The tools of globalization. Ways of regulating and the structure of the international regime for pharmaceuticals

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Biographical note

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Abstract
This article deals with the globalization of regulation in the area of pharmaceuticals. It shows that the current regime complex in this area, in which the setting of international standards through the international conference on harmonization (ICH) plays the greater role and the WHO a more minor one, makes sense in the context of a historical shift towards a different, standard-based and more administrative way of regulating pharmaceuticals. This shift is clearly observable in the history of the monitoring of pharmaceutical products. The article recounts that history, and in so doing highlights a number of factors that are important to understand how the ICH has come to prevail. Overall, the article demonstrates the value of connecting the analysis of international regimes with policy analysis and political sociology, specifically to gain a more precise understanding of why and how neo-liberalism and market-based policy scripts frequently inform international regimes.

Keywords
Regulation, globalization, regime, regulatory tools, pharmaceuticals, neo-liberalism.
Introduction

Transnational regulatory regimes are complex because various sets of rules or international agreements coexist and overlap on a given issue, but also because multiple tools may be used for regulatory intervention. What is the pattern of regulatory globalization and regime formation that one can observe if we consider the regulatory tools and processes that prevail?

The article approaches the regime complex for pharmaceuticals from the vantage point of the various ways of regulating that have prevailed over time, to better understand the current hierarchy between institutions and regimes in the complex.

The international control of pharmaceutical safety is an interesting case because various tools have been deployed transnationally for the monitoring of their safety.

Drug safety monitoring or pharmacovigilance⁠¹ can be operated in two ways. In a first sense, pharmacovigilance is based on systems of spontaneous notification: the systematic collection and analysis of reports signaling potential adverse effects, originating from physicians and other health professionals prescribing or administering medicines. The development of formal systems of spontaneous notification started first, and was international from the start. In the 1960s, several countries launched programmes of collection and analysis of reports of suspected adverse drug reactions in collaboration with the medical profession. The World Health Organization (WHO) also created the “WHO programme for
international drug monitoring” (the WHO programme hereafter) in 1968 – still operated by a collaborating centre based in Sweden, the Uppsala Monitoring Centre (UMC)\(^2\). Evidence produced by systems of spontaneous notification, WHO programme included, seldom motivate the decisions of firms or regulatory agencies to recall drugs.

The second method is more “active”, and involves post-marketing safety studies (also called post-authorisation studies or phase IV studies\(^3\)). They are designed to analyze the adverse effects that arise in a controlled population taking a given medicine. Active pharmacovigilance, whether private or public, is the form of drug monitoring that has been most actively promoted in the past two decades, as testified by the development of public research capacities to conduct such studies or by the adoption of European, American or international guidance applying to such studies (Author 2008, 2011, Abraham Davies 2011).

The guidelines are generally developed in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). In spite of national differences in regulatory approaches (Daemmrich 2004), it is now accepted as the top of the regulatory pyramid, with its norms being adopted nationally by a great number of countries and contributing to their regulatory capacities (Vogel 1998). The ICH routinely produces guidelines, including for pharmacovigilance (Daemmrich 2004, Author 2006), according to an agreed upon procedure involving expert working groups comprised of representatives of the US Food and Drug Administration, the European Union and the Japanese Health ministry, industry groups, and other
observers such as patient associations or the WHO⁴.

The article shows that the rise of the ICH process and the globalization of regulation, was paralleled by a decline in the importance of certain tools and processes, notably those that were controlled by health professionals such as spontaneous notification systems. Over the years, pharmacovigilance was increasingly defined as an exercise of detecting and correcting errors in the pre-marketing evaluation process – a quality assurance of marketing authorization decisions of some sort – through post-marketing studies. Pharmacovigilance as all out detection of accidents emerging in medical practice to improve therapy, by and for medical professionals, clearly eroded. This is linked to various other changes, in the type of organizations and cadres of experts involved, the data and knowledge mobilized in support of pharmaceutical control, and the public problem posed by pharmaceuticals overall. These changes compounded to shape a different way of regulating drugs, in coherence with which the ICH became the main platform for transnational regulatory work in this field, and the WHO programme a minor one.

In the remainder of the paper, I first review the literature and justify the interest there is in focusing on the tools or modes of control used in a given domain to analyze dynamics of regulatory transnationalisation. I then describe empirically the opposite trajectories of the WHO programme and of the ICH, and the related shift in the approach of drug safety monitoring. The third section analyses these trajectories.

The data used for this paper were two-fold. First, interviews were conducted
with people in charge of drug safety monitoring in regulatory agencies in Europe and in the US, as well as in the European Commission, at the WHO and the UMC. About ten different medical experts with a long history of participating in international meetings on pharmacovigilance, at the WHO or in ICH, were also interviewed, along with post-marketing safety officers working in large European firms. Second, I explored the archives of the WHO related to pharmacovigilance, drug safety and medicines policy more generally, covering 1964 to 1988.

**Regimes as ways of regulating**

From a global governance perspective, the globalization of pharmaceutical regulation is the result of two factors (Vogel 1998). The first is the globalization of the political economy itself, embodied by the rise of highly internationalized and specialized pharmaceutical firms and the increasing number of pharmaceutical products that are marketed worldwide. The globalization of regulation follows from the globalization of the market itself. The second factor, more political in nature, is the move of governments towards more international regulatory cooperation.

This move, in turn, has three explanations (Vogel 1998, p.18): the institutional development of the European Union, the political pressures for more rapid drug approval in both Europe and the United States, and the experience of international cooperation itself. The harmonization of data requirements for
drugs at the global level essentially continues the effort that European countries have pursued, since the 1960s, to create more convergence between national standards. The US regulators were led to recognize the virtue of harmonizing data requirements when they found themselves criticized for their slowness in authorizing drugs that other countries already had access to (the “drug lag” debate). The successful first meetings of the ICH also proved that regulatory cooperation was beneficial, and gave more weight to the two other factors to accelerate the whole process of regulatory globalization.

Vogel’s early analysis could be pursued further for two reasons. The first is that the vocabulary of “globalization” implies a form of uniqueness and universality of the regime that is being described. But most regulatory regimes are transnational more than global: they have an international reach, but do not apply over the whole globe. For sure, this is even a matter of debate between the actors involved. Regulatory agencies and health authorities of the “global South” in several key instances have contested the legitimacy and applicability of standards developed within the ICH, which is considered by many to be an arena for developed countries. The second is than other institutions and collectives than regulatory agencies and firms, the representatives of which form the ICH, carry out the tasks of effectively controlling the safety, quality and efficacy of pharmaceuticals. Health professionals, national health authorities and the WHO also play an important role, and indeed have had a more important role than regulatory bodies in the past.

