Pharmaceuticals Policy and Law 18 (2016) 19–29
DOI 10.3233/PPL-160429
IOS Press

The globalization of medicines as a challenge for governments

Jose Luis Valverde
Chair Jean Monnet of EU Law, Granada, Spain
E-mail: jlvalver@ugr.es

Health is a global concern. The need for a globalized response is evident in the pharmaceutical industry. Although pharmaceutical products are developed and marketed internationally, they are currently regulated only at national level. The pharmaceutical agencies regulate medical products in a globalized environment. However, national regulations can create significant barriers to pharmaceutical availability. We must formulate our laws with a global focus. The globalization of regulation weakens national sovereignty but empowers transnational epistemic networks. For this reasons the pharmaceutical agencies are involved in several bilateral and multilateral cooperation activities with international partners. International cooperation is a key area of work for the agencies. This process will benefit of advancement in global governance and progress toward supranationalism. The internationalization of the pharmaceutical industry, highly globalized, involves changes in policies, lifestyle and culture, and has altered drug research, production, and regulation.

Keywords: Pharmaceutical industry, globalization, regulations, ICH, governance, governments, pharmaceutical agencies, products liability, pharmaceuticals inspections

1. Introduction

Globalization is a reality in our world. Globalization means something other than internationalization. We can no longer focus solely on local, state or national regulatory schemes that do not take into account the significant role played by multinational corporations, global capital markets, advancing technologies and new scientific discoveries.

Internationalization refers to cooperative activities of *national* actors, public and private, on a level beyond the nation-state but in the last resort under its control. Globalization as distinct from internationalization denotes a process of *denationalization* of clusters of political, economic and social activities.

Globalization does require that we recognize the interconnectedness of world health and research on health. Global health care must become a priority for all nations. WHO must re-establish its leadership role, which will require significant changes. These could mean changes in the balance of responsibilities between the UN organization and the agencies and bodies involved in creating international health norms and standards. One of these organizations could be the International Council for Harmonization (ICH), which currently has global leadership in the creation of harmonized guidelines and standards for drug development and registration.

The need for a globalized response is evident in the pharmaceutical industry. Health is a global concern. There are the presence of multinational companies and the world-wide market for industry products and the inter-relationship among nations in combating diseases. The drug development needs acceptance of research studies conducted abroad and regulations extending beyond national borders to protect human subjects. We need to reduce the costs of drug development and provide earlier access to innovative therapies worldwide. We must formulate our laws with a global focus.

Today, the line between domestic and international is illusory; we need the kinds of domestic legal reforms necessary to mesh with or respond to global economic and political forces. Whether or not globalization as a phenomenon can and will occur, the present international harmonization effort can be seen as a strong integrative step.

Regional and international agreements are expected to increase globalization in the drug marketplace, and correspondingly to increase the need for regulation.

1.1. Globalization and governance

Globalization represents a major challenge to governance. Governance, understood as the establishment and operation of rule systems facilitating the coordination and cooperation of social actors, is conceptually distinct from government, understood as an organization in charge of administering and enforcing those rules.

The absence of a world government does not mean that governance is impossible beyond the level of individual states. In systems of governance, problem solving is the result of the interaction of a plurality of actors, who often have different interests, values, cognitive orientations, and power resources. Governance without government is a real feature of the global system.

The management of global affairs is not the preservation of governments, but involves a broad range of actors, at the domestic and transnational levels [2].

Pharmaceutical companies are adapting their business models to a new reality for product development by placing increasing emphasis on leveraging alliances, joint development efforts, early-phase research partnerships, and public-private partnerships.

1.2. Global economic governance

Ambitious institutions and regimes have emerged to regulate international economic life as the World Trade Organization (WTO) and the International Monetary Fund (IMF). Alongside these global regimes, numerous regional and bilateral treaties pursue greater trade liberalization and investment protection.

The growth of global civil regulation in part represents a political response to the recent expansion of economic globalization. Civil regulation proposes to fill the regulatory gap between global markets and global firms on the one hand, and government regulation of multinational firms on the other.

