and would guard the integrity of the scientific-based process. Moreover, the very fact that regulators participate was also considered a safeguard of the public interest.[166] The involvement of so three regulatory authorities, each with its internal bureaucracy and extensive internal deliberations and involvement of so many people (effectively a form of internal accountability) is an additional shield against undue influence in favor of particular interests (as opposed to where only a single person is at work and much more easily corruptible). [167]

[Have not covered EU law]

Against this backdrop, the question then is whether due process, adherence to code of ethics, and the participation of regulators in the role of "guardians" of the public interest are sufficient safeguards against undue industry influence. This at least appears to be the US approach, as this is the approach adopted in its rules on participation in (domestic and international) private standard setting (whether generally such as in OMB Circular A-119 and in NTTAA or specifically for the FDA as in the regulation and policy).

This question is open to debate. To some extent the openness of the process may certainly insulate against undue influence. But even were that the case, the networks in this study, though considered "voluntary standard setting bodies" in the US, do not adhere to all of the due process requirements required under US law, such as the availability of an appeals procedure, or balance of interests (Industry may set the agenda and prepare the first draft. Other stakeholders may only comment at a later stage, after the first draft has already been prepared. In the context of domestic administrative law it has often been argued that the right to comment is not adequate as in reality it may serve as ineffective window dressing.[168]) So the first conclusion would be that the procedures would need to be improved and adapted to the requirements under US law.[169]

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[166] Interview
[167] Interview
[168] STEWART, *Accountability, Participation, and the Problem of Disregard in Global Regulatory Governance,* .p.4. Wallach xxx.
[169] See the ICH paper for a detailed overview of accountability problems in the rule making procedure.

But even if these were improved, we are still left with the problem of conflict of interest of the industry participants. At the domestic level, where a conflict of interest is identified, due process is not considered sufficient to insulate against it and there is a whole set of conflict of interest rules which we will examine below. In such cases, why then would due process be a sufficient safeguard at the transnational level, in particular given that these rules are then adopted at the domestic level?

Before moving on, it is important to point out, that different institutions take different approaches to the term "conflict of interest". It can be defined broadly (such as that a conflict exists when a *financial or other* interest could *unduly influence* the expert's position[170]), or rather narrowly (such as that the *financial* interest must have a *direct and predictable effect* on the individual's interest.[171]) Since the networks deal with rule –making, and hence a rather removed topic, rather than make specific decisions say regarding a certain drug, according to the narrow approach one could well argue that there isn't any problem of conflict of interest. In this paper, I'm not getting into the "nitty gritty" of definitions as the intention is to make a general, principle point, rather than an overly legalistic one. More importantly, conflict of interest is very much also regarded as a question of *perception*, and not so much whether undue influence has indeed taken place.

In the next section we explain why conflict of interest and regulatory capture is of particular importance in the pharmaceutical sector, and why, accordingly, the collaboration between the drug industry and drug regulators at the transnational level needs to be further regulated.

3. Conflict of Interest and Regulatory Capture in the Pharmaceutical Sector

Looking beyond the ICH, and more generally at the pharmaceutical sector, it is important to stress that the problems of conflict of interest and capture are inherent to the pharmaceutical sector. The pharmaceutical sector is in particular vulnerable because the value of its market is very high (estimated at over US$ 600 billion), and

[170] WHO definition
[171] http://www.fda.gov/AboutFDA/Transparency/Basics/ucm222231.htm

hence an attractive target for abuse. Another factor making the pharmaceutical sector particularly vulnerable to corruption is the *information imbalance* between the various players. As noted above, information is not shared equally and not all players have the necessary information to make informed judgments and independent assessments of the quality, safety and efficacy of medicines.[172]

Just think of the recent debate on the WHO's reaction to the bird flu pandemic. There were accusations that the WHO had been influenced by the pharmaceutical industry in its decisions, and that key scientists involved in WHO pandemic planning were funded by pharmaceutical firms that stood to gain from the guidance they were drafting and that the WHO had not published the conflict of interest.[173] A recent European Parliament Committee report also criticized the EC for it's handling of the pandemic, saying it was fraught with conflicts of interest that lead to suspicion of "undue influence" and harmed the authorities' "overall credibility".[174]
Another recent example is the French scandal regarding Servier's diabetes drug. A preliminary inspection suggested that Afssaps, France's drug regulator, had been tolerant towards this drug, despite its serious risks, due to industry influence over the regulatory process.[175]

Regulatory capture too is especially problematic in pharmaceutical matters because assessment of a drug is not as objective as you would hope, and regulators rely on industry for information. The risk-benefit assessment of drugs has a high degree of

