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**Global harmonization through public-private  
partnership:  
The case of pharmaceuticals**

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# Global harmonization through public-private partnership: The case of pharmaceuticals

*Stéphanie Dagron*<sup>1</sup>

## Abstract

The harmonization activities of the International Conference on Harmonization (ICH) in the field of pharmaceutical marketing regulation perfectly illustrate the possible normative influence of non-binding instruments adopted by sub-national actors. The ICH is a hybrid organization composed of representatives of the pharmaceutical industry on one hand and the national regulation agencies of three regions on the other. An intergovernmental organization, the World Health Organization (WHO), is associated to the ICH activities through its observer status. The ICH has adopted more than 50 “technical” guidelines which have developed into global standards. It has thus become extremely difficult for national regulators to modify the criteria for drug marketing approval unilaterally. Some guidelines go beyond the standardization of technical requirements. They reflect commercial, political or ethical choices and pose complex legitimacy and accountability challenges. The analysis of the multi-level procedure and institutional framework of the ICH has so far not been conducted from a global administrative law perspective. A closer examination of the ICH process reveals a deficient structure and the need for the development of new legal standards. Some steps already taken by the ICH should be pursued further and could contribute a model for greater accountability and legitimacy for new forms of global administrative decision-making procedures.

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## 1. Introduction

The recent catastrophe in France concerning the prescription of the diabetes drug Mediator, also used as an appetite suppressant, has gripped the attention of the public, catalyzed public opinion and caused political reactions. Mediator was banned from the French market in 2009. In autumn 2010, the French drug agency responsible for the safety of health products<sup>1</sup> revealed that over the last 30 years, approximately 500 to 2000 patients in France who took Mediator have died because of the drug's side-effects<sup>2</sup>. The direct reaction of the French health political authorities was to announce the strengthening of medicine regulations and more precisely the strengthening of the approval criteria for safety, efficacy and quality retained by the competent regulatory agency. But is the decision to reinforce these criteria nowadays still really in the hands of the French or other national (or supranational) authorities?

Safety, efficacy and quality criteria for the assessment of medicines are accepted worldwide as universal criteria conditioning the marketing authorization of drugs. This has been the case since the second half of the 20<sup>th</sup> century<sup>3</sup>. Until then, the majority of drugs on the world market had - at best - been subject to a notification requirement to the responsible agency and had never been tested for pharmacological quality, safety and efficacy<sup>4</sup>. It is only after the Second World War that the whole regulatory system was reshaped globally as a reaction to various unfortunate events across the world.<sup>5</sup> The Thalidomide disaster of 1959-1961, which had worldwide consequences,<sup>6</sup> serves as example. It caused the reshaping of the entire regulatory system globally, to protect consumers<sup>7</sup> in the pharmaceutical industry.

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<sup>1</sup> The AFSSAPS is the French agency for the security of therapeutic goods, i.e. drugs and therapeutic devices.

<sup>2</sup> See *Le Monde* 16. Nov. 2010. Many public reports have been published about the Mediator. See at least the first one: A.-C. Bensadon, E. Marie, A. Morelle, *Enquête sur le Mediator®*, Inspection générale des affaires sociales, January 2011 (<http://lesrapports.ladocumentationfrancaise.fr/BRP/114000028/0000.pdf>).

<sup>3</sup> In Europe these criteria have first been introduced by the Directive 65/65/EEC of 26 January 1965 concerning medicinal products. The directive required an authorization for the marketing of medicinal products (art. 3), the criteria for the marketing being (and still continue to be): proven therapeutic effect, safety in normal use and pharmaceutical quality (art. 5).

<sup>4</sup> See for example the French Statute of the 11th September 1941 which prescribes a visa confirming that a new product has been declared. For an analysis of the French legislation see S. Chauveau, *Genèse de la «sécurité sanitaire»: les produits pharmaceutiques en France aux XIX<sup>ème</sup> et XX<sup>ème</sup> siècles*, *Revue d'histoire moderne et contemporaine* 51 (2004), at 89.

<sup>5</sup> About the decisive events in France and the USA see: C. Bonah, J.-P. Caudillière, Faute, accident ou risque iatrogène? La régulation des événements indésirables du médicament à l'aune des affaires Stalino et Distillène, *Revue Française des Affaires Sociales* (2007), at 123.

<sup>6</sup> Except for France and the USA, patients in almost every developed country have been victims of adverse reactions to the substance Thalidomide. On this event see: B. Kirk, *Der Contergan-Fall: eine unvermeidbare Arzneimittelkatastrophe?*, 1999.

<sup>7</sup> The first worldwide attempt to require drugs to be tested for safety and labeled for use has been made in the USA with the 1938 Food Drugs and Cosmetic Act (FDCA). The mechanism was incomplete. The Kefauver-Harris amendments to the FDCA have been adopted in 1962. Following these amendments, all new drugs have to be approved by the FDA before they can be imported, manufactured, distributed or sold in the USA.

Not surprisingly, drug approval requirements vary from one country to another, mostly as a consequence of differences in the risk-benefit assessments undertaken by the different regulatory agencies as well as differences in the national political or industrial choices. The separate national registration procedures have long presented an important obstacle to the worldwide marketing of drugs. To obtain the authorization to market their products, the pharmaceutical companies have to apply for products approval in each country. These procedures entail substantial costs, both for the governments responsible for their approval and for the industry connected to the variable testing requirements mandated to evaluate the safety, efficacy and quality of a product (for example through the obligation to conduct national clinical trials). These procedures also cause delays in the delivering of new drugs or unavailability of some drugs in some markets.

Efforts to harmonize marketing mechanisms were first made within the European community<sup>8</sup>. These efforts succeeded after four decades of discussion and partial harmonization regulation, through the establishment of the European Agency for the Evaluation of Medicinal Products (today called the European Medicines Agency, EMA) and the progressive emergence of a single market for pharmaceuticals at least for new “innovative” pharmaceuticals<sup>9</sup>. This drug category is the most important for the industry: new innovative drugs are usually sold on prescription and covered by patents. In other words, these drugs should permit the industry to regain the financial investments made for the research and development of the drug; whereas the two other categories, which are the generic or multi-source drugs and the “Over-the-counter” drugs (OTC medicines) are not of interest in this respect<sup>10</sup>.

On the global level, efforts towards harmonization have not yet lead to a central marketing procedure. The most successful enterprise concerns the harmonization of the technical requirements for the registration of drugs<sup>11</sup>. This harmonization is a result of the work of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) created in 1990. The ICH

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<sup>8</sup> On the initial harmonization efforts in Europe and the drug authorization mechanisms see: D. Vogel, The globalization of pharmaceutical regulation, *Journal of Policy and Administration*, vol. 11 (1998), at 1-22 (5).

<sup>9</sup> On the progressive development of European law in the field of drug regulation, see J. Feick, Regulatory Europeanization, National Autonomy and regulatory Effectiveness: Marketing Authorization for Pharmaceuticals, MPIfG Discussion Paper 02/6. On more recent developments: W.-H. Roth, Möglichkeiten und Grenzen eines einheitlichen Binnenmarktes für Arzneimittel, *Europarecht*, Beiheft 2, 2007, at. 9.

<sup>10</sup> Generics are drug products comparable to reference listed drug products that are not protected anymore by a patent. Their price is supposed to be low. OTC medicines are non-prescription medicines that were previously (before reclassification) available only on prescription.