Civil regulations have formally affected the way many global firms, industries and markets are governed. Global civil regulation has become a highly visible and legitimate dimension of global economic governance. Civil regulation has partially reduced the democratic deficit and regulatory failures created by economic globalization

In the absence of international treaties and institutions, national regulators have created informal networks to exchange ideas, coordinate their enforcement efforts, and negotiate common standards. These transnational (or transgovernmental) regulatory networks (TRNs) illustrate a pivotal contemporary phenomenon: the disaggregation of the state in the conduct of its international relations.

TRNs are informal multilateral forums that bring together representatives from national regulatory agencies or departments to facilitate multilateral cooperation on issues of mutual interest within the authority of the participants. This definition distinguishes TRNs from formal treaty-based international organizations, such as the WTO, IMF, World Bank, and European Union (EU). Unlike formal international institutions that are often paralyzed by politics, TRNs have the advantages of speed, flexibility, and inclusiveness, and the capacity to dedicate sustained attention to complex regulatory problems. TRNs can effectively solve some, but not all, problems of international regulatory cooperation.

1.3. Towards harmonization

A "Single Market" has been readily established for most products in the EU. The EU began moving toward a harmonized drug regulatory policy in 1965.

In Japan, for example, a purely national focus presents its own barrier to the marketing of new pharmaceutical products to Japanese consumers. The Japanese drug approval process has been described as designed to protect local pharmaceutical companies as much as Japanese patients because of its insistence on extensive testing in Japan. In the last years Japan enacted stringent drug approval requirements. However, like the United States (USA), Japan is also becoming more receptive to the use of foreign clinical data.

The pharmaceutical regulations of the developing countries with their diverse governments, and laws, rely on the regulatory processes of the developed countries through a certification scheme which permits the drug's use in the developing country if the drug has been approved for commercialization in the country of manufacture. This certification scheme, adopted to combat the dumping of untested, ineffective or dangerous products on the markets of developing countries, is not an ideal solution, but a solution for the moment.

Although pharmaceutical products are developed and marketed internationally, if not globally, they are currently regulated only at the national level. The focus of these national regulations has been on establishing the safety and effectiveness of new products. The FDA, in particular, has been lauded for its role in protecting consumers from unsafe and ineffective products. National regulations can reduce the possibility

that unsafe or ineffective products are introduced into a particular country. However, national regulations can also create significant barriers to pharmaceutical availability. Until recently, new pharmaceuticals were required to be tested and approved in every major market where the drug was to be sold.

1.4. The Transatlantic Trade and Investment Partnership (TTIP)

The TTIP aims to create economic growth while strengthening the Western bloc to contain the regulatory challenges posed by the expansion of the Chinese markets. The objective behind TIPP is to remove trade barriers between the US and EU as a means to stimulate investment, production, and trade between the two regions.

Pharmaceuticals constitute one sector seeking to benefit from more robust bilateral trade. On the pharmaceutical side, US exports of pharmaceuticals on a global basis totaled $48.6 billion in 2012, according to the American Chemistry Council (ACC), and US imports of pharmaceuticals were $89.0 billion.

The US is the most important market for EU pharma exports and is a key market for new pharma products. EU pharma is heavily dependent on global trade and two-thirds of production is exported. Europe and the USA account for more than 80% of global sales of new medicines, and 75% of the global market.

The pharma chapter in the TTIP should strengthen regulations to the highest standards on a global level and improve the regulatory framework. Due to the combined market size of the US and the EU, TTIP can also induce other countries to align their regulatory regimes with the EU and the US. This may reduce trade barriers for EU pharma exporters to third countries. The European Federation of Pharmaceutical Industries Associations (EFPIA) consider that TTIP is expected to increase EU pharma exports contributing to a total increase in extra-EU exports by € 9.2 bn [3].

