EU risk regulation and its Global Standards: the case of Pharmaceuticals

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Abstract:

The European Union in its risk regulation activities is increasingly relying on standards set by international entities. Using the example of standards for pharmaceutical products set by the International Conference for Harmonisation (ICH), this paper points out problems of transparency, participation and the use of expertise in standard-setting processes. It furthermore argues that regardless of the soft law nature of these standards, in fact the European Union without fail implements them into its risk regulation framework, where they receive 'quasi-binding’ value regardless of the flaws in global process.

Introduction
The well known work of Ulrich Beck has coined the term ‘risk society’ as referring to the increased significance of risk for our every day lives owed to the progress in science and technology.¹ These risk are addressed through risk regulation measures taken in order to prevent risks to human health from materializing, as understood for this research, primarily by means of setting and adhering to safety and quality standards of products and production processes.²

In times of an evermore globalized world with interconnected markets, the regulation of risks inherent to consumer products evolves into an exercise carried out at multiple levels of organization. Also the European Union in its risk regulation framework increasingly relies on standards set by international entities.³

The regulation of access to pharmaceutical markets as analysed in this paper used to be ‘virtually synonymous with national sovereignty’⁴, being closely linked to the administrative and socio-economic culture of a state.⁵ However, like many other areas of risk regulation it is experiencing a shift away from the traditional national regulation by public authorities to regulation on the global level.

The PhD research that forms the basis of this paper focuses on a critical analysis of regulatory standards developed at the global level and their influence on the European Union’s risk regulation. The aim is to provide an in-depth understanding of the regulatory processes on the global level, especially in terms of transparency, participation and the use of (independent) expertise. Furthermore, it wants to point out the influential role of these standards on the European risk regulation and question the legitimacy of their use.

First of all, section 1 will introduce the context of a paper with a closer look at standards as tool for risk regulation. Section 2 will then introduce the International

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Conference on Harmonisation (ICH) case study, while section 3 will critically analyse the transparency, the participatory openness, and the use of expertise in the ICH process. In the following section the paper then looks at how the standards are implemented in the European Union.

1. Regulating risks: global standard-setting

Standards in the risk regulation context gain increasing importance as regulatory tool. Often being associated with the compatibility of technical components, today standards evolved into important regulatory tools for organizing markets and regulating risks in manifold ways. They are intended to create a level playing-field in international trade through harmonization. In this context, a standard is defined as voluntary expertise based rule, constituting measurable criteria by which a product or a production process or service can be evaluated on the basis of technical or physical conditions.

The addressees of these standards can be governments, economical actors or other national and international standard-setting institutions. They originate in a variety of processes: On the global level standard-setting occurs (i) purely private by (syndicated) companies or non-governmental organizations (NGOs), (ii) by international committees set up though cooperation of administrative authorities of different countries and regions, (iii) by transnational standardization entities which bring together public and private actors, and (iv) in the framework of existing international organizations. As will be shown, the ICH falls into the third category, being a joint effort of public and private parties.

Although this global cooperation in the form of standard-setting seems to be an imperative response to the complex risks face today, it has been criticised in terms of its legitimacy as taking place in rather technocratic and closed setting, by regulators

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and industry hiding from public scrutiny.\textsuperscript{12} Therefore, after having introduced the ICH and clarified its decision-making process in the following section, in section 3 a closer look is taken at the transparency of the decision-making process, as well as participatory issues and the use of expertise in the standard-setting.

2. Global Standards for Pharmaceuticals: The International Conference on Harmonisation

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical Products for Human Use (ICH) founded in 1990, is currently the leading standard-setting body for pharmaceuticals worldwide.\textsuperscript{13} The members, or co-sponsors as they are called in ICH terminology,\textsuperscript{14} are representatives from the regulatory authorities and research-based pharmaceutical industry associations of the three largest drug markets in the world, the United States of America, Japan and the European Union.

As regulatory authorities, the European Commission together with the European Medicines Agency (EMA), the Ministry of Health, Labour and Welfare (MHLW) from Japan and the US Food and Drug Administration (FDA) are participating in the process. While the industry is represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japan Pharmaceutical Manufacturers Association (JPMA); and the Pharmaceutical Research and Manufacturers of America (PhRMA).\textsuperscript{15} Furthermore, the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), provides secretarial assistance to the ICH and also participates as non-voting member in the ICH’s main decision-making body, the Steering Committee. Additionally to the six parties with full membership rights, the ICH has granted an observer status to the World Health

\textsuperscript{14} http://www.ich.org/about/organisation-of-ich/steering.html.
\textsuperscript{15} The research-based pharmaceutical industry is engaged in the innovation of medicinal products, marketing products developed on the basis of own research, in contrast to manufacturers of generics, which are bioequivalent to existent products.
Organisation (WHO), the European Free Trade Association (EFTA) and Canada. The members agreed to a mandate of harmonizing technical requirements for pharmaceutical products throughout the three regions. It is important to note, that the idea behind the ICH is not the harmonization of the marketing authorization procedure in the sense of a mutual recognition of regulatory assessments in the three regions. Every authority in the three regions will continue to carry out their own scientific assessment and the marketing authorization in one of the three regions has no influence on the decision in the other ones.