This makes the case for an analysis that goes beyond an account of emergence
of a unique global regime for pharmaceuticals, and considers the complexity of the ways in which pharmaceuticals are regulated transnationally.

The international regime complexity literature offers interesting, complementing insights here. This literature looks at regime complexes, or “array[s] of partially overlapping and nonhierarchical institutions governing a particular issue-area” (Raustialia and Victor 2004). This notion of complexes stem from the observation that in any given issue area of regulatory domain, various regimes intertwine and overlap, and co-evolve. The content of one regime, and its capacity to institutionalize, will depend on co-evolutions with other regimes. One of the main interrogations from this perspective concerns the relations between sub-regimes (Gehring and Faude 2013), whether these are overlapping, parallel or nested within one another (Alter and Meunier 2009). The literature considers institutional mechanisms by which overlaps and inconsistencies are resolved or accommodated, but also the strategies of forum-shopping (Raustialia and Victor 2004, Busch 2007) and regime-shifting (Helfer 2004) that bear on the level of integration, coherence and overall direction of a regime complex.

This perspective is useful to look at pharmaceuticals regulation: the effective launch of ICH and the production of more and more rules within this forum appear to be a by-product of the growing regulatory action of international firms, which shows in parallel agreements concerning intellectual property such as TRIPS (Helfer 2004, 2009) but also access to medicines for southern countries by the WHO or development of medicines for neglected or orphan diseases.

One aspect on which the literature is perhaps less clear is the hierarchical
relations between elemental regimes. On the one hand, one of the original
definitions of regime complexes emphasizes their non-hierarchical nature
(Raustiala and Victor 2004), and indeed looks at the ways in which the regime
complex can find its equilibrium and be coordinated or orchestrated (Biermann
et al. 2009, Abbott and Snidal 2009). At the same time, however, it is becoming
quite clear that regime complexes give precedence to certain bodies of rules,
values or aims over others – or, according to other authors, that they reflect a
form of hegemony (Görg and Brand, 2000, 2006). They have a policy order to
them. For instance, research on climate, carbon capture, genetic resources or
genetically modified organisms (Raustiala and Victor 2004, Kleinman and
Kinchy 2007, Reid 2013, Zelli et al. 2013), as well as on pharmaceutical
regulation (Abraham and Reed, 2001, 2004; Abraham 2004), concur in saying
that regime complexes are overall informed by a neo-liberal logic, the
proponents of which are precisely those institutions and actors that are most
powerful in driving the globalization of regulation, such as the United States,
international organizations like the IMF and the World Bank, but also major
international corporations (Braithwaite and Drahos 2000).

In the terms of the policy platform that the regime complex overall deploys, one
can then assume that the institutions and sub-regimes involved are placed in a
sort of hierarchical structure: they do not fulfil the overall policy orientation as
much as the other, do not receive as much attention and do not command as
many resources as the others.

The article thus suggests taking into consideration policy or regulatory tools in
the analysis. The tools of regulatory intervention are generally not included in the definitions of regimes, but are an integral part of what is considered a regime by policy scholars (Elkin 1986, Hood et al. 2001) - what is more a very dynamic part of regimes given the many innovations in the tools used to regulate in general (Baldwin et al. 2010). Attending to tools will help developing even finer analyses of the inter-relations, and hierarchies, between sub-regimes.

Gaudillière and Hess’s framework for analyzing ways of controlling drugs (Gaudillière 2006, Gaudillière and Hess 2013) is particularly helpful for this, because it describes in a systematic manner the different ways in which an issue may be controlled. According to this framework, there are five ideal-typical ways of collectively managing pharmaceuticals, or “ways of regulating”⁷: the administrative, professional, industrial, public and juridical ones. Those can be characterized in four dimensions, the first of which is the tool used. A professional way of regulating relies on tools that influence the behavior of professionals, such as pharmacopeia or prescription guidelines, while an administrative⁸ way of regulating relies on the instrument of the marketing authorization, and an industrial way of regulating focuses, for instance, on methods of controlling the quality of products and on their marketing.

Tools are not simply techniques however (Lascoumes and Le Galès 2007). They have three other attributes of interest: they are attached to particular bodies of knowledge and evidence; they embed specific ways of seeing the problem being addressed; they provide identities to the actors and define a way
for them to organize. Gaudillière and Hess therefore include the type of evidence that is used to define and legitimize regulatory measures (animal experiments, statistical human trials or epidemiological studies), the value and aims of the policy (compliance, public health, competitiveness…) and finally what they call the “social sphere”, that is the dominant actors or operators of the policy intervention (corporations, professional societies, national public administrations, non-governmental organizations…), as components of a way of regulating.

The strategy in the remainder of the paper is to tell the intertwined histories of the WHO programme and of the ICH, paying attention to the dimensions that are constitutive of a way of regulating in Gaudillière and Hess’s framework. What the following sections will show is the following. The centralization of international activity on drug safety in ICH, is inseparable from changes at various levels, which I summarize in the table below using the categories Gaudillière and Hess use to construct “ways of regulating”:

<Table 1. Summary of changes in international drug safety monitoring>

In these terms, the ICH represents an administrative-industrial way of regulating. The ICH defines technical standards and guidelines for firms and regulatory agencies to register or withdraw drugs from the market, responding to an agenda of access to and circulation of drugs across world markets. It is led by both regulatory agencies (as opposed to public health authorities) and large multinational firms. The characteristics of this policy is its focus on the
question of access to medicines (as opposed to their safety for instance), its scientized nature (regulatory decisions are inspired by data produced according to scientific protocols) and the centrality of firms, or of regulators’ relations with firms, in the negotiation of rules. It is in direct contrast with the logic that informs international pharmacovigilance, specifically at the WHO, which is one of improving safety as an experience of patients and a professional competence, and organized by and around public health authorities and health professionals. Each of these items shows that it is what the ICH does that really matters in terms of the actual regulatory intervention on pharmaceuticals and the pharmaceutical industry, and thus explains that the ICH and its standards have taken a greater weight in the overall regime complex governing pharmaceuticals transnationally. The following section describes these changes historically in greater detail.