One of the central goals of TTIP revolves primarily around deepening international regulatory cooperation (IRC); namely, eliminating inefficient and unnecessary incompatibilities created by differing administrative structures that burden industries and trade across the Atlantic. One of the challenges for IRC remains how to achieve regulatory convergence or cooperation by translating broad global governance principles into divergent administrative cultures. Despite the potential benefits of this opportunity, TTIP has sparked promises and criticisms. Questions have been raised about TTIP, its provisions relating to life sciences and the role of the pharmaceutical industry, but will have wider EU societal benefits including increased patient choice and improved access to new pharma products.

2. International harmonization of pharmaceutical regulation

The most comprehensive transnational harmonization of regulation has been achieved within the EU. The regulators representing the world's largest pharmaceutical markets (USA, EU and Japan) have come together with their respective industry

associations in a new forum, the International Council for Harmonization (ICH). Global epistemic networks of technocratic expertise are becoming more important as a source of regulatory authority in pharmaceutical regulation.

The globalization of regulation weakens national sovereignty, the traditional source of authority and legitimacy for regulatory agencies, and instead empowers transnational epistemic networks of technocratic expertise; whose growth can be seen as a transformation from representative democracy to indirect representative democracy.

Globalization of regulations is primarily about setting standards, norms and principles, rather than implementing them; enforcement remains a local responsibility. The problems caused by drug shortages, use of inferior, expired or miss prescribed drugs, and inadequate or ineffective medical supervision are not merely local problems.

Given that the pharmaceutical industry needs a global market to obtain a return on investment, and that the regulations of other countries affect the domestic interests of producer and consumer nations, our perspective on pharmaceutical regulation must be global if we are to adequately protect human rights. Thus, pharmaceutical regulation implicates the need to examine the global, human rights impact of international harmonization efforts on the availability of safe and effective medicines.

The present efforts to harmonize drug regulation laws began in 1990 with an agreement between the Commission of the European Communities, the USA Food and Drug Administration (FDA), the Japanese Ministry of Health and Welfare, and Pharmaceutical industry representatives, to jointly sponsor an ICH.

The problems of high drug development costs and duplicative testing requirements are not unique to the ICH participant countries. Pharmaceutical industry representatives also met to discuss the issue of regulatory harmonization in Latin America, and of truly world-wide harmonization. The consensus was that harmonization should be pursued through regional alliances such as the Andean Pact, Mercosur and CARICOM. Countries in other regional alliances, such as the Asia Pacific Economic Cooperation, have discussed regional harmonization of standards. Developing countries will continue to be affected by the harmonization activities at ICH through the development, manufacture, and export of pharmaceuticals.

Although the WHO and a few countries are patting in the International Harmonization activities as observers, greater attention by the other nations of the world is needed. However, total harmonization requires overcoming obstacles created by different medical and cultural traditions, as well as opposition led by some national pharmaceutical industries.

2.1. The ICH reforms

ICH had drawn up guidelines on nearly 100 topics. Its main achievement had been the drawing up of the Common Technical Document (CTD), a standard form for applications for drug marketing authorizations. ICH is being reorganized in what

could trigger radical changes in the way pharmaceutical regulations are harmonized throughout the world. Regulators must act globally and domestically. The International Pharmaceutical Regulators Forum (IPRF), formed in June 2013, already acts as an offshoot of the ICH.

The IPRF is a technical platform for regulators, while the International Coalition of Medicines Regulatory Authorities (ICMRA) is discussing high-level/strategic issues amongst heads of agencies. A key objective behind the ICH reform is to strengthen its leadership in the drawing up of global pharmaceutical standards by enlarging its membership.

3. The global drug safety system

New drugs, devices, and diagnostics present the greatest opportunity currently available to improve healthcare and the way medicine is practiced; but all medical products pose potential risks.

The drug safety system is on the verge of major transformations driven by the rapid evolution of science, technology, and the healthcare system. This science of safety encompasses the entire life cycle of a product, from premarket animal and human safety testing to widespread clinical use beyond original indications. But the efforts to improve drug safety must not dampen the process of medical innovation that could itself enable safer approaches to drug development and drug use.