The ICH was the first initiative to bring together a group of national regulators in one harmonization forum whilst also the involvement of industry in such a body was a novelty. With regard to its organizational form, the ICH can be qualified as a public-private partnership. Public-private partnerships (PPPs), are forms of cooperation between governmental and non-state actors and increasingly attract academic attention. Even though the term partnership might allude to a certain form of legal incorporation or the establishment as a legal entity, this is not necessarily the case as these partnerships might as well be formed as informal de facto initiatives, sometimes even by not legally established groups of stakeholders. PPPs do not correspond to one specific form of legal establishment and occur in various organizational forms, complicating their placement into traditional legal categories. These partnerships operate outside the classical international law terminology as they usually do not constitute international organizations, due to their lacking basis in from of an international legal act and because they are not necessarily established by entities formally recognized under international law.

The ICH, established as a public-private partnership, epitomizes global regulatory
interaction not formalized in a traditional international organization under international law. It is a manifestation of the increasing trend towards abandonment of traditional, state-centred forms of transnational cooperation.23

These partnerships are mostly driven by the wish to share expertise, which is also the case for the ICH. Furthermore, they ‘typically entail some joint decision-making and sharing of responsibilities, opportunities, and risks.’24 And indeed, in the Steering Committee, the ICH’s main decision-making body, each of the six members has two seats and decisions are taken by consensus, giving the industry equal power in the decision-making process.

Apart from the equal distribution of powers between industry and regulators in the Steering Committee, also in the standard-setting process itself the industry is evolved on equal terms as the regulatory authorities. The standard-setting procedure in the ICH follows a five-step procedure, the core principle being adoption through consensus of the six parties.25 After a topic has been selected for harmonization, the Steering Committee appoints an Expert Working Group responsible for reviewing the existing standards in the three regions and working towards scientific consensus in the matter. Generally Expert Working Groups encompass a maximum of two representatives per party and one for every observer or interested party.26 As consensus is reached, the EWG sets up a Technical Document and passes it to the Steering Committee for adoption.27 Also for the final adoption decision, consensus is the adhered to.28 After adoption, the ICH Steering Committee recommends the

25 http://www.ich.org/about/process-of-harmonisation/formalproc.html; The procedure explained applies to the harmonisation of new topics. Next to this, there are also procedures for the adoption of Q&As, the revision of established guidelines and the maintenance procedure for changes to specific types of guidelines, which will not be discussed.
26 ICH, ICH Procedures Version 1.1, p.3.
28 In June 2012 during the Steering Committee meeting in Fukuoka (Japan), the Committee agreed that where industry and regulatory authorities disagree in the harmonisation of a topic, the consensus of the three regulatory authorities provides a sufficient basis to continue with the harmonisation regardless of the objections of industry. However, the Press Release also emphasises that the process of harmonisation will still be carried out via consensus. (ICH, Steering Committee Report, Fukuoka, Japan, 6–11 November 2010) Currently in the most recent version of the ICH procedure last change in November 2013, does not only emphasize consensus as core principle, for decision-making but also entails what can be called a veto right for industry. Step 4, the adoption of the guideline in the Steering Committee is still described in the following terms: ‘In the event that one or more parties
guideline for adoption by the regulatory authorities of the three regions according to their domestic law and administrative procedures.  

As consensus is the core principle in the ICH decision-making process and the industry associations are represented in the same way as the public regulators in both the main decision-making body, the Steering Committee, as well as in the Expert Working Groups forming the scientific consensus, the industry within the ICH has established itself as a true co-regulator.

The ICH guidelines represent the agreement of the six parties on the requirements that have to be fulfilled in order to ensure the safety, quality and efficacy of medicinal products. They harmonize scientific and technical details such as the necessity of a pharmaceutical product to be tested on cancer causing properties in order to establish its safety. These guidelines have to be taken into account by the industry during the development phase of a product and their compliance needs to be proven by the industry when submitting their dossier for the authorization procedure in the three regions.