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[172] WHO, A Framework for Good Governance in the Public Pharmaceutical Sector (Working Draft for Field Testing and Revision, October 2008, by Dr. Eloy Anello), http://www.who.int/medicines/areas/policy/goodgovernance/WHO-GGMframework.pdf

[173] Deborah Cohen and Philip Carter, « Conflicts of Interest : WHO and the pandemic flu 'conspiracies' », *BMJ* (3 June 2010), available at http://www.bmj.com/content/340/bmj.c2912.full. The WHO was also heavily criticised in a report headed by British MP Paul Flynn for the Council of Europe Parliamentary Assembly. See also Zosia Kmietowicz, WHO admits to "inconsistencies" in its policy on conflicts of interest, BMJ, (15 June 2010), available at http://www.bmj.com/content/340/bmj.c3167.full

[174] European Parliament press release, 25 January 2011, www.europarl.europa.eu/en/pressroom/content/20110125IPR12478/html/Swine-flu-lessons-to-learn-from-disproportionate-EU-response; *Ian Schofield,* MEPs take tough stance on EU H1N1 pandemic response, *26 January 2011,* Regulatory Affairs Pharma, http://www.rajpharma.com/productsector/pharmaceuticals/MEPs-take-tough-stance-on-EU-H1N1-pandemic-response-309196?autnID=/contentstore/rajpharma/codex/d16ee0d6-294d-11e0-a765-d94a6db3342c.xml

[175] *Ian Schofield,* French industry: Mediator crisis a one-off, not a symptom, *03 February 2011,* Regulatory Affairs Pharma, http://www.rajpharma.com/productsector/pharmaceuticals/French-industry-Mediator-crisis-a-one-off-not-a-symptom-309620

technical uncertainty, which is inherent in toxicology, clinical trials, and epidemiology. The pharmaceutical industry and patients interests in the level of the standards are not equal. Pharmaceutical companies want the safety and efficacy standards of regulators to be high enough to avoid frequent drug disasters, which bring the industry into disrepute, but not so high that they threaten their commercial viability.[176] For example, a study published by the British Medical Journal a couple of years ago demonstrated that industry reviews of medicines was less transparent than reviews of non-profit organizations, and that industry supported reviews were more also more likely to endorse a medicine without reservations. [177] It is, therefore, crucial to know how far regulators are willing to give the industry the benefit of scientific doubt about safety and efficacy of their product.[178]

While the problem of capture is best tackled by balanced representation and an open and transparent process that allows for broad participation of differing views, the inherent conflict of interest in the pharmaceutical sector makes it important to regulate this aspect also at the transnational level.

4. The impact of regulatory capture on public health

The purpose of this section is to address the impact regulatory capture/conflicts of interest by industry is said to have had on the agenda setting, and in particular on the levels of standards enacted by the ICH. The standards in turn, it is argued, have had distributional effects on market structure and on access to medicines.

First of all, critics have argued that the industry has dominated the agenda and that industry representatives have initiated most guidelines adopted for international harmonization.[179]

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[176] JOHN ABRAHAM, *The Pharmaceutical Industry as a Political Player*, The Lancet (2002).1

[177] Transparency: BMJ Report finds Industry Reviews of Medicines Less Transparent than Non-Profit Reviews (10 October 200g), Regulatory Affairs Journal-Pharma http://www.rajpharma.com/home/news/Transparency-154236?autnID=/contentstore/rajpharma/codex/2006nov5034.xml (Citing *British Medical Journal*, Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review, 6 October 2006, http://bmj.bmjjournals.com/cgi/rapidpdf/bmj.38973.444699.0Bv1)

[178] John Abraham, 2

[179] Abraham & Reed 2001).

Second, conflicting claims have been made regarding the level of the standards. While many consider ICH guidelines to be "state of the art", some have argued that the inclusion of industry may lead to lower standards,[180] saying that by controlling ICH discussions, and excluding consumer groups from these discussions, the pharmaceutical industry's goal is clear, namely to pave the way for new drug approvals worldwide with as little testing as possible. [181] Several papers have sought to demonstrate, based on an analysis of the rules issued that indeed in at least several instances rules benefiting the industry at the cost of patients have been issued.[182] For example, Tim Reed has argued that while the ICH process may lead to more rapid access to new drugs, the regulatory streamlining has not been achieved without compromising drug-safety standards. Abrahams also mentions examples where apparently safety considerations were compromised. [183]

On the other hand, there have also been opposite claims that harmonization with industry partners has led to a "race to the top".[184] The WHO, for instance, has pointed

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[180] WALLACH. She argues that US standards on the potential carcinogenicity of pharmaceuticals were weakened to harmonize with the ICH proposal. Further, she argues that the United States also has a role in lowering other nations' standards by pushing U.S. policy into international standards. For example, the United States is trying to push its use of placebos in clinical trials onto other countries through the ICH. (The alternative method used in other countries is to compare the new drug to the effects of drugs that have already been approved and are on the market, rather than comparing them in placebo-controlled trials.)