<sup>11</sup> On the contrary, the standards for intellectual property protection, including (drug) patent, have been to a large extent harmonized at the global level through the adoption in 1994 by the members of the World Trade Organization of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). Although there is a strong connection between intellectual property rights and the approval regulatory scheme, the analysis of these standards would exceed the scope of this article. On the conflict between patent law obligations under the TRIPS Agreement and access to medicine, see H. Hestermeyer, *Human Rights and the WTO, The Case of Patents and Access to Medicines*, 2007.

is a public-private partnership<sup>12</sup>, bringing together an intergovernmental organization (the WHO), national regulatory authorities and industry associations from three regions in the world: Europe, USA and Japan. It was created with the fundamental objectives to use resources more efficiently, save substantial time and costs involved in the development and investigation of new drugs and thus serve the interests of the consumer and promote public health<sup>13</sup>. In the ICH, the major association of each nation's (research-based) pharmaceutical industry<sup>14</sup> is accepted as a party on equal footing with the regulatory agencies<sup>15</sup> of the three participating regions. In addition, the International Federation of the Pharmaceutical Manufacturers and Associations (IFPMA) is the secretariat. The industry's influence could not be more obvious.

This active participation of the drug industry in the development of standards applicable to marketing authorization, but also to post-marketing control (pharmacovigilance) has been criticized by many authors<sup>16</sup> and non-governmental associations<sup>17</sup>. Their critiques are mostly directed at the contradictory motivation of the pharmaceutical industry, which has a cost-recovery interest in the development of new drugs and hence would support early marketing of its drugs, and the failure of the harmonization process to be in favor of public health rather than for private profit. These critiques of the legitimacy of the governance activities of the ICH focus on the particular position of one stakeholder – the pharmaceutical industry – in relation to

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<sup>12</sup> On the definition and proliferation of public-private partnerships in the global health landscape since the latter half of the 1990s, see: K. Buse, G. Walt, Global public-private partnerships: Part. I- a new development in health?, *Bull World Health Orga*, vol. 78 (2000), at 549; G. L. Burci, Public-private partnerships in the public health sector, *International Organizations Law Review*, 6 (2009), at. 359.

<sup>13</sup> See the ICH “Terms of reference”, 1990. Unless noted otherwise, all information and documentation on the ICH is to be found on ICH's website: [www.ich.org](http://www.ich.org).

<sup>14</sup> The research-based industry is to be distinguished from the generic industry. In the first case, the pharmaceutical companies invest a part of their budget in discovering and developing new medicines (Research and Development laboratories, R&D). Generic pharmaceutical companies bring drugs to the market after patent expiration as less expensive version. Pharmaceutical (research-based) companies are represented within the ICH through the umbrella organizations EFPIA (Europe), JPMA (Japan) and PhRMA (USA).

<sup>15</sup> Regulatory officials come from the United States (FDA), the European Union (Committee for the Proprietary Medicinal Products (CHMP) within the EMA) and Japan (Ministry of Health, Labor and Welfare).

<sup>16</sup> See the following articles: J. Abraham, T. Reed, Trading Risks for Markets: the International Harmonization of Pharmaceuticals Regulation, *Health, Risk and Society* 2001, at 113; J. Abraham, The Pharmaceutical Industry as a Political Player, *The Lancet* 360 (2002), at 1498; J. Abraham, C. Davis, Interpellative Sociology of Pharmaceuticals: Problems and Challenges for Innovation and Regulation in the 21<sup>st</sup> Century, *Technology Analysis and Strategic Management*, 19 (2007), at. 387. See also the “indirect” criticism from Burci, *supra* note 12, at. 373. Although not mentioning the ICH activities, the author notes more generally that the setting of normative standards is “more appropriately exercised by WHO in view of its constitutional mandate as well as of the political legitimacy, accountability and technical authority conferred by its intergovernmental structure [...]”.

<sup>17</sup> See for example the critiques by Health Action International Europe (HAI) formulated 1996 in the Uppsala Declaration: Statement of the international working group on transparency and accountability in drug regulation, at point 9 (<http://www.isdbweb.org/pages/35>). See also the critics of the *Revue Prescrire*: ICH: an Exclusive Club of Drug Regulatory Agencies and Drug Companies Imposing its Rules on the Rest of the World, *Prescrire International*, August 2010, at. 183.

others such as regulatory authorities, patients, or non-governmental organizations. On the other hand however, many authors applaud the success of the ICH harmonization process arguing that in this field expertise is needed to contribute to the development of common rules. These authors specifically underline the positive influence of the harmonization process which has rendered “national government regulation more efficient and effective”<sup>18</sup> thus assuming that efficiency produces legitimacy.

A more differentiated approach is needed. In this paper I propose to follow the agenda set by the Global Administrative Law (GAL) literature<sup>19</sup> for the analysis of the exercise of public authority by global administrative agencies<sup>20</sup>. This agenda relies on the use of legal concepts (such as rules addressing competences, procedures, participation, transparency, accountability etc.) for the analysis of regulatory activities<sup>21</sup> and offers another perspective for the analysis of the legitimacy of the ICH<sup>22</sup>. My purpose is not to enter the conceptual discussion concerning the existence of a set of legal rules and principles governing the activities of global administrative actors<sup>23</sup>. My approach is deliberately pragmatic: given the fact that the enforcement of standards developed by the ICH has proven very efficient, I propose to search for the forms and procedures that should be applied to this transnational decision-making process in order to make it accountable and legitimate<sup>24</sup>.

The proponents of GAL have come to the conclusion that the legitimacy challenges

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<sup>18</sup> See Vogel, *supra* note 8, at 20. Concerning the clarification in the field of pediatric research through the ICH guidelines, see A. E. Ryan, Protecting the Rights of Pediatric Research Subjects in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, *Fordham Int’L.J.* 23 (1999-2000), at 848. For the field of pharmacovigilance see the positive remarks in the following article: P. Bahri, P. Tsintis, Pharmacovigilance-related Topics at the Level of the International Conference on Harmonisation (ICH), *Pharmacoeconomics and Drug Safety* 2005, at. 377 (383).

<sup>19</sup> See B. Kingsbury, N. Krisch, R. B. Stewart, J. Wiener, The Emergence of Global Administrative Law, *Law and Contemporary Problems* 68 (2005); S. Cassese, Administrative Law without the State? The Challenge of Global Regulation, *Journal of International Law and Politics*, 37 (2005); A. von Bogdandy, P. Dann, M. Goldmann, Developing the Publicness of Public International Law: Towards a Legal Framework for Global Governance Activities, *German Law Journal* 9 (2008).

<sup>20</sup> More specifically on the general legal issues involved by the growing activities of public-private bodies at the international level see: B. Kingsbury, L. Casini, Global administrative law dimensions of international organizations law, *International Organizations Law Review*, 6 (2009), at. 319 (345). On the necessity to address the challenges raised by hybrid actors intervening in the global health landscape with regard to administrative law type principles see: Burci, *supra* note 12, at 366.

<sup>21</sup> See M. Goldmann, Inside Relative Normativity: From Sources to Standard Instruments for the Exercise of International Public Authority, *German Law Journal* 9 (2008), at 1867.

<sup>22</sup> On the question of legitimacy of expert committees, see also the arguments of A. Peters, P. Bürkli, Recht der Forschung am Menschen – Normenentstehung im Kontext von soft law, internationalen Abkommen und Gesetz, *Zeitschrift für Schweizerisches Recht* 129 (2010), more specifically at 387.

<sup>23</sup> For insights into that conceptual discussion see: K. H. Ladeur, The emergence of global administrative law and transnational regulation, *Institute for International Law and Justice Working Paper* 2011/1; D. Dyzenhaus, Accountability and the concept of (global) administrative law, *Institute for International Law and Justice Working paper* 2008/7.