Although the guidelines are of technical nature, still also these issues can contain important policy choices as is exemplified by the ICH guidelines clinical trials. In which –on the pressure of the FDA- placebo controlled trials are advocated over trials with a control group that receives another comparable medicinal product. This entails an important choice on the definition the efficacy of a medicinal product: Is it sufficient if the product has a curative effect, or should it be superior to the existing treatment? The choice made has ethical implications with regard to the control group,
which receives a placebo instead of an actual cure without knowing, and it will also entail implications for the health care system in general, as it means that products can be on the market that are actually inferior to already existing ones. Thus, apart from clarification technical details, the harmonization process also has the potential to influence broader policy choices.

The guidelines set by the ICH, the so-called harmonised tripartite guidelines can be qualified as standards and are thus of voluntary nature. They are not legally binding themselves, but have to be qualified as soft law, since they do not create rights or obligations. This is underlined by the fact that, until now, the ICH has no internal mechanism to deal with a wrong or missing implementation in the three regions. As Kanusky concludes her analysis of the ICH guidelines: ‘(t)he consensus reached through the ICH has neither the force of an international accord nor a treaty.’ However, regardless of their soft law character, the influence of these guidelines should not be underestimated, de facto they are implemented without fail in the three regions, probably due to high epistemic authority and the fact that they are the product of a consensus based standard-setting process.

Thus, through the ICH process, the industry has become a global co-regulator in the area of pharmaceuticals, for the regulation of technical issues and sometimes also important policy choices in the form of voluntary standards, which, however, are rigorously followed in the three member regions.

3. Participation, the use of expertise and transparency: the legitimacy flaws of the ICH process

Looking closely at the decision-making process, it becomes clear that the role of the

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34 Bahri & Tsintis, loc. cit. n. 26, p.379.
35 Kanusky, loc. cit. n. 28, p. 695.
industry as co-regulator in a regulatory field where industry interests need to be balanced with the protection of public health requires needs to be compensated with procedural transparency, participatory mechanism that ensure the incorporation of all concerned interests and the use of independent expertise.\textsuperscript{37}

3.1. Transparency

With regard to the transparency of ICH standard-setting, although in the pre-internet era the ICH has attracted severe criticism as the process was completely hidden from the public,\textsuperscript{38} today through the website (www.ich.org) the ICH is increasingly disseminating information. Most importantly, the final products of the ICH process, the Harmonized Tripartite Guidelines are published on the ICH website, including information on which step of the decision-making process they have reached. Moreover, the interested public can find the terms of reference, which lay down the ICH’s mission, as well as an overview on the ICH history and structure. Also the ICH’s five step decision-making process as well the revision and maintenance procedures are explained.

The website also provides information on the membership of the Steering Committee and since 2005 also summarized versions of the Steering Committee Meeting Reports are accessible via the website, containing short information on organizational issues and new guidelines in the drafting process. Although currently some reports from the recent past are still missing.\textsuperscript{39} Moreover, in the June 2013 Steering Committee Meeting it was decided to from now on publish also the agenda of the Committee meetings.\textsuperscript{40}

Although these steps towards providing more information on the ICH decision-making process are to be welcomed, it needs to be criticised that the key activity of the ICH, the consensus forming process in the Expert Working Groups as well as the


\textsuperscript{38}See: J. Contrera, loc.cit. n. 26.


\textsuperscript{40}ICH, Press Release, La Hulpe, Belgium, June 2013.
Steering Committee remains opaque. Especially more information on the discussions in the Expert Working Groups would facilitate the control of industry influence on decision-making. Regrettably, the procedure also does not foresee a reason-giving requirement which could give more indications as to how the consensus was formed and which arguments were discussed. Therefore, although the ICH worked towards increasing transparency, there is still significant room for improvement.

3.2. Participation

The participation of other stakeholder groups then the industry associations in the ICH process is largely absent. No consumer or public health advocacy group has an institutionalised role in the ICH process. Neither are they conferred observer or interested party status nor are they otherwise involved as a party in the harmonisation process. The only institutionalised representation of public health interests in the procedure is secured through the regulatory authorities and their dual mandate to promote public health while also paying due attention to industrial interests.

The only possibility for other stakeholders to actively get involved in the standard-setting process is the public consultation carried out by the national/regional regulatory authorities in the third step of the ICH standard-setting process. The public consultation procedure itself foresees that the Draft Guideline is submitted to the regulatory authorities of the three regions for public consultation according to their national procedures. Moreover, it is published by the ICH Secretariat for comments from other regulatory authorities, industry associations and stakeholders. Being open to everyone interested, comments can be provided to the regulatory authorities of the three regions or the ICH itself, the consultations being easily accessible on the respective websites.