[181] Id. at 833.

[182] Tim Reed PhD, Public Citizen Paper

[183] ABRAHAM.6 refers to several examples: Before the ICH, most of the 17 regulatory agencies in the EU, Japan, and the USA required expedited reporting (i.e. Within a matter of days) of serious, non-serious, or both ADRs, even if they were expected with the new drug. However, opting for the least safe option on this issue, the ICH recommended that expedited reporting to regulators "is not generally appropriate for expected, unrelated, or non-serious cases".[GORDON AJ., *Clinical safety data management: ICH guideline and reasoning*, *in* Proceedings of the second international conference on harmonisation. (Harron DWG D'Arcy PF ed. 1994).] The ICH also arguably adopted a low standard when considering the carcinogenic risk posed to patients in clinical trials. Even though it is acknowledged by Japanese and US regulators that some clinical trial data must be produced for 12 months before marketing approval, and that the FDA requires carcinogenicity testing for drugs to be used by patients for more than 3 months, the ICH recommended that no carcinogenicity testing needs to be completed before exposure of patients to new drugs for more than 3 months, or even 6 months, during clinical trials.[ABRAHAM.6, refers to INTERNATIONAL CONFERENCE ON HARMONIZATION, Guideline on the need for carcinogenicity studies of pharmaceuticals (1995).]
Similarly, the regulatory agencies agreed to reduce the minimum duration of patient's treatment in clinical trials from 12 to 6 months in initial marketing applications, despite research made available to them showing that about a quarter of serious ADRs that happened in clinical trials of 1 year duration arose after 6 months, and about one eighth first occurred after 6 months.[ANON, *ICH2: status of tripartite harmonisation initiatives*, Scrip 1993. And KAITIN KI BROWN JS, MCAUSLANE N, ET AL., *Population exposure required to assess clinical safety: report to the ICH working group*, Drug Information Journal (1996).[To read]

[184] Interview, WHO official.

out that the ICH has relied increasingly on advanced pharmaceutical technology in its standard setting, on the assumption that this technology will lead to greater safety of new drugs.[185] The additional safety benefits from these rigorous standards, the WHO says, have not been demonstrated, but the costs incurred by manufacturers meeting the requirements are significant.[186] The underlying suspicion is that the multinational pharmaceutical industry is taking advantage of the situation at the cost of small manufacturers. The marginal costs for complying with high, technical standards are lower for them. Higher standards, according to this argument, give the multinational companies a competitive edge over the smaller ones (especially those in developing countries, but also in developed countries[187]), effectively leading to the squeeze out of the latter, with adverse effects on the access to medicines. [188] Tim Reed has conducted a case study demonstrating how this problem caused by ICH standards indeed plays out in Romania. [189]Access to medicines being one of the biggest health problems in the developing world, this situation has led the WHO to recommend that harmonization of drug regulatory requirements be based on "demonstrated public-health needs and should not be driven by technological progress alone".[190]

What we see here is, therefore, arguments that the collaborative rule making efforts have distributional effects on market structures, distributing market power among private actors, in particular from small companies in developing countries to big companies in developed companies. (Cafaggi too has noted the distributional effects of private regulation on market structures.[191]) Worse still it is argued that these distributional effects have adverse effects on the access to medicines.

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[185] WHO, Report of a WHO Meeting: The Impact of Implementation of ICH Guidelines in Non-ICH Countries.21.
[186] Id. at 21. See also P. KOURILSKY & I. GIRI, *Safety standards: an urgent need for Evidence-Based Regulation*, Surveys and Perspectives Integrating Environment and Society 105(2008).113 (arguing that standards are constantly raised, while their cost and impact are not systematically evaluated. This has led to suspect that the associated costs are unjustified, as it has not been proven that these new technologies introduced by high-income countries indeed improve the drugs.)
[187] Dr. Terry Slater (Australia), "ICH-its value to a first-line medicines regulator", 10th ICDRA Proceedings
[188] WHO, Report of a WHO Meeting: The Impact of Implementation of ICH Guidelines in Non-ICH Countries.21.
[189] Tim Reed PhD, WHO Impact Paper
[190] WHO, Harmonization II: Recommendations (24-27 June 2002).
[191] Cafaggi, p.7.