<sup>24</sup> The same pragmatic agenda is followed by L. Boisson de Chazournes in: Changing roles of international organizations: Global administrative law and the interplay of legitimacy, *International Organizations Law Review*, 6 (2009), at 655 (659).



posed by the multiple international instruments differed, depending on how authoritative the international institutions' policies are. Accordingly, the legal standards to be developed for ensuring the legitimacy of each exercise of international public authority could not possibly be the same for all instruments<sup>25</sup>. These conclusions will guide my analysis: the nature of the authority exercised by the ICH guidelines will first be analyzed (I); an evaluation of the legitimacy of the ICH with regard to the authority of these activities and a proposition for considering new legal standards eventually better adapted to the public-private character of the ICH will follow (II).

## **2. The global authority of the ICH-activities: normative influence on technical but also industrial, political and ethical choices**

The ICH has been established to support harmonization of the technical approval requirements in the three participating regions. For this purpose, it has published more than 50 guidelines pertaining to quality, efficacy and safety. It also made recommendations and created instruments for the so-called multidisciplinary areas<sup>26</sup>. The authority of the activities of the ICH has to be measured with regard to the binding character of the guidelines (1) and their real content (2).

### ***a. The normative authority of the guidelines***

The first focus of the ICH was the harmonization of the technical approval requirements in the three participating regions (Europe, Japan and the USA) through the development of non-binding instruments<sup>27</sup>. The success of this process is confirmed by the fact that these instruments have developed into global standards, thus receiving more attention than the standards developed for the same areas by the World Health Organization<sup>28</sup>, the World Medical Association (WMA)<sup>29</sup> or the Council for International Organizations of Medical Sciences (CIOMS)<sup>30</sup>. The guidelines and instruments adopted by the ICH exercise a normative influence in many countries within (1.1) but also outside the group of the ICH participating regions (1.2).

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<sup>25</sup> See Goldmann, *supra* note 21, at 1868. The same argument has been developed in the German constitutional case law and literature concerning the legitimacy of certain kind of administrative authorities as for instance expert committees. On this point see: S. Dagron, La théorie allemande de la légitimité démocratique de l'administration, *Revue européenne de droit public* 18 (2006) 4, at 1279.

<sup>26</sup> The Medical Terminology Dictionary (MedDRA), the Common Marketing Application Form for New Pharmaceutical Products (Common Technical Document, CTD) and the Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI) belong to this section.

<sup>27</sup> Statement by the ICH Steering Committee, Tokyo, 1990.

<sup>28</sup> See for example the GCP guidelines of WHO which are considered as being informative tools for less experienced users.

<sup>29</sup> Only a few standards applicable to drug regulation have been developed by the WMA. See the ethical principles for medical research involving human subjects in the Declaration of Helsinki.

<sup>30</sup> The CIOMS has been established jointly by WHO and UNESCO in 1949. Drug safety topics have been covered by CIOMS and developed into "consensus guidelines". CIOMS Reports concerning the international reporting of adverse drug reactions have been largely used by ICH for the formulation of the Pharmacovigilance-related guidelines. On this influence see P. Bahri et al., *supra* note 18, at. 380.

## I. The normative authority of the ICH guidelines in the ICH regions

The normative influence of the ICH guidelines and instruments is manifest in all ICH participant regions. The regulatory authorities of the USA, Europe and Japan have committed themselves to making use of the guidelines and instruments developed and adopted by the ICH. The implementation in the national system is carried out according to the national or regional procedures that apply in the three regions<sup>31</sup>.

ICH guidelines are not *de jure* binding in the ICH regions. However, they have a significant *de facto* binding force that cannot be ignored. According to the document concerning the procedure for European Union guidelines first adopted in 2005 by the EMA, “once adopted by the CHMP, ICH guidelines have the same status as other European scientific guidelines and replace existing guidelines on the subject covered” (§ 4.1.3). This status is specified in § 2.2 as follows: scientific guidelines “are ‘soft law’”; they have a “quasi-binding character that can derive from the legal basis when the guideline intends to specify how to fulfill a legal obligation”. This “quasi-binding” character has been confirmed by national courts that refer to the ICH guidelines (as adopted by the CHMP) as evidence of the state-of-the-art of pharmaceutical research and development<sup>32</sup>. In the practice, applicants have no other choice than to follow and respect the ICH guidelines. This obligation is strictly framed through the so-called Common Technical Document (CTD) that has been adopted in the three participating regions<sup>33</sup>. The CTD is a common (electronic) marketing application form for new pharmaceutical products. It combines all ICH guidelines and provides detailed instructions for the registration dossier to accompany an application for a new product<sup>34</sup>. If applicants wish not to follow the guidelines, they have to provide reasons and justifications for deviation from the dispositions.

The strong and multi-leveled impact of the guidelines is illustrated perfectly in the

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<sup>31</sup> In the European Union for instance, the ICH guidelines are adopted by the Committee for Medicinal Products for Human Use (CHMP) which is the scientific committee of the EMA and incorporated into the list of scientific guidelines that has to be adhered to by applicants. See the document concerning the procedure for European Union guidelines adopted by the EMA (§ 4.1.3): [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/10/WC500004011.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004011.pdf). On the implementation mechanism in the USA see J. G. Contrera, The FDA and ICH: How harmonious will international pharmaceutical regulations become? *Admin. L. J. Am. U.* 927 (1994-1995), 928 (946). See also the Comprehensive list (2010) containing all ICH guidelines at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>32</sup> See for example the decision 2009 by the German Administrative Court of North Rhine-Westphalia cited by K. Engelke, Transnationalisierung der Arzneimittelregulierung, *MedR Schriftenreihe Medizinrecht* (2010), 619 (623).

<sup>33</sup> ICH M 4. The CTD is always described as the key instrument of the ICH. See for example: S. K. Branch, Guidelines from the International Conference on Harmonisation (ICH), *Journal of pharmaceutical and Biomedical Analysis* 38 (2005), 798; J. J. Lee, What is Past is Prologue: the ICH and Lessons learned from European Drug Regulation Harmonization, *University of Pennsylvania Journal of International Law* 26 (2005), 151.

<sup>34</sup> An application conformed to the CTD format has 5 parts called module. The first module is not part of the CTD and authorizes individualization, each region being able to require additional information. Module 2 contains summaries on quality requirements, and non-clinical and clinical information. Module 3 is dedicated to quality, module 4 to non-clinical study reports and module 5 to clinical study reports.

European Union, where all 27 member-states have to comply with the process initiated by ICH by virtue of their EU membership. This is a consequence of the directive 2001/83/EC, according to which every application for marketing authorization within the European Union has to take into account the ICH guidelines<sup>35</sup>. Thus, compliance with the ICH standards is necessary not only within the scope of the centralized application procedure<sup>36</sup> for which the European Commission is responsible, but also within the national procedures. The centralized procedure was established in 1993 and allows applicants to obtain a marketing authorization that is valid throughout the EU. However, this procedure is only compulsory for all human medicines derived from biotechnology and other high-tech processes as well as medicinal products containing new substances, intended for the treatment of certain diseases like cancer or diabetes<sup>37</sup>. It is optional for any other products containing new active substances not authorized in the Community before 2004, products which constitute a significant therapeutic, scientific or technical innovation or products for which a Community authorization is in the interest of the patients. For medicines that do not fall within these categories, the marketing authorization is accorded by the national regulatory authority under a national procedure for medicinal products to be marketed in one Member State only or for products to be marketed in the EU. In the latter case the so-called “mutual recognition” procedure<sup>38</sup> and the “decentralized” procedure<sup>39</sup> both presume the existence of a national marketing authorization awarded in terms of national rules.