The WHO and the ICH: Opposite policy trajectories in international pharmaceutical safety control

The origins of international pharmacovigilance

The safety of medicines broadly speaking is regulated through two types of controls. On the one hand, regulators review the safety of drugs as established through pre-marketing toxicological and clinical testing by pharmaceutical companies, following laws and guidelines established by regulators. Alternatively, post-marketing surveillance or pharmacovigilance serves to collect
data about adverse drug reactions and result in regulatory decisions, such as revision of marketing authorizations and of labelling, or (much more rarely) withdrawal.

The first attempt to organize drug safety monitoring at the international level was based on the notification, collection and analysis of reports of suspected adverse drug reactions by physicians. It originated in the aftermath of the thalidomide disaster in the 1960s. The substance thalidomide (commercial name Contergan®, Grippex® or Distaval®) was developed by the German company Grunenthal, and massively marketed across the world for all sorts of clinical indications. This product was widely used, in quantities comparable to aspirin. Among other uses, it was prescribed to pregnant mothers as a solution to morning sickness. In 1961, Dr. McBride, an Australian physician, reported in a medical publication an observed increase of 20% of phocomelia (shortening of the limbs in newborns), correlated with the intake of thalidomide. This publication alerted other physicians across the world, notably Dr. Lenz in Germany. The convergence of observations by these two physicians led to the confirmation that thalidomide was causing these malformations. This discovery initiated a “policy tragedy” (Carpenter 2010), and had a direct impact on ongoing legislative discussions in the US, towards the institution of mandatory pre-market safety and efficacy drug reviews. The very way in which the epidemics was discovered – via concurrent medical publications written by practitioner physicians – inspired physicians with the idea that the systematic exchange of observations by physicians, and their centralization in a common
database, could result in quicker identification of adverse events and ascertaining of causalities, even in cases of infrequent and dispersed adverse events.

In 1962, the American Medical Association (AMA) tested a country-wide reporting program, based on the reporting of suspected adverse drug reactions by hospitals. Five years later, the program was made official through an agreement between the FDA and the pharmaceutical industry. In May of the same year, the World Health Assembly (the assembly of representatives of WHO’s member states) adopted a resolution requesting a study of the means for rapid transmission of information concerning adverse drug reactions to national health authorities. A year later, the Assembly adopted a further resolution, requesting to take action without delay to accelerate the dissemination of such information among national health authorities, so that the latter may take rapid decisions to restrict the use of or withdraw medicines with proven safety problems. This resolution required the WHO to study the feasibility of a collection of this information at an international level. It also invited the member-states to put in place national systems for the collection of adverse drug information, similar to what the US experimented. In the UK, the “yellow card scheme” (named after the yellow forms which physicians across the country used to report their observations) was launched in 1968 (Inman 1993). Similar systems were put in place in Australia, Canada or Czechoslovakia.

The WHO took the decision to set up a pilot centre to develop and run a
monitoring programme in 1967. The centre made an operational start in February 1968, with ten member countries (Australia, Canada, Czechoslovakia, Federal Republic of Germany, Netherlands, Ireland, New Zealand, Sweden, United Kingdom and United States), represented by the professor of medicine that headed the corresponding national surveillance centre. During those years, the centre focused on developing the various tools that were necessary to the functioning of the central database. The first of these tools was a standardized form for reporting of adverse drug reactions, to be used by national centres, for data to be consistent and rapidly processed. The second working tool was a dictionary of all known adverse drug reactions, classified by organ. This terminology was supposed to help harmonize the description of effects and reactions in the report, for easy retrieval and analysis in the database. The dictionary will soon be known as WHO-ART (for Adverse Reaction Terminology). In parallel, a third tool started to take shape: a drug dictionary (now WHO Drug Dictionary). This dictionary was also instrumental for a reliable analysis of adverse reactions, and more importantly for imputation of these reactions to drugs. Other tools were developed, such as various algorithms to create a signal in the case of a rapid increase in notifications concerning a given medicine, as well as various publications. Even though the centre was only at an experimental stage, and strictly limited in its resources and thus in its early achievements, those tools – the forms and dictionaries in particular – will prove instrumental for the later development of pharmacovigilance internationally, by firms specifically.
By 1969, the project was already deemed a success (Venulet and Herring-Borda 2009). However, there were notable difficulties. Funds were hard to find, as were competent staff. WHO officials toured American hospitals, insisting with doctors and professors that they direct potential applicants with relevant medical and statistical expertise to the project, only to be faced with the answer that no acceptable candidate could be found. The funding of the centre had become an issue though, since the US government had refused to fund the centre beyond 1968.

The WHO found itself obliged to look for other funds to be able to move to full functioning of the centre. Member countries were asked to fund the program themselves. To limit the costs of it, the WHO decided to repatriate the centre within its headquarters in Geneva by the end of 1970. During the period extending between the move of the centre of Geneva and its relocation in Uppsala in 1978, more countries joined the program. (There were 20 member countries by the end of 1974, that is after France and Japan joined.) The centre became better known, not for its analyses of drug reactions or major drug safety alerts, but rather for methodological developments in the science of “pharmacovigilance”, then in its infancy. The centre benefited from an influx of drug safety expertise from the transnational network of medical scientists and pharmacology professors supporting it.

One supplementary difficulty came from the opposition of the pharmaceutical industry. The pharmaceutical industry in general did not support the WHO programme, and even fought against it. The firm Geigy actively worked against
any temptation to give powers to the WHO to recall drugs based on the data collected through its programme. According to this company, the latter should remain a medical programme, aimed at improving the use of therapeutic products, not one with regulatory impact. National health authorities also had to complain, at times, about the ambition of the staff of the centre to publish papers in medical journals about key adverse drug reactions, using confidential and proprietary safety data provided by national health authorities and by pharmaceutical businesses.

Technically also, the strong hopes that the database could function as a sort of automated detection device, thanks to its large statistical base and powerful IT instruments, gradually declined along the 1970s. The enthusiasm around the principle of computer-aided statistical analysis of drug safety data, as a way to prove the responsibility of drugs in causing an adverse health event, and thus in motivating health authorities to authoritatively recall drugs, slowly started to decay. Even though the database kept growing, the centre was only issuing a small number of interesting signals or alerts for national authorities. The officials in WHO headquarters continuously complained about errors in the coding of drugs and classification of reactions, of poor medical analysis, as well as of poor printing quality of the documents distributed to national centres. The WHO also criticized the lack of capacity for medical research, minimal competences of the pharmacist and IT technician of the centre, as well as the poor membership of its scientific advisory board.