While it is difficult to judge whether ICH guidelines are indeed biased and tilted towards commercial concerns, or whether the development of new scientific discoveries supported these reductions (or even if they represent a legitimate compromise between the countries), or whether science supports the improvement of standards[192], what becomes clear from this debate is that the current ICH structure raises skepticism regarding the integrity or legitimacy of the rule making process.

In their defense, persons involved in the ICH have argued that the loyalty of the experts (all scientists) participating in the ICH is first and foremost to science, and to their profession, much and above their loyalty to their employers. After all, the guidelines are open to the public, and their professional reputation would be at risk.[193] Moreover, those actually involved in the process were industry scientists, who are more concerned about their scientific reputation than with commercial aspects.[194] The industry, therefore, is only moderately influential. [195]

Seen from this perspective, the ICH is first of all an "epistemic community",[196] a group bound by its shared profession (science), the loyalty of its members towards peers (scientists) rather than towards employers (industry). In other words, a system of peer or reputational accountability[197] was at work here. And indeed, judged by the global adoption of the guidelines, and the fact that guidelines are commonly referred to as he "gold standard" and "state of the art", it is plausible to conclude that the ICH enjoys output or epistemic legitimacy by most.

Having said that, conflict of interest is very much regarded as a question of *perception*, and not so much whether undue influence has indeed taken place. This alone suggests that this problem should be addressed at the transnational level too.

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[192] Fernand Sauer, in reply to Abrahams criticism mentioned in footnote xx above, says that the reductions were made following extensive international and domestic consultations and scientific inquiries, that demonstrated the adequacy of these tests (these tests had always been considered adequate in Europe and Japan).
[193] Interview
[194] Interview
[195] Dr. Petra Doerr, Interview.
[196] Haas, Epistemic Communities and International Policy Coordination.
[197] Keohane and Grant, Abuses of Power in World Politics.

In the following section we examine conflict of interest rules that exist at the international and at the domestic level to get a better idea of how collaborative rule making could be better structured.

5. Committee Composition and Conflict of Interest Rules

Two different kinds of rules are in particular relevant when we examine collaboration between regulators and industry in rule making. The first kinds of rules that are relevant are rules on the composition of committees that develop scientific guidelines.

As is well known, there isn't any international code on good governance that sets out rules regarding balanced representation in rule making bodies. However, the different accountability projects now on the global scene, such as the INLAW project, the Global Administrative Law Project, the One World Trust Global Accountability Project, and more generally the scholarly literature on accountability and legitimacy, as well as the ILA Report on the Accountability of International Organizations, all provide a theoretical framework based on discursive democratic theory[198] on the basis of which one can argue for balanced representation in global rule making bodies. Moreover, looking at rules at the international (WHO, Institute on Medicine) and domestic level (US and EC) we find that while the specific content of the rules differs, the dominant trend is to establish balanced committees, representing a range of points of views, and to balance potentially biasing backgrounds.

The second kinds of rules that are relevant are rules on managing conflicts of interest. Not very surprisingly, there isn't any international code on conflicts of interest, but from an analytical perspective the task is a bit more complicated as the global governance accountability projects and literature mentioned above have all focused on the procedural aspects of accountability, such as transparency, participation, reason giving, and complaints mechanisms, but to a lesser extent on the value/ethical aspects, or on how to balance between conflicting interests of stakeholders. That said, the prohibition on conflict of interest could be considered as an additional factor required in fair and accountable decision making process (next to transparency, participation etc.). It is also worth mentioning the ILA Report on the Accountability of

[198] Habermas

International Organizations which sets out a recommended rule entitled "The principle of objectivity and impartiality", that says that: "An IO should conduct its institutional and operational activities in a manner which is objective and impartial and can be seen to be so". [199]

But even without a pre-developed theoretical framework, there are plenty of conflict of interest rules that reflect current practice and can serve as an inspiration. At the international level, there are rules by the WHO, rules which it uses for its expert committees, CIOMS rules, or rules by private, highly regarded bodies such as the US Institute on Medicine. At the national level we examine in this paper the rules of the US FDA and EMA. From a normative perspective, at best these rules can be considered to reflect an international practice, or one could argue that the regulators participating in the network are legally bound by their national conflict of interest rules in both their domestic and international activities. At worst they can simply serve as a model against which the appropriateness of the networks can be estimated, reformed or future networks modeled against.

A. Domestic Law

Both the EC and the US have adopted a system whereby regulators may rely on employees of pharmaceutical companies, in some cases even when they have conflicts of interest, but always limited to an advisory status, with decisions taken by the regulators. In this sense, the ICH proves the fear of "agencies on the loose" right,[200] as at the transnational level industry has more power than would be considered legal or appropriate at the domestic level.