## II. The normative authority of the guidelines beyond the ICH regions

The ICH was not intended as a worldwide harmonization effort, but the impact of the guidelines has extended beyond the ICH regions. First, most of the guidance has been adopted by the regulatory agencies of the two observers to ICH with no voting rights which are the Swiss Agency for therapeutic products (Swissmedic) representing the European Free Trade Association and the Canadian Agency (Health Canada)<sup>40</sup>. In these countries, the ICH guidelines have become administrative documents with no legal but a *de facto* binding force<sup>41</sup>.

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<sup>35</sup> The directive 2001/83/EC (art. 6, 8 and Annex 1) imposes the CTD presentation for all types of marketing applications.

<sup>36</sup> Council Regulation (EEC) 2309/93. The system was revised 2004 (Regulation (EC) 726/2004), whereby its central features were retained and strengthened.

<sup>37</sup> In 2002 this represented 36% of all new drug approvals since the introduction of the new centralized European drug approval system in 1995. See the analysis of G. Walsh, Pharmaceutical Biotechnology Products approved within the European Union, *European Journal of Pharmaceutics and Biopharmaceutics* 55 (2003), 3.

<sup>38</sup> This procedure is based on the principle of the mutual recognition by EU Member States of their respective national marketing authorization. See for the basic arrangements, directive 2001/83/EC.

<sup>39</sup> This procedure is based on recognition by national authorities in the EU of a first assessment performed by one of the member States. See Directive 2004/27/EC.

<sup>40</sup> See about the *de facto* binding force of the guidelines in Canada: J. Lexchin, Who’s Calling the Tune, Harmonization of Drug Regulation in Canada, 2011, Canadian Center for Policy Alternatives ([www.policyalternatives.ca](http://www.policyalternatives.ca)).

<sup>41</sup> See for example the Notice adopted by Health Canada concerning the application of the CTD and the endorsement of ICH guidance by Health Canada (<http://www.hc-sc.gc.ca/dhp->

Second, the growing interest outside the ICH participants' regions and observer countries for ICH activities had to be acknowledged by the ICH Steering Committee (ICH-SC) which is the governing body of the ICH<sup>42</sup>. At the fourth ICH meeting in Brussels in 1997, the ICH members thus decided to add new objectives to the Conference and more specifically the objective "to facilitate the dissemination and communication of information on harmonized guidelines and their use such as to encourage the implementation of common standards"<sup>43</sup>. In this perspective the Global Cooperation Group (GCG) was created in 1999 as a subcommittee of the Steering committee. It is made up of representatives from each of the six parties and observers to ICH but also representatives from five Regional Harmonization Initiatives (RHIs), which are the Asian-Pacific Economic Cooperation (APEC)<sup>44</sup>, the Gulf Central Committee for Drug Registration (GCC-DR)<sup>45</sup>, the Pan-American Network for Drug Regulatory Harmonization (PANDRH)<sup>46</sup>, the Southern African Development Community (SADC)<sup>47</sup> and the Association of Southeast Asian Nations Pharmaceutical Product Working group (ASEAN-PPWG)<sup>48</sup>. These RHIs pursue the aim of promoting harmonization of drug regulation among their members<sup>49</sup> and have agreed through their participation in the ICH "to promote a mutual understanding of regional harmonization initiatives in order to facilitate harmonization processes related to ICH guidelines regionally and globally"<sup>50</sup>.

Finally, the growing interest for the ICH activities has been concretized in some Non-ICH countries through the implementation or intended implementation of ICH guidelines into the national approval system. The *de facto* binding character of ICH guidelines in these countries has been acknowledged so far by the decision of the steering committee in 2007 to invite the Drug Regulatory Authorities or Department of health of eight Non-ICH countries (so far)<sup>51</sup> to participate directly in the ICH GCG. These countries respond to the following criteria defined by the ICH GCG: use or intended use of ICH guidelines and whether a country or region is a source of active pharmaceutical ingredients, medicinal products or clinical data for the ICH regions<sup>52</sup>.

### ***b. The commercial, political and ethical environment of the "technical" guidelines***

The ICH has always claimed that the content of its guidelines is of scientific and

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[mps/prodpharma/applic-demande/guide-ld/ich/multidisciplin/ctd\\_m4\\_notice-eng.php](https://prodpharma/applic-demande/guide-ld/ich/multidisciplin/ctd_m4_notice-eng.php)).

<sup>42</sup> For procedural and institutional details, see Part. II

<sup>43</sup> Statement by the ICH steering committee, Brussels, 1997.

<sup>44</sup> 21 current members.

<sup>45</sup> 7 current members.

<sup>46</sup> PANDRH is composed of all the American States which are members of the Pan-American Health Organization (36 current members including the USA).

<sup>47</sup> 15 current member States.

<sup>48</sup> 10 current members.

<sup>49</sup> See the GCG criteria for selection of the RHIs.

<sup>50</sup> Final GCG Meeting report, 11.16.04.

<sup>51</sup> Australia, Brazil, China, Chinese Taipei, India, Russia, Singapore and Republic of Korea.

<sup>52</sup> See the document called: Criteria/Considerations for ICH Global Cooperation Group Membership.

technical nature<sup>53</sup>, thus arguing that “technical” harmonization in the field of pharmaceuticals is possible, since technical requirements can be distinguished from their social and political environment<sup>54</sup>. The real nature of the guidelines is of particular importance since political, social or ethical choices pose more complex legitimacy challenges than “simple” technical content, based on scientific assessment. A closer analysis of the activities of ICH shows that some guidelines go beyond the standardization of technical requirements. In fact, the standards developed to frame the evidence base for drug quality, safety and efficacy can reflect commercial (2.1), but also political or ethical choices (2.2).

## **I. Technical harmonization versus commercial/industrial issues**

The guidelines adopted by the ICH are dedicated to be applied during the different phases of drug development that lead to approval. The 13 safety guidelines adopted so far apply in the preclinical (also called non-clinical) phase, where *in vitro* studies using human cell fractions but also animal investigations are conducted to identify compounds that are most likely to have biopharmaceutical and clinical properties in humans. Animal experiments provide clinically useful information, predict drug class liability with respect to safety and generate exposure-response relationships for efficacy and safety which can be extrapolated from animals to humans. In order to minimize the use of animal testing, the different guidelines in this section have determined which tests have to be conducted, designed and interpreted<sup>55</sup>. The 21 guidelines on pharmaceutical quality adopted so far address the different phases of development and manufacturing of new substances and products. The objective of this set of guidelines is to ensure that the substances or products are of good quality during the cycle of their “life time”. Standards concern how stability testing<sup>56</sup> is to be done and which information has to be generated for submission in registration application or which light sources are to be used, e.g. for photostability testing.

The technical nature of the guidelines developed for these phases of drugs development is obvious. However it should be clear that the requirements related to the process of registration of new chemical entities and products also reflect commercial interests. The scientific level of each guideline has been interpreted by WHO as very high and as reflecting state-of-the-art technology<sup>57</sup>. But a high scientific level can lead to advantages for pharmaceutical companies who have the necessary resources to achieve

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<sup>53</sup> See the statement of the steering committee at the first Conference in 1990. See also the statement by the ICH steering committee at the fourth International Conference in 1997 in Brussels. The harmonization of technical requirements remains in 2010 the key instrument. See the publication written by the drug regulatory authorities associated with the ICH steering committee, the Global Cooperation Group and the Regulators Forum to salute two decades of ICH’s work in harmonizing drug regulatory requirements (2010, [www.ich.org](http://www.ich.org)).