*Shifting agendas and WHO policy*
From 1975 onwards, WHO officials in charge of the programme started to express doubts about the value of the programme and the benefits for the WHO of supporting its development. The WHO soon stopped investing in its drug safety policy. It delegated the running of the programme to the Swedish government in January 1978, when a “WHO collaborating centre”, funded by the Swedish social and health affairs ministry, was created. The Uppsala Monitoring Centre (UMC), as it came to be known, was to run the WHO programme, with small financial support (around 10,000 dollars to cover printing and publication costs) but strong policy supervision from the WHO headquarters – which retained most policy prerogatives, such as the definition of the programme’s objectives, and management of relations with member countries.

The disinterest of policy managers at the WHO headquarters for drug safety must be understood in the context of the rise of another agenda: that of the access to essential medicines. The essential medicines policy originated in a resolution of the Assembly of 1975, calling for the WHO to provide support to developing countries in the selection and distribution of pharmaceutical products of sufficient quality, and at a reasonable price. The first list of essential medicines was published in 1977. The Alma Ata conference of 1978 established the access to essential medicines as one of the 8 constitutive elements of a primary care system (Laing et al. 2003). The essential medicines policy was a better policy to pursue for the WHO, in a context in which its role was being redefined as one of supporting developing countries, against the interests and priorities of northern countries – pharmacovigilance being typically
a concern of developed countries. Sten Olsson, a pharmacist who has been with the UMC since the early 1980s, observes that the WHO simply overlooked the issue of drug safety after the signature of the memorandum with the Swedish government in 1978: “Drug safety never was a priority in WHO HQ, that always focussed more on access to medicines and essential medicines. So what is true is that there is a slight bitterness here that we have been left on our own. [...] WHO basically sold it out.”

In retrospect, perhaps the most perceptive and straightforward summary of events is that given by the person in charge of pharmacovigilance at the European Commission in the 90s: “In reality, there was a strong impetus after thalidomide, but it did not last.”

One factor was instrumental in the evolution of WHO’s positioning towards the problem of drug safety, and also explains the later rise of ICH: the development of private, industrial pharmacovigilance. The importance of this involvement of firms in regulation can be seen in a policy memo that the policy officer in charge of supervising the monitoring programme and the activity of the UMC, John Dunne, sent to the director general of the WHO in 1984.

In this memo, written at the very moment when the UMC gained autonomy and the monitoring programme proved inefficient, Dunne informed the director general of a strategic new development, which he called upon his director to give support to: “Conditions have changed radically since the scheme [the monitoring programme] was introduced. Pharmaceutical manufacturers are now widely required to assume responsibility for monitoring their products as a precondition of marketing. They are also, in some cases, required to apprise
regulatory authorities on a timely basis of all serious reactions attributed to their products wherever they may have been reported. Thus, a large majority of reactions now reported in the United States derive from manufacturers. These changes, and the ascendancy of epidemiologically-based approaches to drug monitoring, create a need to embark on a broader review of existing mechanisms and I attach, for information, a project proposal that I am now developing in conjunction with CIOMS."

This letter sketched out a number of dramatic developments concerning drug safety. The first is that drug safety was increasingly becoming a regulatory domain in and of itself, and what is more a global one. In effect, more and more countries were then contemplating to condition the delivery of marketing authorization to obligations of monitoring of adverse reactions occurring after marketing of the drug. This new rule was a blow to the very design of the programme: given the likely increase in reporting of information by manufacturers, the industry will gradually become a more comprehensive source of data than physicians.

The second is that national authorities would most likely be in the position to request pharmaco-epidemiological studies from manufacturers, making the now-criticised spontaneous notification systems redundant. In contrast with clinical trials, the number of people actually taking the drug is not known, hence the proportion or frequency of the adverse drug reaction out of the total number of prescriptions of the drugs can not be computed. Secondly, the adverse drug reaction is only in the first place an adverse health event, which is not with
certainty caused by the drug, but possibly by a host of other factors on which no
data is available in the database. This lacking information can only imperfectly
be reconstituted if the data analyst has medical, clinical experience, or a close
contact with the practitioner that observed the event – in both cases, it
minimizes the efficiency of data mining. Last but not least, it is estimated that
only 10% of physicians actually notify the suspected adverse drug reactions
they observe (Leiper and Lawson 1985). When they do, they probably only
report a fraction of what they observe. All of the above are definitive limits for
the detection and action on adverse drug reactions through spontaneous
notification systems, that have become increasingly obvious to experts of the
field as years passed (e.g. Barnett and Woods 1987, Tubert et al. 1992).

The letter also boasts an initiative of the Council for the International
Organization of Medical Sciences (CIOMS). The CIOMS is a permanent
consensus conference of the medical profession, with close links to the WHO,
which hosts its meetings and publishes its proceedings, as well as UNESCO. It
is the forum within which such international rules or charters as the one that
forbids the use of human subjects in medical experiments were developed. A
group of pharmaceutical companies chose this venue for its projects to
proactively develop international pharmacovigilance standards. These
companies were reacting to the recent request by the FDA to report all
information concerning serious adverse drug reactions occurring worldwide,
within 15 days. They knew all too well that they did not have the tools to collect
safety information in a standardized manner from across the world on all of their
products. They also anticipated that other regulators would emulate the FDA. At about the same time, the heads of national pharmacovigilance systems in Europe had indeed started to meet regularly within a “pharmacovigilance working party”, exchanging ideas about harmonized European rules in the matter.

The first CIOMS meeting on pharmacovigilance took place in 1984, and was dedicated to the elaboration of a standardized form for the reporting of suspected adverse drug reactions, and the establishment of a terminology – similar to what had been undertaken as part of the WHO programme. The second CIOMS session, extending over the second half of the 1980s, focussed on the development of a guideline for establishing « periodic safety update reports » (PSUR): a report that collects and analyzes all incidents related to a given drug, at regular intervals (e.g. 5 years). The PSUR standard was integrated into EU law in 1993. It was also a prefiguration of the future “risk management plans”, which the ICH formatted just a decade later14. That standard had a major impact on firms, by forcing them to put in place resource intensive processes of collection and analysis of data, infrastructures of traceability of products and uses, as well as dedicated services. This standard contributed to create a massive transfer of analytical work from public agencies towards firms. Since the WHO does not have the power to request those data, the UMC does not collect them. Vigimed was thus deprived from the most substantial sets of data on drug safety available.

The WHO did not and still does not have the legal power to regulate the
pharmaceutical industry, and was not seeking to obtain such powers from member states at the time. The CIOMS project was thus advantageous: it allowed the WHO to participate in transnational regulatory developments. Furthermore, the WHO could obtain from the CIOMS the sort of results that the UMC was seemingly incapable of offering: the development of accepted and reliable technical standards for reporting of drug safety information. What is more, the support to CIOMS was without financial consequence for the WHO, since the pharmaceutical companies had pledged to fund the project themselves. It was essentially an opportunity for the WHO to maintain minimal activity in the area of drug safety, and free resources to advance on the other policy front of the access to essential medicines.