US

In the US, the FDA may rely on *advisory* committees to provide the FDA with advice from outside experts, including on the development of guidance documents.[201] The composition of the committee should be balanced (i.e. include consumer, patients and industry representatives), and it may only issue recommendations – the FDA makes

[199] .ILA Report.
[200] Slaughter.
[201] US FDA, Draft Guidance for the Public and FDA Staff on Convening Advisory Committee Meetings (August 2008).(Sets out reasons to convene an advisory committee, and includes situations where the "FDA has significant questions or concerns regarding the development or implementation of a regulatory policy or guidance document")

final decisions. [202] Moreover, while usually decisions are reached by vote, vote is typically not taken in meetings on the development of a guidance document.[203] (This would seem to suggest that on development of guidance the agency's independence is particularly guarded, but I would need to look further into this issue.)

The FDA administers several laws and regulations that govern conflict of interest determinations; these laws set forth different standards for determining whether participation in advisory committee meetings may be permitted. These rules prohibit the participation of persons with conflict of interest in the advisory committee, unless a waiver has been granted.[204] FDA is authorized by statute to grant waivers to allow individuals with potentially conflicting financial interests to participate in meetings where it concludes, after close scrutiny, that certain criteria are met, [205]For example, when "the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved,[206] or if "it is necessary to afford the committee essential expertise."[207] Whenever a waiver has been granted, the FDA must disclose and make publicly available information on the conflict of interest, and its reasons for granting the waiver.[208]

In practice many of the top authorities in specific areas have conflicts of interest, and some meetings require expertise that is limited to a handful of experts, and those

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[202]"Advisory committees provide FDA with independent advice from outside experts on issues related to human and veterinary drugs, biological products, medical devices, and food. In general, advisory committees include a Chair, several members, plus a consumer, industry and sometimes a patient representative. Additional experts with special knowledge may be added for individual meetings as needed. Although the committees provide advice to the Agency, final decisions are made by FDA." See US FOOD AND DRUG ADMINISTRATION, Questions and Answers Regarding Advisory Committee Membership.;Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees" from August 2008, http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125646.pdf

[203] GUIDANCE FOR FDA ADVISORY COMMITTEE MEMBERS AND FDA STAFF, Voting Procedures for Advisory Committee Meetings, August 2008

[204] 18 U.S.C. § 208; section 712(c)(2) of the Act (replacing former 21 U.S.C. § 355(n)(4))

[205] *See* 18 U.S.C. § 208(b)(1), (b)(3) and § 712(c)(2)(B) of the Act (added by FDAAA § 701 (effective October 1, 2007)). The Agency has also issued a guidance document that implements a more stringent policy for considering eligibility for advisory committee participation. *See* FDA's "Guidance for The Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees" (August 2008) http://www.fda.gov/RegulatoryInformation/Guidances/ucm122045.htm.

[206] (18 U.S.C. 208(b)(3)).

[207] Section 712 (c)(2)(B)

[208] Section 712(c)(3) of the Act.

experts can often have conflicts of interest. The FDA, hence, used its waiver authority to a large degree. Seeking to counteract this development, Congress enacted in 2008 Section 701 of FDAAA[209], which focuses on recruitment of advisory committee members with no conflicts of interest. It encourages the FDA to focus efforts on recruitment of advisory committee members with fewer potential conflicts of interest by capping the numbers of waivers that the agency may grant in a given year (By 2012, the agency may issue waivers at a maximum rate of 75 percent of the rate issued in 2007.)

Consequently, the FDA issued a more stringent waiver criteria policy.[210] According to this policy, the FDA will not grant a waiver when the conflict is "significant", or when the financial interest exceeds 50,000USD. Moreover, in granting a waiver it will apply a stricter test than would be required under the law. That is, while the statute enables to give a waiver when "the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved (see above), the FDA will only grant when "it is necessary to afford the committee essential expertise." [211]

More recently, in 2010, in an attempt to improve transparency regarding conflicts of interest, the FDA announced a draft guidance that would expand transparency and disclosure when it grants a conflict of interest waiver to permit an individual's participation at an FDA advisory committee meeting. [212]

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[209] (section 712 of the Act)

[210] *See* FDA's "Guidance for The Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees" (August 2008) http://www.fda.gov/RegulatoryInformation/Guidances/ucm122045.htm.

[211] *See* FDA's "Guidance for The Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees" (August 2008) http://www.fda.gov/RegulatoryInformation/Guidances/ucm122045.htm.