The pharmaceutical agencies regulate medical products in a globalized environment. Medical products are discovered, developed, authorized, marketed, transported, promoted, and used by practitioners, patients, and other consumers throughout much of the world. For many years, FDA and the European Medicines Agency (EMA) have leveraged scientific and human resources dedicated to product safety with those of many foreign counterpart regulatory authorities. In addition, the agencies are involved in formal harmonization initiatives, such as the ICH with counterpart regulatory authorities and the regulated industry [4].

The practice of medicine and the provider-patient interaction have undergone great transformation in the last two or three decades. The increasingly complex interface between innovation and regulation has been characterized by binary opposites: speed vs. safety, tight preapproval regulation vs. loose post approval regulation, etc. The polarity of approach and emphasis is inconsistent with the widely accepted notions that risk must be considered in the context of benefits.

3.1. Innovation and patents

The science and technology that underpin drug discovery are in a process of dramatic transformation. The practice of drug discovery and drug development research has also changed substantially in response to scientific and technological advances.

Technological innovation is widely recognized as a key determinant of economic and public health progress. Patents and other forms of intellectual property protection are generally thought to play essential roles in encouraging innovation in biopharmaceuticals. This is because the process of developing a new drug and bringing it to market is long, costly, and risky. Patents confer the right to exclude competitors for a limited time within a given scope [5].

Patents and regulatory exclusivity provisions are likely to remain the core approach to providing incentives for biopharmaceutical research and development. Reimbursement, regulatory, or patent policies that target the returns to the largest-selling pharmaceuticals can have significant adverse consequences for R&D incentives in this industry.

Significant patent time is lost by pharmaceutical products by the time of approval. This implies a reduction in the effective patent life of drugs relative to the nominal life of twenty years. In light of this, the USA, the European Community, and Japan have all enacted patent term restoration laws. Patent and regulatory exclusi- vity terms, together with market entry decisions by generic drug firms, determine the market exclusivity period of a new branded drug. The average market exclusivity period remained relatively constant between 1995 and 2012, varying between 12.2 and 13.7 years.

Some critics of the patent-based system have advocated replacing it with prize systems, government contracting, or other options that they argue could better balance the dual objectives of price competition and innovation incentives. These proposals present both theoretical and practical problems. However, prizes and other voluntary supplements could play a useful role in addressing unmet needs and gaps in specific circumstances [6].

4. International cooperation activities

The EU is involved in several bilateral and multilateral cooperation activities with international partners. The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation aims at harmonizing inspection procedures worldwide by developing common standards in the field of good manufacturing practices (GMP) and by providing training opportunities to inspectors.

Mutual Recognition Agreements (MRAs) are official agreements on the mutual recognition of assessment of conformity of regulated products which are negotiated and signed at EU level. Currently, the EU has operational MRAs in place with Australia, Canada, Japan, New Zealand and Switzerland. An MRA between the EU and the USA was signed in 1999.

The EU as well as other medicine regulatory agencies [7] participate in the activities of the ICMRA. ICMRA is an initiative which aims at providing global strategic coordination and direction on areas that are common to many regulatory authorities' missions worldwide. The manufacturing and distribution supply chains are complex,

globally integrated and may at times be unclear; there is growing complexity in medicines and managing the risks and benefits requires international collaboration among regulators.

A less formal form of cooperation is the Alliance International Partnership (API). The API's objectives include the sharing of information on inspection planning, policy and inspection reports and joint inspections on manufacturers located outside the participating countries [8]. In this perspective, the EU has identified the recognition of GMP inspections carried out in the EU and the USA in third countries as a main objective for the pharmaceutical sector in the context of the negotiations of the TTIP [9].

Also it is necessary to discuss the creation of one international agreement for identification of Medicinal Products to explore adoption of substances registration software, to forming a global identification system for medicinal products. During the past decades there have been significant changes and trends in the global pharmaceutical industry. These global changes have a significant impact on safety, competitiveness, and the outlook for the pharmaceutical industry and drug development. These changes need to be consolidated under one global regulation. It is the big challenge of the Governments and the international organizations. In this challenge the WHO need to have one primary initiative.

5. Cooperation in global regulation between agencies

As drug development occurs in an international environment, regulatory agencies must collaborate and there is renewed focus on such interactions through dedicated strategies formalizing the processes involved.