Towards global standards and operations

The establishment of a European regulatory regime for pharmaceuticals further accentuated the opposite trajectories of the international monitoring programme and of the nascent regulatory work around international standards.

The process of Europeanization of national pharmaceuticals policies in Europe accelerated in the second half of the 1980s, as part of the process of creating the internal market. It is around this time that the European Commission, led by Fernand Sauer for that matter, decisively shaped the two-level system for the common licensing of medicines that was eventually adopted in 1993 (with a centralized procedure run by the European Agency, and a decentralized procedure coordinated by member-states). According to Sauer’s vision, the integration of the regulation of medicines at the European level was a necessity.
to evaluate increasingly complex and globally distributed products. A European agency pooling the available national expertise would have far greater weight towards the increasingly internationalized industry and the gold standard of pharmaceutical regulation, the US Food and Drug Administration. This vision gained tractability as European national administrations similarly engaged in the creation of agencies specialised in regulatory operations for pharmaceuticals, such as the UK in 1989 or France in the early 1990s. These sorts of agencies soon hosted and ran national systems of collection of adverse drug reaction reports and databases. By competing and interacting among themselves, national regulatory agencies allowed the development of a common European space for the regulation of pharmaceuticals (Hauray and Urfalino 2009).

One of the first concrete consequences of the Europeanization of pharmaceutical regulation as regards pharmacovigilance and the WHO programme is the development of a common European database of adverse drug reactions, EudraVigilance (EV). The setting up of Eudravigilance was foreseen by the European regulations adopted in 1993 to create a European licensing system. More than a decade was necessary to make it fully operational, with routine data transfer between national databases and Eudravigilance. But it is now a more comprehensive than Vigimed, since European Union member states, and thus companies that report to them, contribute their data to it. In reality, it was developed in full awareness of the fact that it would eventually duplicate and soon make Vigimed redundant. For Sauer, the EU had no other choice but to build its own database, in so far as the
UMC was not technically capable of transmitting back to the European Medicines Agency the reports that were sent to it by the various member states of the programme, and that the database was imperfect (duplications, gaps…). The issue of the collaboration with the UMC and of the interconnection between Eudravigilance and Vigimed was dealt with only after the Eudravigilance was fully up and running. It was not until 2003 that an official of the European medicines agency started to attend the annual meetings of the programme in Geneva. The automated transmission of adverse drug reaction reports from Eudravigilance to Vigimed will only be effective in 2015, nearly 20 years after the European medicines agency pledged it would fully cooperate with the WHO on pharmacovigilance issues (EMEA, 1998). The EMA did make sure not to interfere in the relation between the UMC and European countries that were part of the programme15.

Eventually, Eudravigilance has de facto replaced Vigimed for most countries, including southern countries: they first consult the former when they are in search of information on a product. Vigimed is a large database, but 60% of its reports come from the USA, making it unrepresentative and unfit for detecting signals. Also, the database only contains data collected from professionals, who reportedly notify only about 10% of the adverse drug effects they encounter in medical practice. This lack of completeness and representativeness make it unlikely for this database to generate robust and confirmed signals of adverse drug reactions, which other databases would not spot.

A second concrete consequence of the rise of a Europe for pharmaceuticals is
the acceleration of the ICH process itself. The Europeanization of national regulatory activities was but one element of an on-going globalization of pharmaceuticals control, to which Sauer thought Europe should decisively contribute. He did put his weight in the launch of the ICH process\textsuperscript{16}. The ICH became a space for cooperation between regulatory agencies, including on pharmacovigilance. Projects that overshadowed the work of the UMC and of the WHO programme emerged there, notably that of creating a common dictionary of regulatory terms.

In 1992, the UK medicines agency took the initiative to propose to other ICH countries to generalize the use of its own dictionary of medical terms, MEDDRA (MEDical Dictionnary for Regulatory Affairs), without considering how this initiative would effectively shut off all efforts to develop and use the WHO terminology. This initiative shocked the UMC and the experts associated to the programme, as it simply risked killing the UMC: since the early 1980s, it had started to live off the money made selling its dictionary and terminology to firms for their own internal use and databases. The European Commission and other ICH participants accepted the UK proposal. The European Commission official in charge of pharmacovigilance issues, in retrospect, minimizes the conflict that soared around this issue, but still recognizes that hard battles were fought between institutions and dictionaries.

Even if MEDDRA is in part structured around the hierarchy of terms designed by the experts of the UMC for the WHO-ART dictionary, it is slowly evolving as a very different product. WHO-ART requires less training in the use of
dictionaries, because it uses more generic descriptions of adverse drug reactions and fewer terms. MEDDRA is maintained and distributed by a committee comprised of representatives of the industry and of regulatory agencies, under the aegis of ICH, something which the people at the UMC call a technocratic approach, which contrasts with the inclusive approach of the UMC and WHO, towards developing countries specifically. WHO-ART itself has become less used, at least by regulatory agencies of the North and by firms.

The technocratic style of ICH organization was noted to be a problem by those medical experts that historically participated in the programme and the development of its tools. While the programme was a platform for international expertise in pharmacovigilance, and a center for many important scientific and methodological developments, medical researchers and practitioners that aren’t associated with regulatory agencies, find it difficult to participate in ICH developments. As a result, their impression is that the standard-setting process has disconnected from research and experimentation of drug safety methodologies, and diminishes the value of the latter. Several of them complained, to no avail, when the ICH initiated the development of a guideline on pharmacovigilance planning. They were of the view that the adoption of this guideline was purely opportunistic – there was a consensus on the idea, and the ICH was seeking topics on which to produce new standards. But medically speaking, no evidence was available to demonstrate the net benefits in terms of saved lives and reduction of morbidity, of generalizing such tool in the industry globally.
The divorce between the two policies and sets of institution is clear looking at the position of the WHO and UMC in ICH. The WHO has only an observer status within the board of MEDDRA and ICH\textsuperscript{19}. It consistently refused to take a leading position in the process. It did not defend either the value of the tools developed by UMC, which may have served as a working basis for new ICH standards. It reduces its role to sensitizing this forum to the heavy requirements in technical, analytical and human resources that many of the rules that are being adopted in ICH imply for developing countries. Instead of playing the game of harmonization, the WHO and the UMC focus on other aspects.