[212] Draft Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members' Financial Interest Information and Waivers, http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM209201.pdf. The draft guidance would expand the information disclosed about waivers prior to committee meetings. Specifically, the FDA proposes to post online the name of the company or institution associated with the financial interest along with the type of conflict of interest. Under previous practice, when the agency grants a conflict-of-interest waiver for an advisory committee meeting it identifies the nature of the interest only as sponsor, competitor or another affected firm. "This approach was informed, in part, by a survey in 2001 of active advisory committee members that asked whether members would decline to participate based on varying levels of disclosure," the agency said.

Under the draft revised guidelines, the waivers posted on the FDA website would identify the name of the firm or institution that is implicated in the conflict.

Another point is that in 2009, President Obama launched the Open Government Initiative, and just recently he issued a Memorandum for the Heads of Executive Departments and Agencies on Transparency and Open Government.[213] It informs the departments that in view of reducing the influence of special interests the Administration is writing new ethics rules that prevent lobbyists from coming to work in government or sitting on its advisory boards. It further determines that in order to address the disproportionate impact achieved by lobbyists on government decision-making at the expense of the public at large, federally registered lobbyists should no longer be appointed to agency advisory boards and commissions. [214] This new policy would appear to put a limitation on the participation of groups like PhRMA, a registered lobbyist of the pharmaceutical industry in the US, and a co-member of ICH, to sit on advisory committees. (The memorandum does not mention the international activities of federal agencies, but arguably should be interpreted or amended to include international activities. At the very least at the persuasive level it points out the problematic of the ICH's structure)

EMA

EMA rules on committee composition xxx

The proposed change would bring the agency more in line with standard disclosure practices in the academic community, the FDA said. Academic institutions, peer-reviewed journals and scientific symposia have recently developed more rigorous policies for disclosure of potential conflicts, and many provide for revelation of the company or entity at issue. The agency specifically cited the disclosure policies adopted by the International Committee of Medical Journal Editors
See US FDA plans expanded conflict-of-interest disclosures for advisory panels
22 April 2010, Sue Sutter, http://www.rajpharma.com/productsector/pharmaceuticals/US-FDA-plans-expanded-conflict-of-interest-disclosures-for-advisory-panels-251676?autnID=/contentstore/rajpharma/codex/9681ffaf-4e01-11df-8fab-a1522d3ef0e5.xml;
FDA, Guidance for the Public, FDA Advisory Committee Members, and FDA Staff: Public Availability of Advisory Committee Members' Financial Interest Information and Waivers, March 2010, www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM209201.pdf: FDA press release, 21 April 2010,
www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm209119.htm;FDA Commissioner Hamburg's letter to FDA staff on disclosure of financial conflicts of interest, 21 April 2010,
www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/ucm209001.htm

[213] http://www.whitehouse.gov/the_press_office/TransparencyandOpenGovernment/
[214] See http://www.whitehouse.gov/blog/2010/01/13/fighting-against-special-interests-and-public-interest-a-year-change, and Norm Eisen, special consultant to the present on ethics and government reform http://www.whitehouse.gov/blog/Lobbyists-on-Agency-Boards-and-Commissions/

EU legislation (Article 63 in Regulation (EC) No 726/2004) clearly states that the members[2] of the Scientific Committees and experts shall not have financial or other interests in the pharmaceutical industry that could affect their impartiality.

The new EMA policy on "Handling of Conflicts of Interest of Scientific Committee Members and Experts" (which also applies to the development if guidelines) [215] determines that persons employed by a pharmaceutical company are banned from participating in any of the agencies activities, including involvement in guidance development,[216] except as an "expert witness" [217] in an advisory position (while declaring the conflict of interest in a transparent manner). Previously there had been a stricter conflict of interest policy, but it was amended as its overly strict approach resulted in that on new types of medicines, EMA found it difficult to find scientific experts who are not connected to industry.[218] Consequently, drugs being reviewed were not subjected to as high a level of scrutiny by the EMA as they should be, as under the previous strict rules there were scientific advisory groups without experts. [219]While enabling external scientific advisors to sit on the agency's advisory committees even though they might have a conflict of interest possibility has raised concerns, [220] it has been defended by the EMA as a necessary trade off.

What is striking is that during the consultation process on the new policy, the suggestion by one commenter to use a ICH joint agency/industry working group

[215] EMA/513078/2010, European Medicines Agency policy on the handling of conflicts of interests of scientific committee members and experts (13 October 2010), available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/10/WC500097905.pdf (Accessed 1 March 2010). The first policy on conflict of interests was issued in 2004, and has been amended twice since (once in 2005, and most recently in 2010). See

[216] Sec. 2, EMA/513078/2010, EMA Policy on the Handling of Conflicts of Interest of Scientific Committee Members and Experts , 13 October 2010.