With Europe and the US representing the two largest pharmaceutical markets in the world, cooperation between the agencies has several potential benefits. Cooperation between the two agencies has been increasing significantly during the past few years. The arrangements allow both agencies to exchange confidential information as part of their regulatory and scientific processes.

International cooperation is a key area of work for the agencies. EMA has placed a growing emphasis on collaborating with international pharmaceutical regulators in areas such as inspections, safety of medicines and exchange of information on issues of mutual concern. This focus is to ensure a more global approach for the manufacture and supervision of medicinal products in the long term. The increased interactions between the two agencies have been driven by the Transatlantic Administrative Simplification Action Plan, which was established in 2007 to remove the administrative burden involved in interactions between regulators in Europe and the US. The objective was to simplify regulations wherever possible.

An additional boost to cooperation was the appointment of a permanent representative from FDA to EMA's office in London in 2009. Although the two agencies have upped their level of cooperation and share many similar roles, it is important

to remember that they remain very different organizations. Whereas the FDA is a unified regulatory agency, the EMA is an administrative organization that relies on the agencies in individual member states to carry out the functions required.

In addition to the US, EMA also has long-standing agreements with partner regulatory bodies in Canada, Switzerland, Australia and New Zealand, and supports the European Commission's collaboration on pharmaceuticals with China, India and Russia. In 2010, EMA and the Chinese State Food and Drug Authority (SFDA) also agreed to cooperate on GMP and GCP inspections. Another important partner for EMA is the WHO.

The EMA has also been increasingly interacting with its counterparts in Japan. The Japanese regulators have been very committed to improve their relationship with both EMA and FDA. Confidentiality agreements between EMA and its Japanese partners have been in place since 2007. Such agreements facilitate the exchange of confidential information (e.g. advance drafts of legislation) between the pharmaceutical agencies. EMA personnel also meet regularly with their Japanese counterparts from the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceutical and Medical Devices Agency (PMDA). In November 2009, Japan sent a Liaison Officer to EMA's offices. Cooperation between Europe and Japan has been particularly beneficial in the area of advanced therapy medicinal products and both regulators share an interest in rare diseases.

In India, EMA works with regulators for the application of international standards in manufacturing and clinical trial activities. The EMA's work with Russia is part of the European Commission's existing arrangements with the country in the area of pharmaceuticals. FDA, the Australian Therapeutic Agency, and the USA Pharmacopeia have done similar exchange programs.

5.1. The need for international harmonization of pharmacopoeias

Efforts to harmonize pharmacopeial standards in different regions, over several decades, have been stymied by differences in legal authority and traditional practices in different countries. Pharmacopeial harmonization now is shifting to a more prospective approach, working with the WHO to develop common testing practices and standards-setting processes.

Global expansion has been a prominent theme at the USA Pharmacopeia (USP), which now has offices and laboratories in India, China, and Brazil to provide local manufacturers with access to reference standards, test methods, and training programs on correct procedures for testing and ensuring product quality. USP's promoting the Quality of Medicines initiative, which is funded by the US Agency for International Development, also assists manufacturers in developing nations produce medicines that meet quality and safety standards.

Globalization and expansion in international trade present a growing need to develop global quality standards for medicines. The harmonization among the world's

three major pharmacopoeias, the European Pharmacopoeia, the Japanese Pharmacopoeia and the USP, is an important and challenging task. Each pharmacopoeia is responsible for a program of international harmonization. This process triggered the Pharmacopoeial Discussion Group (PDG) in 1989.

This group meets regularly in Europe, Japan and the USA. Monographs and general methods of analysis proposed by national associations of manufacturers of pharmaceutical products are selected for convergence and harmonization among the three pharmacopoeias. Each pharmacopoeia is therefore responsible for a program of international harmonization.