The UMC retains a particular importance as provider of the WHO Drug Dictionary, of various commercial services for data analysis, and also as center of reference for developing countries (providing training and infrastructure support for the development of drug safety policies)\textsuperscript{20}, but is broadly speaking peripheral in the global regime for drug safety, which has turned much more administrative and rule-oriented than it was when the WHO launched its monitoring programme.

**Globalization and shifting ways of regulating drugs**

The global regime for the control of pharmaceuticals is, as is clear from the literature and also from the above history, centered on the activity of the ICH and of its members – regulatory agencies and firms. It is embodied by the high level of acceptance of the harmonized rules that are adopted within this forum.

The global regime for pharmaceuticals is not without some complexity. Although
the WHO and the UMC have declined, and almost disappeared from the picture, they are not fully absent. They represent a sort of sub-regime. They are institutions that may be qualified as peripheral in the global regime for drug regulation, both in the sense that drug monitoring by means of spontaneous notification has a marginal impact in pharmacovigilance, which itself has become a marginal instrument in drug regulation. They fulfill complementary or “support” functions (development of the drug dictionary, training in drug safety systems of southern countries), but are nearly un-influential in the global identification of alerts and adverse drug reactions and in drug withdrawal decisions.

There is also more interaction and cooperation between governments and between firms through ICH where pharmaceutical safety is concerned, than through the WHO programme. More decisions about products are made through ICH standards, than derived from the activities and people of the WHO programme – despite initial ambitions to the contrary. The WHO programme failed to fully integrate states’ drug safety activities, and also had little bearing on the activities of multinational firms. The globalization of rules for registration and post-marketing surveillance is driven by regulatory agencies of the northern hemisphere and multinational firms that develop product primarily for these markets. On the contrary, there is a form of discrete “global South” network of countries, the problems of which are considered through other forums, such as the WHO and the UMC. The preference of the latter for the problems of the south makes full sense only in the light of the shift between ways of regulating,
the retreat of the WHO from issues of pharmacovigilance – considered to be a problem of richer countries – and from the ICH more generally, but also the voluntary shift of the UMC and the staff running the WHO programme towards the promotion of drug safety policies in southern countries.

The picture of the global regime thus obtained is one in which there is a clear hierarchy between actors, problems and tools for pharmaceutical control. The ICH, associated regulatory agencies of the global north, multinational companies, clearly take precedence over other actors like the WHO. The issue of the rapid access to innovative medicines is the main problem on the international agenda. Standard-setting to improve the capacity to review the benefits and risks of drugs quickly and effectively through safety studies is the main approach or tool in use. An approach in terms of “ways of regulating”, with attention to the historical process involved, helps highlighting the factors behind the emergence of this particular regime structure.

The first key dimension is that of the tool employed to control the safety of pharmaceuticals. What is observable over the period of time studied above is the increasing importance of registration as a regulatory instrument, and the ensuing redefinition of monitoring as an exercise related to the control of marketing decisions post-hoc, through dedicated safety studies.

The decline of the international monitoring of adverse reactions by means of spontaneous notification is in part explained by the failure of the WHO programme. This failure is the consequence of political and technical difficulties that appeared very soon after the launch of the program in the 1970s. The
program was slowed down by technical difficulties, which the weakening political support did not allow solving. As early as 1978, one could probably tell that the UMC would never prosper and gain a major role in drug safety. The technical difficulties of the UMC only got worse because of its geographical and institutional remoteness.

However, the context of this failure is the growing investment in the tool of marketing authorization worldwide. From the 1950s onwards, internationally, more and more governments have put in place precise formal requirements for data to be presented before any use of the product by patients, resulting in the emergence of a standard system of marketing authorization (Carpenter 2010). In the history above, this change materializes with the creation of an EU licensing system. The rise of the tool of marketing authorization also reflects in the activity and organization of major pharmaceutical firms, most of which have developed massive R&D and regulatory affairs departments to be able to interact with regulators during the generally stringent process of evaluating of the toxicological and clinical data produced in support of their applications. From the 1970s onwards, firms collectively invested in the development of rules for pre-marketing testing of their products, and in lobbying regulators that were establishing such norms.

The result of this shift is a re-structuring of the control of pharmaceuticals in terms of a divide between pre- and post-marketing controls, which greatly redefined what surveillance or monitoring of drug safety means. As marketing authorization assumes a greater importance in national laws and guidelines, in
the work of regulatory agencies and in the internal organization and resources of firms, pharmacovigilance became the activity of checking out on marketing decisions in the light of drug use data. Given the proprietary nature of the safety data, but also the incapacity of spontaneous notification systems, and of the WHO programme, to definitely and statistically prove causal relations between an adverse event and a drug, it seems comprehensible that the preferred process evolved towards what is now called “risk management”, or firm-controlled epidemiological studies. Spontaneous notification systems or pharmacovigilance was never conceived by the medical profession as an auxiliary to the main mode of regulatory control, registration, but as a sui generis system of professional learning and improvement in the use of therapeutic products. As market access rose as the main challenge and regulatory mode, this professional tool, that could nonetheless be useful in that context, was clearly retrograded.

This shift in the preferred tool for controlling pharmaceuticals then connects to several other evolutions, all of which contribute to explain the launch of the ICH process and the establishment of global standards for registration and for post-marketing surveillance of products.

One of these evolutions is emphasized by Vogel (1998): it concerns the aims and values underpinning the control of pharmaceuticals. The globalization of regulation corresponds to an agenda of rapid access and approval of medicines. When approaching this dimension from a historical perspective and from the outside as it were, that is from the WHO’s view-point, one can see that
the problem of the safety of medicines has waned to be replaced by a notion of access to medicines (essential ones as concerns countries in the South, innovative ones as concern the North). Safety has become less of a problem of potential disasters affecting the public and its health, and more of a technical criterion for the evaluation of drugs. This is precisely the vision of the problem of safety that is embedded into the rising tool of risk management and pharmaco-epidemiological studies: safety as a condition defined by pre-marketing tests and trials that must be validated or verified ex-post, through dedicated protocols.