[217] EMA/358101/2010, Overview of the Allowable Interests for the EMA Scientific Activities (13 October 2010), available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/10/WC500097906.pdf.

[218] Vibha Sharma, New EMA policy on conflicts of interest of advisors draws concern, 2 July 2010, available at http://www.rajpharma.com/productsector/pharmaceuticals/New-EMA-policy-on-conflicts-of-interest-of-advisors-draws-concern-298984

[219] Vibha Sharma, New EMA policy on conflicts of interest of advisors draws concern, 2 July 2010, available at http://www.rajpharma.com/productsector/pharmaceuticals/New-EMA-policy-on-conflicts-of-interest-of-advisors-draws-concern-298984; Vibha Sharma, EMEA reviews policy on conflicts of interest (6 February 2009), RAJ Pharma

[220] EMA adopts new policies on conflicts of interest, access to documents, *08 October 2010,Vibha Sharma, Regulatory Affairs Journal - Pharma, available at http://www.rajpharma.com/productsector/pharmaceuticals/EMA-adopts-new-policies-on-conflicts-of-interest-access-to-documents-304067*.

structure in the development of EMA guidelines was straightforwardly rejected by EMA, saying that "careful consideration has to be given to equal treatment of all relevant interested parties. Direct cooperation with rapporteur is generally considered not appropriate".[221] It further explained that "drafting suggestions from industry are always welcomed but careful consideration has also to be given to equal treatment of all relevant interested parties". [222]

To sum, the requirements as to balanced representation and the management of conflicts of interest that apply to the domestic activities of the EMA are stricter than those that apply to its transnational activities. It is hard to see why industry involvement in guidance development would be prohibited in the EMA scientific committees (where EMA guidelines are developed), but allowed in the ICH EWGs -- particularly given that the ICH guidelines have the same effect as EMA guidelines.[223] This result supports the "agency on the loose" claim made in the literature.

B. International Law

WHO

The WHO "Regulations for Expert Advisory Panels and Committees"[224] stresses balanced representation (though it is more concerned with equitable geographic representation, and to a lesser extent with the public/private or industry/consumer divide). It determines that "In the selection of members… shall consider primarily their *technical ability and experience*, but he shall also endeavor to ensure that the panels have the broadest possible international representation in terms of diversity of knowledge, experience and approaches in the fields…. He/she shall encourage nomination of experts from developing countries and from all regions…."[225] And that "As a general rule, the Director-General shall select …. members of an expert committee on the basis of the *principles of equitable geographical representation, gender balance, a balance of experts from developed and developing countries, representation of different trends of thought, approaches and practical experience in*

[221] AGENCY.12
[222] Id. at 3.
[223] EUROPEAN MEDICINES AGENCY, Procedure for European Union Guidelines and Related Documents within the Pharmaceutical Legislative Framework (2009). Section 4.1.3. determines that: ICH guidelines have the same status as other European scientific guidelines".
[224] WORLD HEALTH ORGANIZATION, REGULATIONS FOR EXPERT ADVISORY PANELS AND COMMITTEES.
[225] Section 3.2

various parts of the world, and an appropriate interdisciplinary balance…"[226] (italics added)

As regards conflict of interest, following the bird flu scandal, the WHO issued new guidelines on conflicts of interest in June 2010, entitled. the "Guidelines for Declaration of Interest (WHO Experts)" [227]According to these guidelines, all experts s must disclose any circumstances that could present a potential conflict of interest (i.e., any interest that may affect, or may reasonably be perceived to affect, the expert's objectivity and independence). This includes financial, professional or any other interest. If a declared interest is determined to be potentially or clearly significant, three possible measures apply: full participation, with public disclosure of the interest, partial exclusion, that is from the portion of the meeting related to the declared interest, or total exclusion. All declarations are published in resulting work products. Furthermore, if the objectivity of the work is subsequently questioned, the declaration may be made available by the Secretariat to persons outside WHO

In any event, experts (whether with an interest or not) do not make decisions, and may only provide advice.

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6. Conclusion

To conclude, the above reviewed rules on conflicts of interest are helpful in our analysis of the ICH (and other joint networks with health regulatory authorities) at several levels:

First, they demonstrate, at least at a persuasive level, that the joint decision making structure of the ICH is inappropriate in accordance with the practices concerning conflict of interest in the pharmaceutical sector that prevail in the US, Europe and the WHO today. The specific rules differ, and the management of conflicts of interest is a "moving target" due to changing attitudes about collaboration with private interests. Nevertheless, certain principles (of general international law?) do emerge:

[226] Section 4.2.
[227] Document on file with me.