<sup>54</sup> About this distinction as a basis for harmonization in Europe see E. Cadeau, *le médicament en droit public*, 2000.

<sup>55</sup> ICH S 1 (carcinogenicity studies), S 2 A & B (genotoxicity testing) and S 4 and S 8 (toxicity and immunotoxicity studies).

<sup>56</sup> See ICH Q 1 A to Q 1 E.

<sup>57</sup> See Report of WHO meeting, 2001, The impact of implementation of ICH guidelines in non-ICH countries, at 21 (<http://apps.who.int/medicinedocs/pdf/h2993e/h2993e.pdf>).

the requested standards. Smaller industries in developing countries, but also generic producers, might not be able to meet these standards. Thus ICH standards could be seen as non-tariff barriers to trade forbidden by the Agreement on Technical Barriers to Trade<sup>58</sup>. According to K. Timmermans, “increasing the standards beyond the technological capacity of pharmaceutical companies in developing countries would effectively exclude their competitive, generic products from the international market”<sup>59</sup>. The production of generics but also of pharmaceutical starting material in developing countries is endangered. In fact, ICH guidelines have introduced a tightening of specifications for pharmaceutical starting materials which is not always justified by additional safety benefits<sup>60</sup>. Another source of prohibitive costs for smaller companies is the Good Manufacturing Practice Guide for active pharmaceutical ingredients adopted by ICH in 2000. The guide contains recommendations for the manufacturing of active pharmaceutical ingredients, i.e. all operations of receipts of materials, production, packaging, labeling, quality control, release, storage and distribution. For WHO, this guideline “creates increased rigidity in the starting material supply system, with consequent effects on starting material prices and availability”<sup>61</sup>.

## II. Technical harmonization versus political or ethical choices

Efficacy guidelines are – for the most part<sup>62</sup> – concerned with the design, conduct, safety and reporting of clinical trials, which take place in the phases I, II and III of drug development. Phase I encompasses early human pharmacology studies, usually carried out in healthy volunteers or patients, who are not intended to be the end-users of the particular drug. The first studies in patients are conducted in phase II and aim to assess and confirm the therapeutic concept, explore the dosage safety and regimens as well as lack of acute safety issues in patients. These studies are conducted in small numbers of patients and precede the confirmatory phase (III) where studies are conducted in a larger number of patients. More complete information on clinical safety and efficacy, on adverse reaction and dosing are expected. Harmonization in the field of clinical studies may address technical and scientific issues; but some of these guidelines are also based on political and ethical choices.

The first example is given by the guideline that relates to the extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life threatening conditions<sup>63</sup>. The objective of the guideline was to harmonize the position of

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<sup>58</sup> The Agreement on technical barriers to trade (TBT) has been adopted in 1995. It aims to ensure that technical regulations and standards do not “create unnecessary obstacles to international trade” (preamble, art. 2.2). Generally on the TBT Agreement see: R. Wolfrum, P.-T. Stoll, A. Seibert-Fohr (ed.), *WTO-Technical Barriers and SPS Measures*, 2007.

<sup>59</sup> K. Timmermans, Harmonization, Regulation, and Trade: Interactions in the Pharmaceutical Field, *International Journal of Health Services*, 34 (2004), at 651 (656). Same interpretation for M. H. Eliason, Regulatory Marketing Approval for Pharmaceuticals as a non-Tariff Barrier to Trade: Analysis under the WTO’s Agreement on Technical Barriers to Trade, *San Diego International Law Journal* 2007, at 559 (574).

<sup>60</sup> On this point see the critics in: WHO Report 2001, *supra*, note 57.

<sup>61</sup> Report *ibid.*, at 22.

<sup>62</sup> Phase IV concerns the post-approval phase (so-called pharmacovigilance phase).

<sup>63</sup> ICH E 1.

the three regions on the issue of how much testing is required before a conclusion can be reached that a drug is safe for long-term treatment. Although scientific data reveals that some adverse events might only occur after drug treatment for more than six months, the guideline recommends that a clinical trial should include 300 to 600 patients for a period of six months<sup>64</sup>. With this solution, ICH makes a political choice: in reducing the level of scientific information on the security of the drug before drug approval, it gives national authorities an incentive to employ post-marketing regulation more effectively, so that it can rapidly withdraw a drug from the market after a major adverse reaction has been identified<sup>65</sup>.

Another example is given by the guideline for Good Clinical Practice approved by the ICH steering Committee and recommended for adoption in May 1996<sup>66</sup>. According to this guideline, non-therapeutic trials, i.e. studies where there is no direct clinical benefit to the subject<sup>67</sup>, may be conducted in subjects who are incapable of giving personal consent (e.g. in the case of children or adults who are unconscious or suffering from severe mental illness or disability). This possibility is extremely limited since it is conditioned by the delivery of the consent of a legally acceptable representative, provided some conditions like “low” foreseeable risks to the subjects and “minimized and low” burden on the subject’s well-being are respected. It is also conditioned by the recommendation that such trials “should” be conducted in patients having a disease or condition for which the investigational product is intended<sup>68</sup>. Nevertheless, the formulations adopted by ICH concerning the participation of vulnerable persons in trials are more flexible than the ones retained by international guidelines in this field<sup>69</sup>. First, the relation between principle and exception retained by the Helsinki Declaration or by the Oviedo Convention on human rights and biomedicine is not respected in the ICH guideline. In § 27 of the Helsinki Declaration the principle that incompetent subjects must not be included in non-therapeutic studies is stated before the conditions for exceptions. The Oviedo Convention is even clearer. It states in its article 6 the principle that “an intervention may only be carried out on a person who does not have the capacity to consent, for his or her direct benefit”. The conditions for the exceptional inclusion of non-competent persons in a non-therapeutic study are stressed in a separate article<sup>70</sup>. More importantly, a distinction has to be made between “low” foreseeable risks and “minimized and low” burden as foreseen in the ICH guideline on one hand, and the

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<sup>64</sup> § 4 of the guideline.

<sup>65</sup> On this example, see Abraham (2007), *supra* note 16, at 49.

<sup>66</sup> ICH E 6.

<sup>67</sup> That is the case for Phase I studies in healthy persons as described above or clinical studies conducted for the development of generic drugs, where a proof for the therapeutic equivalence and interchangeability of the generic product with a reference product is needed for marketing authorization.

<sup>68</sup> ICH E 6, at § 4. 8. 14.

<sup>69</sup> It is to be noted that different responses to the problem of non-therapeutic studies with subject incapable of giving personal consent exist. The Nuremberg Code on one hand forbids studies with non-consenting subject. The Helsinki Declaration on the other hand sets (broad) conditions for the conduct of such studies. On the different rules see: L. M. Kopelman, What Conditions justify Risky Nontherapeutic or “No Benefit” Pediatric Studies: a sliding Scale Analysis, *International and Comparative Health Law and Ethics*, 2004 at. 749.

<sup>70</sup> Art. 17, Oviedo Convention.

“minimal risk and minimal burden” required by the above cited texts on the other hand. According to the interpretation of “minimal risk” given by the Additional Protocol to the Oviedo Convention, the “research bears a minimal risk if [...] it is to be expected that it will result, at the most, in a very slight and temporary negative impact on the health of the person concerned”<sup>71</sup>. It is difficult to argue that “low” and “very slight and temporary” are synonymous. As already noticed by some commentators, it would also be misleading to consider “minimized” risk or burden as equivalent with “minimal”, since the minimization of risks is a general requirement for all kind of study on human subjects<sup>72</sup>. Finally, the interpretation in the WHO guidelines for GCP seems to categorically exclude the inclusion of subjects incapable of giving personal consent in a non-therapeutic study<sup>73</sup>.