However, the public consultation is flawed due to the fact that it takes place rather late in the process and that no feedback is provided on how the comments are taken into account. The public consultation takes place after a consensus is reached in the EWG and before the final adoption of the guideline through the Steering
Committee. Therefore, it is questionable how much influence stakeholder comments still have, since the consensus among the experts is already formed.

The harmonisation procedure foresees that the comments are discussed in the Expert Working Group, however, since no feedback is provided it cannot be traced whether this indeed takes place and to what extent. Apart from general issues with transparency in this regard, it also hinders the efficient provision of comments by stakeholders, disabling them to engage in active discussions and it also certainly has a demotivating effect, as the impact of the comments is not visible and unsure.

In contrast to the practice of the European Medicines Agency, which sets guidelines in the European regulatory framework, publishing a summary overview of the comments received including short responses to them, once the comments are submitted to the ICH process they leave no visible trace.

In addition, the fact that comments or summaries are not published, also conceals who has taken the opportunity to actually comment via this procedure. For the US where information on who is commenting seems to be available, Berman comes to the conclusion that industry comments are in the ‘overwhelming majority’.

Therefore, although the public consultation procedure opens the door to participation of societal interest, the possibilities for actual influence on the procedural outcome conveyed through this are limited and unsure.

3.3 The use of expertise

Also the expertise used in the process deserves critical attention, since as it has been indicated before that expertise and resources offered by the industry often constitutes the trigger for regulating in the form of a public-private initiative. Still, independence of expertise is a prerequisite for creating legitimate standards, this especially so in an area where public health and industrial interests both deserve protection.

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In this regard, it is remarkable that in the ICH no effort is undertaken to address the issue of conflicts of interest at all. Realizing that in public-private standard-setting bodies the parameter should not be whether there are conflicts of interest, but rather how they are dealt with the following questions arise: are the affiliations and interests of the experts involved communicated within the body? Are they communicated to the outside world? Is any consequence attached to conflicted interests?

On the Steering Committee level, the membership is nowadays communicated via the website, making visible that the three industry parties are currently represented through one participant from the industry association and one from a specific company (at the moment Boehringer Ingelheim Pharmaceutical, Daiichi Sankyo Co., Ltd. and AstraZeneca).46

However, as the membership of the working groups is not made public – maybe also due to their fluctuating nature – and there is no policy or any requirements published on the choice of experts for the working groups apart from the statement on the website that ‘in the discussions, they reflect the views and policies of the co-sponsor they represent’.47 It remains impossible to retrace who has been involved in the drafting of the guidelines and whether and in what way the expert might have had an interest in interfering with the harmonization outcome.

Leaving aside the communication of possible conflicts to the outside world, from the information publicly available there also seems to be no internal policy on conflicts of interest – one could for example think about whether the affiliation of the individual experts on the working groups is communicated to the other members and how scientific information provided by the industry representatives is assessed on its reliability.

Admittedly, dealing with conflicts of interest in public-private settings is challenging, however, at least a transparent dealing with them is a prerequisite for legitimate standard-setting. Here, the ICH falls short of securing a non-biased scientific basis for its guidelines.

4. From the global to European: the implementation of ICH standards in the European pharmaceuticals regulation

The procedural deficiencies nonetheless do not prevent the influential position of the ICH as the dominant source of pharmaceutical standards and the guidelines agreed upon within the ICH process are also reliably implemented in the European Union. For this purpose, they are adopted as guidelines of the Committee on Human Medicinal Products (CHMP), which is the main scientific committee within the EMA. Where the CHMP has adopted the ICH guidelines, they ‘have the same status as other European scientific guidelines and replace existing guidelines on the subjects covered’. 48

These scientific guidelines are referred to in Annex 1 of Directive 2001/83, which according to Art. 8(3) of Directive 2001/83 and Art. 6(1) of Regulation 726/2004 provides for the required format and documentation to be submitted for a marketing authorization application of a pharmaceutical product in the context of the Union’s pharmaceutical regulation. 49

Their purpose is to in detail clarify the legislative requirements for proving the quality, safety and efficacy of a medicinal product, forming the basis of the assessment of a marketing authorization. Although these guidelines do not create legally enforceable obligations, the Agency itself qualified them as ‘quasi-binding’ as they provide further detail to legal obligations. 50 As is explained in the EMAs clarification of the legal status of these guidelines:

‘scientific guidelines are to be considered as a harmonised Community position, which if they are followed by relevant parties such as the applicants, marketing authorisation holders, sponsors, manufacturers and regulators will facilitate assessment, approval and control of medicinal products in the

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Thus, although the guidelines are of a soft law character, their application to marketing authorisation requests is compelling and will only allow for exceptions where this is duly justified, meaning that in practice they are very influential on the development process and following authorisation of pharmaceutical products. Essentially, adherence to them is necessary to provide the documentation to prove the quality, safety and efficacy in order for pharmaceutical products to be admitted to the European market.