1. A conflict of interest must be disclosed by the expert to the body
2. A person with a conflict of interest should not be sitting in a committee
3. However, a “hard line” opinion that no one with any kind of connection at all to the pharmaceutical industry should be involved in drug assessment "doesn't work any more". Exceptions are, therefore, acknowledged.
4. Where an exception was granted, depending on how significant the conflict is, or how necessary his or her expertise is, we may see some range between full participation, partial participation etc.
5. Transparency towards the public as to the experts (names, companies) and their conflicts of interest
6. But in any case, experts (whether they have a conflict or not) may only advise. Decision-making is left to the regulators/WHO
7. Inclusion of patients for balanced representation

These principles, if indeed to be considered general principles of international law, would apply to all regulatory authorities in the network on the basis of Article 4 of the Articles on State Responsibility. Ideally, they would be included in an international code of conduct. The International Conference of Drug Regulatory Authorities, a universal network of drug regulatory authorities that convenes every two years, would be a possible venue to raise this possibility.

Second, the US and EC rules do not expressly mention the international activities of the regulators. Hence, this indeed raises the concern that the regulators participating in the international networks are “on the loose”, as they are not bound by the same rules that apply to their domestic activities. One possible way to overcome this problem is on the basis of broad interpretation. That is, by arguing that since transnational activities have become such a central part of the regulators’ job, that the rules should apply equally to domestic and international activities, and that they should be prohibited from drafting guidelines with persons found to have a conflict. Alternatively, they should be amended in the US and EU to address the transnational activities of regulators. As international regulatory cooperation will become more prominent and people will become more conscious about this, we may expect to see

such adjustments. That said, at least in the US, given its very narrow definition of conflict of interest, it is doubtful whether they would consider guidance development an issue that raises conflicts of interest.

In light of the above, the three two main changes that should be introduced in the networks are, (i) industry experts (or experts more generally) should be advisors rather than decision makers (irrespective of whether they have a conflict or not); (ii) Increase the transparency of the expert selection (as well as the guideline drafting process); (iii) Demand experts to declare conflicts, and be transparent about this information.

Interestingly, the International Cooperation on Cosmetic Regulation (ICCR),[228], a harmonization network of cosmetic regulatory authorities from the United States, Japan, and Canada, set up in 2007 to which the FDA is a member, and which in most of its features is structured like the other networks, differs on this point. Its membership is composed of regulatory authorities only, but they are expected to "enter into a constructive dialogue with their relevant cosmetics' industry trade associations".[229] This allows for effective industry advice, but without the decision making power it has in the other networks. I have not had the opportunity yet to investigate the background that led to this design, but it may very well be related to criticism on the inappropriateness of the other networks' design.

III. Part III: Conclusion

Collaboration of regulatory authorities with industry associations on the harmonization of drug and other health related rules is best explained by the dependency of regulators on industry for information on technical matters and on trade barriers, as well as their resource limitations. It can also be explained by historical institutional theory as essentially the public-private network structure was copied from the European harmonization experience, and reflects a diffusion of European practices to the international level.

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[228] Previously known as the "Cosmetics Harmonization and International Cooperation" (CHIC), active in 1999-2000.
[229] ICCR Terms of Reference, Article 1, on "Membership", at http://www.fda.gov/InternationalPrograms/HarmonizationInitiatives/ucm114522.htm.

The networks at the center of this study are characterized by a tension between epistemic and political legitimacy. On the one hand, the ICH enjoys very broad "epistemic legitimacy". It is generally not contested that the ICH issues state of the art standards on the safety, efficacy and quality of drugs, and is often referred to as the "gold standard". This legitimacy also explains why the guidelines have become de facto global standards adopted by non-member countries worldwide. The inclusion of the industry generates this legitimacy as it enables the best experts on every topic to bring their minds together. The point is that if we look at it from this perspective, then we understand that the inclusion of the industry has actually increased the ICH's (epistemic) legitimacy. On the other hand, due to the imbalanced representation of industry and patients, the ICH lacks political legitimacy.

The conclusion coming out from this analysis is that in order to maintain the epistemic legitimacy of the ICH, while also increasing its political legitimacy, a balance between the two concepts needs to be struck. The most appropriate solution would be to include both of them – but as advisors.

Moreover, to deal with conflicts of interest in the rule making process, the principles set out should be followed, such as that conflicts must be declared and made transparent, that experts have the role of advisors rather than deciders etc. While the example here is health, the principle on the prohibition on conflict of interest should be embraced in the accountability debate, and applied in other policy areas too.