The second dimension to which the shift in tools connects, which also explains the globalization of control through ICH standards, is that of knowledge and evidence. The story of the WHO programme and of the UMC contains various indications that spontaneous notification systems run by health professionals failed to produce globally accepted knowledge about drugs and their adverse reactions. The failure of the programme opened the possibility for a redirection of WHO’s agenda and resources towards the CIOMS and later the ICH. It contributed to prove that one tool – collection and analysis of safety reports by professionals – could not be effectively organized internationally, and that other tools should be preferred. On the contrary, post-marketing safety being so critical for the preservation of their markets, firms have engaged in the development of infrastructures, competences and rules to run post-marketing safety studies, or at least to collect data about their products in view of reporting them to regulators. The CIOMS initiative and the industry’s purchasing of the
terminologies and dictionary developed by the UMC both exemplify this. The result is that firms and regulatory agencies reached a level of standardization of information and methods of interpretation that was never achieved within the WHO programme, which supports the sort of “mechanical objectivity” (Porter 1992) that is required to be able to use safety data as evidence to take regulatory measures transnationally. Quasi-experiments like pharmaco-epidemiological studies are considered to have more reliability and objectivity to them than systems of data collection, in which agents are notably more difficult to enroll. With this epistemic change, the approach of the WHO, that conceived of adverse drug reactions as epidemics, to be monitored and controlled by professionals in the field, lost mileage.

The third factor of globalization to which a tool shift connects is what Gaudillière and Hess call the social sphere, or the actors that are deemed legitimate to be in charge of the intervention.

As detailed above, the WHO abandoned the UMC, causing heavy frustrations among the actors of global drug safety, but also failed to defend these values within the ICH forum. It did not embrace, and did not become an actor of, harmonization of requirements for benefits and risks of medicines.

On the other hand, the disaffection for spontaneous notification and the rise of a more mechanical and standardized form of post-marketin surveillance coheres with the “agencification” movement in Europe, that is the creation of more national regulatory agencies. Agencification means that national administrations are established which, more than preceding ministries, specialize in and depend
on the existence of rules, are also faced with the need to assert their authority towards the regulated entities. Again, tools that produce regulatory evidence, better than what experience has shown spontaneous notification systems to be able to do, are preferred by agencies. The priority given, in the UK particularly, to the development of rules for post-marketing safety studies exemplify this.

Another change at the level of actors, touched on above, is noticeable in the kind of experts that populate transnational policy networks. The WHO programme and the UMC have typically mobilized hospital physicians, that systematically gave a central place to the therapeutic exercise and the scientificization of their use of medicines. These experts have increasingly felt disconnected from the world of ICH, which is populated by experts with dual competences and experiences in science and regulation.

The most striking historical evolution is that the identification of adverse drug reactions after the marketing of drugs, during the time of prescription and use by patients, has been integrated into the global regime and performed in a new way. Drug safety and monitoring has moved from being addressed through a mainly professional and federalist system, towards another way of intervening, organized around national or regional institutions with regulatory missions, based on rules applied to businesses, driven by regulatory agencies with the power and aim to control the circulation of products, through private data and international guidelines.

What we learn, then, by looking at the international cooperation in pharmaceutical control, from the outside as it were, that is from the viewpoint of
the WHO programme, and historically, is that the ICH represents an effective and successful form of regulatory globalization in so far as it enacts a particular way of regulating, the constituents of which all became more pervasive before and during the launch of the ICH process.

**Conclusion**

The aim of this paper was to study the globalization of regulation of pharmaceuticals in a longer historical perspective and from the point of view of an institution and tool – the WHO programme for international drug monitoring – that are not central in the contemporary global regime for pharmaceutical safety embodied by the ICH, its standards, and the regulatory agencies and firms that negotiate and apply these standards. The benefits expected from this perspective is to gain a capacity to compare the existing global regime with what it was before and/or what it could have been, and thus to put some lights on factors of globalization that one does not see when considering the regime on its own, through its constitutive institutions, rules, or values.

The paper shows that the globalization of pharmaceutical regulation produced a regime of harmonization of registration and post-marketing requirements by firms and regulatory agencies, because several other evolutions occurred at the same time, that contributed to install and legitimate a new way of controlling drugs: one that proceeds through controlled safety studies aimed at confirming marketing authorizations, that operates under the assumption that such studies produce appropriate knowledge to inform regulatory action, and that is driven by regulatory agencies, firms and associated regulatory-scientific experts to
maintain the rapid access of the public to drugs.

Both of the ways of regulating that develop under the WHO and under the ICH are transnational in their own way, and prevail in different parts of the world: the ICH and its standards for post-marketing safety matter more in the North than in the South for instance, where WHO policies on pharmaceuticals continue to play a great role. But in so far as the global regime for pharmaceuticals regulation is embodied by the activities of the ICH and associated regulatory agencies (the American, European and Japanese ones), one may say that the administrative-industrial way of regulating drugs, and its specific tools, have globalized more effectively than other ways of regulating drugs. One may say that one is the major regime, the other a more minor one.

The case of pharmaceutical control is, like all case studies, too specific to inform a general theory of regulatory globalization. However, it helps highlighting a number of more general mechanisms that partake in and define the actual pattern of regulatory globalization that is observed: the change in the type of experts involved; the rise of organizations, public or private, that are dedicated to running processes of control, and therefore get actively involved in their design; the demand for what may be called global regulatory evidence, or forms of knowledge that can prove that a given regulatory measure is warranted to solve a given problem. It also helps taking distance with the notion that there is one unique “global” regime, and that various ways of regulating can coexist, all of which are transnational, although they cover distinct parts of the world.

This paper has tried to show that regulation by and for the market is not a self-
explanatory preference, or does not deploy in a vacuum, all by itself. It is a policy or, for the sake of this paper, a particular way of regulating, embodied in a particular process or tool. Tracing the emergence of this particular tool, one realizes that the rise of a transnational market oriented regime occurs if simultaneously, changes happen at the level of the aims, agents and evidence used to control. Those changes are contingent, and not necessarily simultaneous. All of them involve actions and conflicts. They do not necessarily mean that a unified neo-liberal order is settling in, but that various ways of regulating, some more market oriented or neo-liberal than others, take precedence over others, as illustrated here by the relation between WHO/UMC and ICH, and between pharmacovigilance by medical professionals and firms-based safety studies. Analyzing the diverse ways of regulating in presence thus helps going beyond grand narratives of sweeping progression of neo-liberalism, to more precise mechanisms by which it settles down concretely in domains that are in the process of globalizing, through several, simultaneous and structured transnational policy courses.
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References


Table

Table 1. Summary of changes in international drug safety monitoring

<table>
<thead>
<tr>
<th>Tool</th>
<th>From spontaneous notification to post-marketing studies</th>
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<tbody>
<tr>
<td>Evidence</td>
<td>From local/professional reports of incidents to private synthetic data about products</td>
</tr>
<tr>
<td>Aim/value</td>
<td>From safety to access/marketing</td>
</tr>
<tr>
<td>Social sphere</td>
<td>From medical profession and public health authorities to regulatory agencies and regulatory-scientific experts</td>
</tr>
</tbody>
</table>
The WHO broadly defines pharmacovigilance as “The science and activity concerning the detection, evaluation, analysis and prevention of adverse drug effects or any other problem related to the taking of a medicine” (WHO 2002).