In May 2001, the PDG welcomed the WHO as an observer. While not part of the ICH, the PDG usually meets in conjunction with ICH and provides the ICH Steering Committee with reports of its progress. The PDG considers proposals made by national associations of manufacturers of pharmaceutical products and excipients in order to select general methods of analysis and excipient monographs for addition to its work program. Each text drafted by the three coordinating pharmacopoeias is published for public comment in each of their respective forums. Harmonization of pharmacopoeial documents in the PDG occurs based on decisions of the expert bodies of each pharmacopoeia. Each pharmacopoeia incorporates the harmonized draft according to its own procedure [10].

5.2. Future trend: From cooperation to integration. "The Supranationalism"

Globalization is a major external driver for regionalism. Increasingly, regional cooperation and integration has become more developmental. States are the master of regional organizations, but for cooperation and integration the key driver is economic interdependence.

Cooperation and integration became two distinct outcomes of regionalism. Regional cooperation entails the joint exercise of state-based political authority in intergovernmental institutions to solve collective action problems. Regional integration, by contrast, involves the setting up of supranational institutions to which political authority is delegated to make collectively binding decisions.

European integration is by definition more than cooperation among states; states are the masters of a process, but they increasingly delegate authority to supranational institutions. Successful integration requires a sense of community. Integration theories mainly emerged from explaining the peculiarities of European integration. As a result, integration theories applied to EU regionalism while cooperation theories covered regionalism outside Europe.

Intergovernmentalism, neofunctionalism and multi-level governance approaches, by contrast, privilege domestic actors, which press for further integration, emphasizes the role of interest groups, professional associations, producer groups and labor unions, which do not equally benefit from regionalism. The governance assumes all this different approaches. Governance gives similar status to state and non-state actors and does not prioritize formal over informal institution.

In the Intergovernmentalism, nation states cooperate on the intergovernmental level without formally questioning parts of their sovereignty or limiting the execution of their sovereign rights. In the Supranationalism, nation states transfer certain rights or parts of their sovereignty to a supranational authority constituted as an independent international actor by international treaty. Supranationalism thus takes inter-state relation beyond cooperation into integration, and involves some loss of national sovereignty. This is the case of the EU.

The internationalization of the pharmaceutical industry, highly globalized, involves changes in politics, lifestyle and culture, and has altered drug research, production, and regulation.

References

[1] jlvalver@ugr.es.
[2] Koenig-Archibugi, Mathias (2011) Global governance. In: Michie, Jonathan, (ed.) The handbook of Globalisation. Edward Elgar Publishing Ltd, Cheltenham, pp. 393–406.
[3] EFPIA. How a Strong Pharmaceutical Chapter in TTIP will Benefit the EU. http://www.efpia.eu/topics/industry-economy/trade/ttip.
[4] The Future of Drug Safety: Promoting and Protecting the Health of the Public. Committee on the Assessment of the US Drug Safety System, Alina Baciu, Kathleen Stratton, Sheila P. Burke, Editors. This PDF is available from the National Academies Press at: http://www.nap.edu/catalog/11750.html.
[5] Innovation.org (2007) Drug discovery and development: Understanding the R&D process. Washington DC: Pharmaceutical Research and Manufacturers of America. http://www.innovation.org/drug_discovery/objects/pdf/RD_Brochure.pdf/.
[6] H.G. Grabowski, J.A. DiMasi and G. Long, The Roles of Patents and Research and Development Incentives In Biopharmaceutical Innovation, *Health Aff.* **34**(2) (2015), 302–310.
[7] Authorities in Australia, Brazil, Canada, China, Japan, Korea, Mexico, New Zealand, Nigeria, South Africa and the United States. The European Commission is also a member and the World Health Organisation (WHO) is an observer.
[8] It includes the following participants: the EMA and all EU member States, the European EDQM, the U.S. FDA, the Australian Therapeutic Goods Administration (TGA) and WHO.
[9] https://www.pda.org/pda-letter-portal/archives/full-article/gmp-oversight-of-medicines-manufacturers-in-the-european-union.
[10] The Working Procedures of the Pharmacopoeia Discussion Group (PDG) for further information. See more at: https://www.edqm.eu/en/international-harmonisation-614.html#sthash.P8uSO514.dpuf.