Apart from the implementation of the ICH guidelines through the CHMP, the ICH harmonization can also have an impact on legislative provisions. The prime example here is the ICH Q7 guideline on good manufacturing practice (GMP). In the aftermath, of the agreement on the ICH good manufacturing practice the Pharmaceuticals Directive had to be amended. As the ICH guideline not only requires the application of the good manufacturing practice for the finished medicinal product, but also applies to the starting materials used, the requirement of good manufacturing practice also for starting materials had to be introduced into Art. 46(f) of Directive 2001/83, thus extending the scope of application of the Directive.

Therefore, the influence of the ICH guidelines on the European pharmaceutical regulation is not to be underestimated. All in all, currently over 60 CHMP guidelines have been based on ICH guidelines, now forming an essential part of the Union pharmaceuticals framework. Moreover, as shown above, the ICH guidelines occasionally also affect EU legislation.

53 ICH Harmonised Tripartite Guideline, Good Manufacturing Practice (Q7), Current Step 4 version, 10 November 2000.
This significant ICH influence is exercised regardless of the influential role of the pharmaceuticals industry in the standard-setting process and the flaws with regard to transparency, participation and the use of expertise as revealed in the above.

A remarkable point to note in this regard is that the European Medicines Agency, in the context of setting its own procedure for the adoption of guidelines, reacted to comments suggesting that more industry involvement should be facilitated, advocating the ICH mode of decision-making in the following way:

‘The procedure takes over many aspects of the ICH/VICH model. However it does not propose to systematically involve industry in all steps of the process, nor does it propose that industry would draft guidelines. In view of the need to have a harmonised position among all 25-member states, systematic early involvement of industry would not be appropriate. (...) Overall there are plenty of opportunities for industry to comment. Drafting suggestions from industry are always welcomed but careful consideration has also to be given to equal treatment of all relevant interested parties during the procedure.’

This raises the question why early industry involvement is not acceptable in the procedure harmonizing the standards in the Member States, while it is accepted in the harmonization of standards on the global level – later having the same status as other EMA guidelines in the Member States.

A rejection of the ICH standard-setting as role model is certainly comprehensible, given that it shows the same characteristics as the Union’s risk regulation in the food safety area prior to the BSE crisis with an industry-focused regulatory body operating under conditions of secrecy and advice given in small closed groups of experts. In essence, the ICH standard-setting is the epitome of a mode of governance that the EU aims to overcome for a more legitimate form of regulation though good governance since the beginning of this millennium.

56 European Medicines Agency, Overview of comments received on draft guideline procedure for EU guidelines and related documents within the pharmaceutical legislative framework, emphasis added, p. 3.
Conclusion

Through the International Conference on Harmonisation, the pharmaceutical industry and the regulatory authorities of the EU, the US and Japan became privileged stakeholders in the international regulation of pharmaceuticals. Therewith, the pharmaceuticals industry established itself as a true co-regulator, while input from e.g. patient’s and doctor’s associations is largely absent. This led severe criticism, claiming that ‘the ICH process has permitted scientists from industry to renegotiate extensively the scientific standards that the regulatory agencies are supposed to be using to protect public health’. 59

Although the inclusion of the industry as equal partner might be justified by the access to expertise and resources that this opens up, in the ICH no effort is undertaken to counterbalance these institutionally with the representation of other stakeholders. In addition to that, although especially in the recent past steps have been undertaken towards more transparency, the standard-setting process itself and the scientific expertise used remain opaque.

It is remarkable that while the EU increasingly aims at improving the legitimacy of its own decision-making by means of increased transparency and participation, global standards are absorbed into the legal framework of the European Union without being measured against the same benchmarks of good governance. This finding is highly problematic as it shows that existing good governance requirements can be circumvented through ‘outsourcing’ of regulatory power to the global level. Therefore, the research shows that a discussion on increasing the transparency, participation and independence of the Union’s risk regulation is incomplete as long as it falls short on paying attention to the global standard-setting bodies that influence it.

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