The WHO programme helps countries in their pharmacovigilance activities, but also centralizes all national safety data in a global database, to analyze larger sets of data and make the detection of rare adverse drug reactions more efficient – and the recall of unsafe drugs more effective.

In this that they follow the first three phases of testing that take place before marketing of the drug. See Carpenter 2010 for details about the institutionalization of this concept and practice of “phased trials”.

At its origins, the ICH is a common initiative of industry associations and dominant regulatory agencies of the planet in the early 1990s to advance towards harmonization of the requirements of those regulators for putting drugs on the market. That process of standard-setting at the global level was imagined at the turn of the 1980s-1990s, and took off immediately after an initial meeting in Brussels in 1991. Through regular, highly attended meetings, the process gained momentum, and proved of great interest to all participants. While it was set to last only six years, it is still ongoing. It even attracted more participants (Vogel 1998, Daemmrich 2004).

Jean-Paul Gaudillière also kindly shared a couple of records from the archives of the Swiss company Ciba-Geigy.

This resonates with such themes as the end of “embedded liberalism” (Ruggie 1998) or the “global diffusion of regulatory capitalism” (Levi-Faur 2005), or the argument that the world has undergone a broad epochal change towards more neo-liberalism, observable in international policy affairs too. The case of pharmaceutical regulation illustrates a broader historical shift towards more market-oriented regulatory policies at the global level, and the fact that international regimes tend to reflect a different type of grand social compromise that the one which prevailed until the 1980s (Bernstein and Pauly 2008).

In their work, Gaudillière and Hess approach “regulation” not in the restricted sense of controlling an industry through the setting and enforcement of rules, but in the sense of societal modes of managing a collective issue. They assume that regulating is the outcome of an interplay between what various actors do towards the issue, with their specific aims, values and tools.

The administrative way of regulating corresponds directly to regulation as control of an industry via setting and enforcement of rules (see preceding footnote).

This dictionary is based on a unique identifier for each drug, the “medical product ID”, which allows to make correspondence across various types of classifications of drugs (by substance name, by proprietary name, by marketing authorization holder as well as by Anatomical-Therapeutic Classes). It provides dosage, countries in which the product is marketed, and so on. It is the dictionary of reference for regulators and for the pharmaceutical industry, as well as for the now vast IT industry that helps the former building internal product and distribution databases for its multiple products.
Fernand Sauer, who represented the French government at the WHA in the 1970s thus remembers that “Until the fall of the Berlin wall, the delegates of Eastern countries spent a good deal of time during official sessions disparaging multinational companies, and boasting the high quality of health care in their countries. Faced with multiple contradictory demands from member states, the WHO then gave priority to essential medicines and traditional remedies, and tended to consider that trials and pharmacovigilance were issues that were specific to richer countries.” Interview with author, May 2012.

Interview with author, June 2012. Olsson is a pharmacist by background, and a staff member of the UMC since its creation in 1978. He is now a chief officer for the WHO monitoring programme, splitting his time between Uppsala and Geneva.


Interestingly, the CIOMS project had been presented to John Dunne by Venulet, the former director of the WHO monitoring programme. After leaving the WHO in 1975, he joined the Swiss company Geigy, where he was in charge of drug safety issues. That very company had been among the first to disapprove, back in 1964, the project of giving an international WHO centre the power to take direct decisions to withdraw products following adverse drug reaction reports. Through his contacts with Dunne, Venulet obtained the support of the WHO headquarters for the CIOMS project.

In fact, the CIOMS later became a preparatory forum for ICH work. Several guidelines adopted by ICH were first conceptualized and sketched out within CIOMS, sometimes by the same participants.

It was agreed in 1998 that EU member-states would have to send ADR reports to Vigimed as well as to Eudravigilance, but the UMC was requested at the same time to export the reports of Vigimed towards EudraVigilance. This rule was the object of a major conflict between the WHO and the European Commission.

According to Vogel, the EU has an interest in implementing global standards on its territory, since EU member-states generally agree on these standards in the first place. The EU is the area in which ICH guidelines are most directly and frequently applied (Vogel 1998).

The generalization of MEDDRA in European countries and later in ICH forced the UMC to modify WHO-ART, and to align many of its definitions with those of MEDDRA. This was even more imperative after 2001 when the US, the country from which the greatest part of Vigimed data originate, decided to switch to MEDDRA. It is now possible to query Vigimed using MEDDRA terms, which are more frequently updated than those of WHO-ART, thanks to the working groups of the “maintenance organization” that the ICH set up for it. Since 2002, the UMC also aligned its dictionary with the norms for identification of pharmaceutical products developed in the European Committee for Standardization. In 2005, the CIOMS working group 1A and the ICH expert group ICH-E2b were put in place to standardize “data sets for international exchange of adverse reaction information”. The UMC has to comply with the guidelines that result from this work.

That is, on the introduction within applications for the marketing authorization of drugs, of plans for activities of pharmacovigilance to be conducted after granting of the marketing authorization.

Ralph Edwards, who was director of the UMC at the time of the dictionary battle, is also quite explicit about, and critical of, the technocratic approach that prevails at ICH, and the ensuing difficulties for southern countries to appropriate tools and guidelines that are designed for
countries with high levels of expertise and resources: “There is a strong desire to involve the pharmaceutical industry [in ICH]. And there is very little input from consumers, patients. And it has created some difficulties. – Like what? – Well... A political decision was made to use a new ADR terminology. And it’s one that I was particularly concerned about. Because I thought the way it was developed was not good science but was more political. And, that now has become a very complicated terminology, which people find very difficult to use, and therefore becomes very difficult to train their staff in. It is not so much the cost of the software, but the terminology is quite difficult, and it is not possible really for developing countries really to afford that. So you have two different systems. We try to keep some degree of interaction between the two sets of terminology. But it does make the exchange of information very difficult. And the aim, originally, was to have one terminology that would be easy for everyone to use. So that’s... one thing difficult.” Interview with author, October 2003.

20 The UMC employs 33 staff members for the development and distribution of the drug dictionary, 11 for consulting activities, and only 7 for the work around the database.