### 3. The legitimacy and accountability of the ICH activities: the search for complementary sources of legitimation

The proliferation of public-private partnership characterizes the field of global health since the 1980s. The WHO has intensively engaged in partnership with the corporate sector cooperating in different areas such as development or distribution of drugs and vaccines<sup>74</sup>. ICH stands out with regard to this group of transnational organizations because it is the only institution that has been successful at developing global regulations applicable to pharmaceuticals. The ICH has been even more successful than the WHO in harmonizing approval requirements, although the latter, a UN organization, is the only organization that enjoys legitimacy under international law to adopt binding global standards for “the attainment by all peoples of the highest possible level of health”<sup>75</sup>.

As a result the ICH guidelines are today more or less explicitly accepted as including the “relevant international standards” for the approval of drugs. This situation is highly problematic with regard to the international rules applicable to trade since the TBT Agreement encourages national regulators to use international standards as a basis for their technical regulations<sup>76</sup>. National measures conforming to such standards benefit from a presumption of consistency with WTO law. The ICH has not been accepted so far by WTO members as a specialized organization or body in charge with the formulation

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<sup>71</sup> The CIOMS guideline Nr. 9 states that the risk should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons.

<sup>72</sup> See R. Andorno, *Regulatory Discrepancies Between the Council of Europe and the EU Regarding Biomedical Research*, in A. den Exter (ed.), *Human Rights and Biomedicine*, 2010, at. 117 (126).

<sup>73</sup> § 3.3 points (f) in relation with (g), Guideline for GCP for trials on pharmaceutical products, WHO Technical Report Series n° 850, 1995, Annex 3. According to § 3.3 (g): “In a non-therapeutic study, i. e. when there is no direct clinical benefit to the subject, consent must always be given by the subject and documented by his or her dated signature”.

<sup>74</sup> See the typology established by K. Buse, G. Walt, *Global Public-Private Partnerships: Part II, Bulletin of the WHO*, 2000, at 78.

<sup>75</sup> On the objectives of WHO see art. 1, 21 and 22 of the WHO Constitution. On the comparison of the relevance of WHO standards as regard to the ICH standards, see: WHO (2001) *supra* note 57.

<sup>76</sup> See § 2.4 of the TBT Agreement.



of standards such as for instance the Codex Alimentarius Commission for food safety<sup>77</sup>. But the *de facto* relevance of the ICH standards makes this evolution probable rendering the question of legitimacy and accountability of the ICH even more acute.

The efficiency of the ICH's harmonization efforts alone should not be accepted as basis for its legitimacy. The partnership between pharmaceutical industries and public authorities creates a need to test the application of the legal standards identified as principles applicable to global administrative law (1) and to search for new instruments in an effort to develop and reinforce the legitimacy of this particular institution (2).

***a. The extremely limited accountability: actual institutional and procedural arrangements***

The global interest in the ICH-activities has provoked the evolution of the institutional framework of the ICH, to authorize a greater participation of non-ICH members within the process<sup>78</sup>. Nonetheless these institutional and procedural developments assure only a restricted participation to non-participant regions in the decision-making process (1.1). The transparency of the harmonization process is also too limited with regard to the authority and the nature of the guidelines exposed above (1.2).

**I. Participation**

The governance structure of the ICH is relatively simple. It does not allow the participation in the decision-making process of national regulatory authorities, departments of health and companies like generic manufacturers from outside the ICH regions or other non-state actors representing groups within the civil society (professional associations, patient or consumer advocacy group). The governing body is the ICH Steering Committee (ICH-SC) that is composed by the six founding members, who each have two seats, and by non-voting participants designated by the three observers. The steering Committee oversees all activities: first, it determines the harmonization activities to be pursued (i.e. initiative for guidelines and other instruments). Second, it adopts the guidelines and instruments that have been finalized and accepted by the parties through consensus. Third, it supervises the implementation and monitoring of ICH commitments. The IFPMA exercises an important role since it provides the secretariat and participates, like the three observers, as a non-voting member on the ICH-SC.

The other organs are the new organs created in 1999 and 2008 and the different expert working groups. As mentioned above, in 1999 the ICH-SC created the Global Cooperation group as a subcommittee, to allow the "participation" of representatives from non-ICH regions. In 2008, the ICH-SC also created a structure called the Regulators Forum. But these two structures do not offer any participation opportunities

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<sup>77</sup> See § 3.4 of the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement). On the influence of international standards edicted by this commission in the field of food safety, see: R. A. Pereira, Why Would International Administrative Activity be any less Legitimate? A study of the Codex Alimentarius Commission, *German Law Journal* 9 (2008), at. 1693.

<sup>78</sup> K. Timmermans (*supra* note 59, at. 655) explains this evolution with reference to the intention of the ICH to become a global standard-setter in accordance with WTO law.

to their members within the elaboration process of the ICH guidelines. They only constitute platforms for discussion, information, and training. Their role is to allow the dissemination of ICH standards worldwide. Eventually the Regulators Forum could be of some use, since it offers a discussion platform for the sharing of information directly between regulatory authorities associated or represented in the GCG.

The experts' groups are the informal working groups, the expert working groups (EWG) and the implementation working groups. They are composed of official representatives nominated by each of the six official ICH members (two representatives per party) and of one representative per observer. According to the ICH documents, other parties may be invited by the ICH-SC to nominate experts to ICH working groups. These parties include ICH Regional Pharmacopeias and the so-called ICH "interested parties", which are those organizations that are expected to implement or to be regulated by the outcome of ICH efforts such as the World Self-medication Industry and the International Generic Pharmaceutical Alliance or such as "other parties" as determined by the steering committee over time. Some drug regulatory authorities from non-ICH countries belong also to this group<sup>79</sup>. Regrettably no more information on when and how the participation is to take place are given. The expert working groups are created at the different stages of the decision-making procedure by the ICH-SC which is a staged, extremely elaborate procedure. Participation of regulatory authorities and industry associations in non-ICH regions can also occur at step 3 after the approval by the ICH-SC of the draft guideline<sup>80</sup>. Step 3 is characterized by regulatory consultation and discussion. The consultation takes place in the three ICH regions but also beyond them. The comments are thus discussed and addressed by the experts group at step 4. Since the possibility to formulate comments is not associated with an opportunity to discuss the comments with the working group and vote on the result, it is difficult to consider this an opportunity for real participation. Moreover, the importance attached to science in the standard-setting procedure eventually diminishes the contribution of developing countries. In this perspective, the absence of transfer of information and publicity of the process within the working groups constitutes an additional obstacle to participation.

## II. Transparency

The ICH website gives access to many documents: e.g. the guidelines and instruments in the first and revised forms; the documents called Questions and Answers that give more information and explain the implementation of a specific instrument; the reports of the ICH-SC and GCG meetings reports; a glossary and other documents explaining the elaborate procedure, the institutional structure of the ICH. Public conferences or public meetings are also organized, to give an overview of ICH activities as well as an update on the instruments and improvements in the implementation in the different regions of the world<sup>81</sup>.

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<sup>79</sup> The ICH "interested parties" are listed in the ICH glossary.

<sup>80</sup> With this approval, the ICH-SC confirms that there is sufficient scientific consensus on the technical issue. The consent of 6 of the 12 voting-members of the ICH-SC is required for approval.

<sup>81</sup> See for example the proceedings of the ICH Japan Symposium 2009.

However, decisional transparency will not exist as long as there is no public access to internal documents. There is no information on the work and discussions that lead to the consensus building at step 2, nor is there information on discussions and work after comments have been received at step 3. This lack of transparency is a critical issue for various reasons. It first constitutes a real obstacle for the non-ICH members in the formulation of comments. Second, it leaves open the question of the potential influence of organizations or specialists in *ad hoc* consultations by the working groups. In fact, for the elaboration of the draft guidelines the working groups refer to guidelines that have been already adopted on the same questions at the international level by other expert groups or organizations. For example, the ICH working groups makes reference in several guidelines to the work of the CIOMS<sup>82</sup>. The ICH could make use of the multitude of the sources to reinforce the authority of its instruments. In the same way, the “concept papers” that are the documents giving the impulse for the development of a guideline, often recommend to include experts from any “interested party” in the EWGs, in addition to those from the 6 ICH parties and observers. It would be interesting to examine more systematically where and how the “interested party” are implicated in the elaboration procedure.

Finally, the confidentiality of the debates within the EWG is unfortunate since there is no ICH code of conduct. No special conditions are imposed for the designation of the experts to the different working groups. The ICH-parties are free to designate anyone within their “Contact network of experts”. The experts designated by the regulatory authorities are subjected to the rules developed in their countries or region. In the European Union for instance, it is accepted that the evaluation of scientific evidence in the health field requires high scientific quality by the experts, but also integrity and high standards of independence. The rules that have to be followed for the designation of experts intend to insure that they do not “have any financial or other interests in the pharmaceutical industry which could affect their impartiality”<sup>83</sup>. By contrast, for the experts designated by the pharmaceutical industry there are no such rules. This is very unfortunate and casts doubt upon the capacity of ICH experts groups to formulate the scientific assessments that constitute the basis for the technical harmonization. This is even more problematic since the only condition concerning the experts and defined by the ICH founding documents is that they should be chosen “to ensure that, in the discussions, they reflect the views and policies of the co-sponsor they represent”<sup>84</sup>. This condition should be suppressed and rules for the management of conflicts of interest should be developed and applied to all experts.

#### ***b. The search for new forms and procedures improving accountability and***

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<sup>82</sup> This Council had been created under the auspices of the WHO and the UNESCO in 1949. Several CIOMS guidelines have influenced the regulatory approach to medicines safety as for instance ICH E 2 A (international reporting of adverse drug reactions) and ICH E 2 B (electronic case submission of individual case safety reports).

<sup>83</sup> See art. 63 (2) Council regulation (EC) 726/2004 and the EMEA Code of conduct as revised in 2004 through the guidance on conflict of interests. See also the rules of procedure that apply for the EMA scientific committees ([www.ema.europa.eu](http://www.ema.europa.eu)).

<sup>84</sup> See ICH website, Working Groups.

## *legitimacy*

The assessment of the ICH's decision-making procedure under the legal standards of Global Administrative Law provides a clear result: the accountability and legitimacy of the ICH are extremely tenuous. But one should not forget that the ICH as an international public-private partnership creates a new – and very successful – form of global administrative decision-making procedure. Some authors have already pleaded for the creation of new forms of accountability and legitimation for new “transnational administrative networks of agencies”<sup>85</sup>. These new instruments are diverse, and include for instance: the reinforcement of the domestic legitimation and accountability of the national agencies participating with the transnational system<sup>86</sup>; an increased information and participation of all constituencies subjected to the exercise of normative authority by non-state standard setters<sup>87</sup>; judicial and non-judicial review mechanisms<sup>88</sup>.

Doctrinal analyses are very helpful and cast a new light on some steps already taken by the ICH to promote the participation of non-ICH members with the process (2.1) and to engage in closer cooperation with the WHO (2.2).

### **I. Taking into account new constituencies and their proper needs**

In creating new structures for the participation of non-ICH members within the harmonization process, the ICH has proven the flexibility of its particular structure and enhanced in some ways its democratic legitimacy. It has underlined the necessity to identify and take into account all constituencies in order to reinforce its accountability and legitimacy<sup>89</sup>. The identification of the pertinent actors appears generally to be controversial<sup>90</sup>. The ICH has identified generic and over-the-counter drugs manufacturers on one hand, and regional Harmonization Initiatives and some non-ICH states represented through their regulatory agencies on the other. Therefore particular stakeholders and – in accordance with the internationalist approach – the national states as a whole body are now represented<sup>91</sup>. This move was not self-evident because it supposes that the ICH activities concern objectives common to all states. This is the case for the ICH because human rights issues are at stake<sup>92</sup>. In fact, the contemporary content of the right to health as a human right authorizes such an interpretation of the ICH standards developed originally for the marketing of new medicinal products.

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<sup>85</sup> See K. H. Ladeur, *supra* note 23, at 3.

<sup>86</sup> See for example K.-H. Ladeur, *ibid.*, at 25; S. Cassese, *supra* note 19, at 689.

<sup>87</sup> See for example M. S. Barr, G. P. Miller, Global Administrative Law: the View from Basel, *The European Journal of International Law* 17 (2006), at 24.

<sup>88</sup> See E. de Wet, Holding international Institutions Accountable: the Complementary Role of Non-Judicial Oversight Mechanisms and Judicial review, *German Law Journal* 9 (2008), at 1987; B. Kingsbury et al. (2005), *supra* note 19, at 39-40.

<sup>89</sup> According to K. Timmermans (*supra*, note 59, at 655), these efforts are only directed at transforming the ICH into an organisation fulfilling the criteria of the TBT Agreement for the definition of international standards.

<sup>90</sup> See N. Krisch, The Pluralism of Global Administrative Law, *European Journal of International Law* 17 (2006), 247 (more specifically at. 249).

<sup>91</sup> On the three competing constituency approaches, see Krisch, *ibid.* at. 253.

<sup>92</sup> On the different approaches of the stakeholders see N. Krisch, *ibid.* at 249.

The right to health has been acknowledged by most countries in the world directly in their constitution or indirectly through judicial pronouncement<sup>93</sup>. Thus, these countries comply with regional and international instruments such as the International Covenant on Economic, Social and Cultural rights (ICESCR). This right is not equivalent to a right to access all kind of medicines and a fortiori it seems difficult to invoke the right to health as equivalent to a right to access new drugs. However, it has been argued that the right to health is equivalent to a right to access “essential medicines”. According to the interpretation of Article 12 of the ICESCR, formulated by the UN Committee on economic, social and cultural rights in the General Comment n° 14 in 2000, state parties have to make sure that “essential medicines” are available in sufficient quantities for everyone within their jurisdiction. The concept of “Essential medicines” has been introduced at the World Health Assembly in 1975 and refers to the drugs defined by the WHO Program on essential drugs that have to be provided as a component of “primary health care”<sup>94</sup>. Analyses have shown that a very small percentage of the Medicines on the WHO list of essential medicines are new, patented drugs<sup>95</sup>. In fact a large amount of the drugs retained by WHO are available in generic forms. However, rejecting the argument that the ICH standards interfere with individual rights on this basis and therefore, that there are no other constituencies than the ICH members, would be ignoring two facts: first, the need of developing countries for new product as essential medicines to combat infectious diseases is real<sup>96</sup>; second the influence of the ICH activities as set out above. In fact, the ICH standards are today applicable to all kinds of medicinal drugs. This is true, first of all, for the ICH-members. In Europe for instance, the application of the Common Technical document concerns all type of medicinal products<sup>97</sup>. This is also true for many developing countries: although the production of pharmaceuticals in these countries is focused on generics and not on new medicinal products, they have decided to comply at least with the most important guidelines (quality requirements, analytical procedures and pharmacopoeial standards)<sup>98</sup>.

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<sup>93</sup> About the judicial recognition of the right to health in Germany, see S. Dagron, *Droit à la santé et jurisprudence constitutionnelle: les enseignements de l'expérience allemande*, in: Mélanges Breillat, *Les voyages du Droit*, 2011, at. 155.

<sup>94</sup> See the Alma Ata Declaration that closed the International Conference on primary health care organized by WHO, para. VII (3). “Primary health care” has been defined by the Declaration (para. VI) as “essential health care based on practical, scientifically sound and socially acceptable methods and technology made universally accessible to individuals and families in the Community through their full participation and at a cost that the community and the country can afford to maintain [...]”.

<sup>95</sup> According to D. Matthews (WTO Decision on Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health: a Solution to the Access to Essential Medicines Problem? *Journal of International Economic Law* 7 (2004), at. 73) fewer than 5 per cent of the drugs listed by WHO on the Model List of Essential Medicines are patented.

<sup>96</sup> That point has been acknowledged and underlined by the UN General Assembly in its Millennium Declaration. See UN Millennium Declaration, points 19 and 20.

<sup>97</sup> See art. 6 and 10 (1) of the Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use, in connection with § 2 of the Annex 1. There is one exception: the application for the approval of a generic does not have to respect the form of the CTD in the case where the reference product has been authorized under the CTD conditions.

<sup>98</sup> See the viewpoint of an industry representative from a non-ICH country in: Proceedings of the

In developing new structures for the participation of the non-ICH members, the ICH Steering Committee has reinforced its democratic legitimacy. However this enhancement is limited and insufficient as regard to the particular needs of its new constituencies. In fact if the realization of the right to access medicines in the concerned regions is dependent on the marketing of generics, a stronger participation in the decision-making process should in theory improve the democratic legitimacy of the Conference. However, in practice, this will probably not improve the fulfillment of the proper needs of the non-ICH countries. So far, the adoption of common rules applicable worldwide has not been possible because the interests in this field are hardly compatible. The argument in favor of a stronger participation of developing countries would rely on the unrealistic and empirically unsupported assumption that all stakeholders will have the necessary scientific and financial capacity as well as the willingness to advance the “global” public interest<sup>99</sup>. The request formulated by regulatory authorities participating with the GCC at the Regulators Forum in 2009 illustrates perfectly the fact that scientific and financial capacities are missing. At the Forum, the participants did not request voting rights but solely expressed their interest to participate in the EWGs discussion which would allow them to better understand the development process of a guideline and facilitate its implementation. The focus should be on the concerned rights, interests and particularities of the non-ICH members as identified constituencies of the ICH.

## II. Reinforcing the “public” part of the public-private partnership

Public-private partnerships constitute new forms of international governance and it might be necessary to develop new standards applicable to them. National administrative law has already developed new frameworks in order to authorize the public-private collaboration for the delivering of public services and infrastructures. A common question attached to the creation of these partnerships always concerns the extent to which risks (and responsibilities) can be passed to the private sector. A common feature is accordingly the important weight of the public authority within the partnership<sup>100</sup>.

In the reinforcement of the collaboration with the WHO the ICH has already started another (complementary) step, that could constitute an important element favoring the legitimation and accountability of international public-private partnership forms of administrative activities more generally. The WHO is the only organization that has a legal mandate from 193 member states to set global standards for the promotion and protection of public health. According to its Constitution, WHO is competent to “develop, establish and promote international standards with respect to [...] pharmaceuticals”<sup>101</sup>, while the Health Assembly has authority to adopt regulations

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8th International conference of Drug Regulatory Authorities, 1996.

<sup>99</sup> See on the capacity to participate of Estonia, L. Rägo, Proceedings of the 8th International conference of Drug Regulatory Authorities, 1996.

<sup>100</sup> On the regulation of public-private partnership in the United Kingdom see C. Harlow, R. Rawlings, *Law and Administration*, 2009, at 413.

<sup>101</sup> Art. 2 (u).

concerning “standards with respect to the safety, purity and potency of biological, pharmaceutical and similar products moving in international commerce”<sup>102</sup>. WHO has already drafted guidelines concerning quality, safety and efficacy of medicinal products (also generics and medicinal products for use in self-medication)<sup>103</sup>. It has also adopted a scientific technical code on the quality of medicinal products called pharmacopoeia that takes the needs of developing countries more strongly into account. The international pharmacopoeia constitutes a collection of recommended procedures for analysis and specifications for the determination of pharmaceutical substances, excipients and dosage forms that is intended to serve as a source material for reference or adaptation by any WHO member State wishing to establish pharmaceutical requirements.

Cooperation with WHO used to take the form of reference to WHO documents<sup>104</sup> and reports<sup>105</sup> as sources for the elaboration of draft guidelines. However, many elements have revealed an intensification of the cooperation. For instance, in its decision to withdraw the guideline Q 1 F on stability - Data Package for Registration Applications in Climatic Zones III and IV (outside the ICH-regions) - in 2006, the ICH-SC has acknowledged the divergence between the requirements specified in its guideline and the standards for storage conditions retained in the concerned countries. It decided to leave the definition of storage conditions in these climatic zones to the respective regions and WHO<sup>106</sup>. Also of note is the reinforced collaboration between ICH and WHO concerning the use of the Medical Dictionary for Regulatory Activities (MedDRA) developed by ICH to facilitate the coding and the sharing of regulatory information (biopharmaceutical development, clinical trials, reporting of adverse events)<sup>107</sup>. MedDRA is intended for use in the pre- but also postmarketing phase of the medicines regulatory process thus entering a domain where the WHO has been extremely active. WHO has in fact also developed a dictionary meant to serve for coding clinical information in relation to drug therapy. The so-called WHO Adverse Reactions Terminology (WHO-ART) serves also as a basis for a worldwide applicable coding of adverse reactions. In 2001 WHO experts had expressed their concerns about the difficulties for the developing countries connected with the use of MedDRA and proposed to involve WHO in the review of the ICH dictionary. Since 2007, the MedDRA is fully implemented in the WHO global safety database which allows WHO to review data and conduct analyses in both WHO-ART and MedDRA.

#### 4. Conclusion

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<sup>102</sup> Art. 21 (d).

<sup>103</sup> See for instance the Blue Book edited by WHO in 1999 and 2011 on Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products (Manual for National Medicines Regulatory Authorities).

<sup>104</sup> For example WHO GCP. See also *supra* at note 30 on the influence of CIOMS guidelines on pharmacovigilance.

<sup>105</sup> See elaboration of ICH Q 1A and the WHO Report on climatic zones.

<sup>106</sup> See explanatory note in the withdrawal of ICH Q 1 F.

<sup>107</sup> ICH M 1.

The ICH has proven to be a very efficient structure for the harmonization of requirements for the approval of new drugs. The guidelines and instruments adopted exercise a normative influence in many countries within and outside the group of the ICH participating regions and constitute real global standards with technical but also industrial, political and social implications. Despite the authority of its decisions, the ICH does not allow a broad participation in the decision-making process nor provide for the transparency of the harmonization procedure. Nevertheless, the recognition of new constituencies and their needs reflects a certain flexibility of the structure. There is also a broader collaboration with the WHO as sole legitimate organization with a legal mandate to set global standards in the field of pharmaceuticals. The ICH should heed the special need of its constituencies better and should be more transparent concerning the intervention of the WHO. A clarification of the ruling powers of the participating national regulatory authorities, in particular for the European Union, could also constitute an advantage and represent a supplementary way of strengthening the legitimacy and accountability of the ICH.